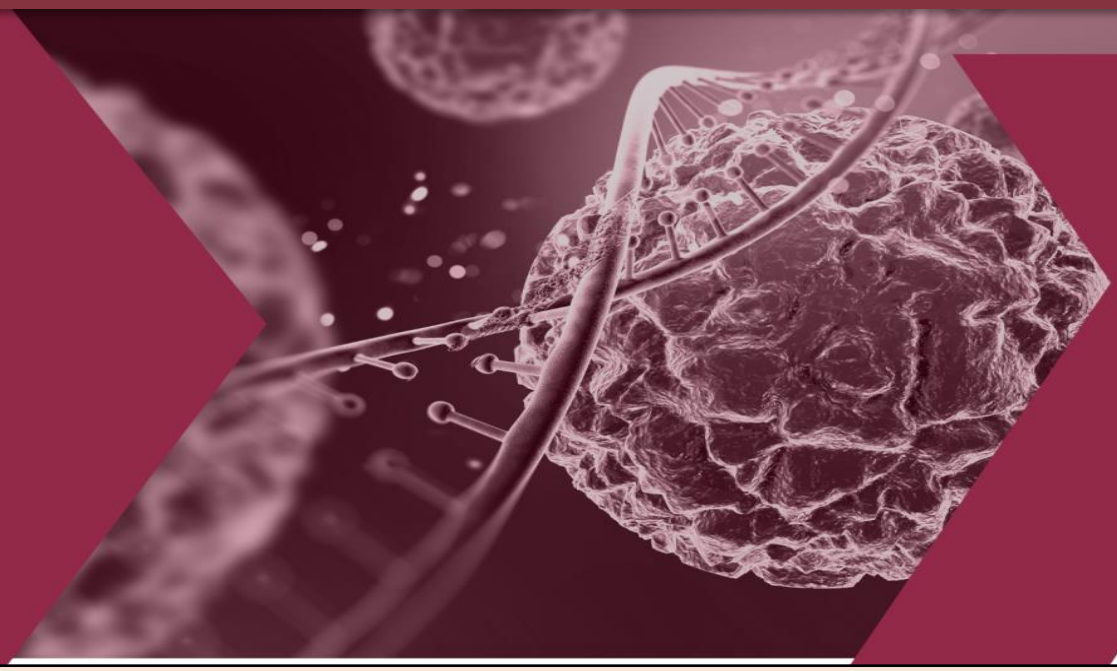
Value-based Pricing of Anti-cancer Drugs



Cost-effectiveness Analysis & Value-Based Pricing for Anti-Cancer Drugs: Implications for Patients, Industry, Insurer and Regulator

Health Technology Assessment in India

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New Delhi (India)

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List of Abbreviations

AB-PMJAY	Ayushman Bharat - Pradhan Mantri Jan Aarogya Yojana
AC	Autocorrelation
ACM	All-Cause Mortality
AE	Adverse Effects
AHSCT	Autologous Hematopoietic Stem Cell Transplantation
AIC	Akaike's Information Criterion
AIIMS	All India Institute Of Medical Sciences, New Delhi.
AIOCD	All Indian Origin Chemists and Distributors
AP	Accelerated Phase
ASCO	American Society Of Clinical Oncology
ATC	Anatomical Therapeutic Chemical
AWACS	Airborne Warning And Control System
BC	Blast Crisis
BCT	Breast-Conserving Therapy
BIC	Bayesian Information Criterion
BR	Bendamustine plus Rituximab
CaDCQoL	National Cancer Database For Cost And Quality Of Life
CBC	Complete Blood Count
CDK-4	Cyclin-Dependent Kinase 4
CDK-6	Cyclin-Dependent Kinase 6
CEA	Cost-Effectiveness Analysis
CECT	Contrast-Enhanced Computed Tomography
CGHS	Central Government Health Scheme
CGHS	Central Government Health Scheme
CNS	Central Nervous System
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Intervals
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
CML	Chronic Myeloid Leukemia IN Chronic Phase
CP	Chlorambucil plus Prednisolone
CR	Complete response
CRT	Conformal Radiation Therapy
CT	Computed Tomography
DALYs	Disability Adjusted Life Years
DC	Death Resulting From Cancer
df	Degrees of freedom
DFS	Disease-Free Survival
DID	Difference-in-difference
DPCO	Drug Price Control Order
DVRd	Daratumumab Plus Bortezomib, Lenalidomide, Dexamethasone
EBM	Evidence-Based Management
ED	Extended Dominated
EphMRA	European Pharmaceutical Market Research Association
ER	Estrogen Receptor
ESI	Employees State Insurance
ET	Endocrine Therapy

FDA	Food And Drug Administration
FinHER	Finland Herceptin Study
GBM	Glioblastoma Multiforme
GCSF	Granulocyte-Colony Stimulating Factor
GDP	Gross Domestic Product
GIPAP	Glivec International Patient Assistance Program
GOG	Gynecologic Oncology Group
GoI	Government Of India
Hb A1 c	Haemoglobin A1c
HBP	Health Benefit Package
HDU	High Dependency Unit
HER2	Human Epidermal Growth Factor Receptor 2
HERA	Herceptin Adjuvant Trial
HR	Hazard Ratios
HR+	Hormone Receptor-Positive
HRQoL	Health-Related Quality Of Life
HTA	Health Technology Assessment
HTAIn	Health Technology Assessment In India
IARC	International Agency For Research On Cancer
ICER	Incremental Cost- Effectiveness Ratio
ICIs	Immune Checkpoint Inhibitors
IFN-α	Interferon-A
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-2	Immunomodulatory Cytokines Interleukin
INR (₹)	Indian National Rupee
IQR	Interquartile range
IRIS	International Randomized Study of Interferon vs imatinib
ITS	Interrupted Time Series
KPd	Carfilzomib, Pomalidamide, Dexamethasone
LC	Limited complications
LDH	Lactate Dehydrogenase
LL	Lower Limit
LFT	Liver Function Test
LMICs	Low and middle income countries
LR	Locoregional Recurrence
Lys	Life-Years
MBC	Metastatic Breast Cancer
MM	Multiple Myeloma
MoHFW	Ministry Of Health And Family Welfare
Mos	Median Overall Survival
mPFS	Median Progression Free Survival
MRI	Magnetic Resonance Imaging
MRP	Maximum Retail Price
mRCC	Metastatic Renal Cell Carcinoma
mTOR	Mammalian Target Of Rapamycin
mTOR	Mammalian Target Of Rapamycin
NCCN	National Comprehensive Cancer Network

NCCTG	North Central Cancer Treatment Group
NCG	National Cancer Grid
NCG	National Cancer Grid
ND	Non Dominated
NDMM	Newly Diagnosed Multiple Myeloma
NHSCD	National Health System Cost Database
NLEM	National List of Essential Medicines
NPPA	National Pharmaceutical Pricing Authority
NPPA	National Pharmaceutical Pricing Policy
NR	Not Reported
NSABP	National Surgical Adjuvant Breast And Bowel Project
NSSO	National Sample Survey Organization
OOPE	Out-Of-Pocket Expenditure
OPD	Out-Patient Department
ORS	Oral Rehydrating Solution
OS	Overall Survival
PAC	Partial Autocorrelation
PCV	Procarbazine, lomustine, vincristine
PD	Progressive Disease
PD2	Progressive Disease
PET	Positron Emission Therapy
PFS	Progression Free Survival
PGIMER	Post Graduate Institute Of Medical Education And Research, Chandigarh.
PHARE	Protocol For Herceptin As Adjuvant Therapy With Reduced Exposure
PomDex	Pomalidomide And Dexamethasone
PR	Progesterone Receptor
PSA	Probabilistic Sensitivity Analysis
PSA	Probabilistic Sensitivity Analysis
PTR	Prices to Retailers
QALY	Quality-Adjusted Life-Years
QoL	Quality Of Life
RCC	Renal Cell Carcinoma
RFT	Renal Function Test
RISS	Revised International Staging System
RMSC	Rajasthan Medical Service Corporation
RT	Radiotherapy
SC	Severe Complications
SC	Standard Chemotherapy
SD	Standard Deviation
SE	Standard Error
Sig	Significance
SRS	Sample Registration System
STG	Standard Treatment Guidelines
SU	Standard Units
T3	Triiodothyronine
T4	Thyroxine
TKIs	Tyrosine-Kinase Inhibitors
TM	Trade Margin
TSH	Thyroid Stimulating Hormone
UL	Upper Limit

US	United States
USG	Ultrasound Sonography
VCd	Bortezomib, Cyclophosphamide, Dexamethasone
VEGF	Vascular endothelial growth factor
VMP	Bortezomib, Prednisone And Melphalan
VRd	Bortezomib, Lenalidomide, Dexamethasone
VTd	Bortezomib, Thalidomide, Dexamethasone
WTP	Willingness To Pay

Executive Summary

Introduction

The rising economic burden of cancer on health-care system and patients in India has led to the increased demand for evidence in order to inform policy decisions such as drug price regulation, setting reimbursement package rates under publically financed health insurance schemes and prioritizing available resources to maximize value of investments in health. Economic evaluations are an integral component of this important evidence. In order to facilitate such analyses, strong information systems are needed to be put in place. High out-of-pocket payments and the indirect costs associated with cancer treatment, often result in financial toxicity. Therefore, characterization and prediction of these costs, alongside other health outcomes such as both quantity and quality of life, is important for planning strategies to mitigate the financial hardship due to cancer treatment.

The draft Indian reference case for undertaking economic evaluation as part of health technology assessment (HTA), recommends the use of quality adjusted life years (QALYs) as an index to measure the health consequences. Computing QALYs requires valuation of health related quality-of-life (HRQOL) or utility scores for different health states. Estimating the utility scores by collecting primary data in each study is time consuming and resource intensive. The evidence on HRQOL for different health states of cancer patients would go a long way to facilitate quick HTA analyses. The second important evidence need for HTA analyses is cost data. In the context of health financing in India, cost of a service comprises of two parts – health system cost and out-of-pocket expenditure (OOPE). A national health system cost database has been recently created. Another nationally representative study (Costing of Health services, CHSI study) to measure health system cost of tertiary care hospitals, which includes oncology services, is being carried out in more than 100 hospitals in 11 states. For OOPE, while National Sample Surveys assess the expenditure for all types of morbidities, the sample of cancer patients in this data is a mere 500 at all-India level. Several types of specific cancers do not even have a single case. Thus, another important evidence for conducting HTA is robust data for OOPE among cancer patients, which can be stratified by type of cancer, its health states, levels of severity and type of treatment.

Considering the increasing costs of diagnostics and therapeutic interventions for cancer, their formal assessment is imperative to inform value-based standard treatment guidelines. Therefore, the present study aimed to evaluate the value-based prices for 42 anticancer drugs, which have come under price regulation. Several cancer treatments have been evaluated on grounds of cost-effectiveness as part of the **first objective** of the study. A total of **eight economic evaluations** have been conducted as part of this project. One of the economic evaluations assessed the cost-effectiveness of CDK4/6 inhibitors (Ribociclib and Palbociclib) in the second line treatment of hormone receptor (HR) positive HER2 negative metastatic breast cancer (MBC) among post-menopausal women in India. In this study, we evaluated the cost-effectiveness of ribociclib/palbociclib combination therapy, Fulvestrant monotherapy, single-agent Paclitaxel and single-agent Capecitabine in the Indian context from two different viewpoints: Scenario I – as per the prevailing market prices of the drugs; and Scenario II – as per the reimbursement rates set up by the publicly financed national-level health insurance scheme. The use of ribociclib/palbociclib is not a cost-effective treatment option in the Indian context. A reduction of 78% and 72% respectively in the price of Fulvestrant monotherapy in both the scenarios, is required to make it cost-effective.

The second analysis was done to compare the cost-effectiveness of Bevacizumab plus chemotherapy versus chemotherapy alone among advanced metastatic cervical cancer in India. We found that the addition of bevacizumab to the standard chemotherapy is not cost-effective for the treatment of advanced and metastatic cervical cancer in India at a threshold of 1-times per capita GDP.

The third economic evaluation was done to assess the cost-effectiveness of novel agent regimens for transplant-eligible newly diagnosed multiple myeloma patients in India. The cost-effectiveness of seven treatment sequences was evaluated-(1) Bortezomib, lenalidomide, dexamethasone (VRd) alone (2) Bortezomib, thalidomide, dexamethasone (VTd) alone (3) Bortezomib, cyclophosphamide, dexamethasone (VCd) alone (4) VRd followed by AHSCT (5) VTd followed by AHSCT (6) VCd followed by AHSCT (7) Daratumumab plus VRd (DVRd) followed by AHSCT for treating transplant eligible NDMM patients in India. It was found that *none of the novel treatment sequences were cost-effective* at the current WTP threshold of ₹1,46,890 (US$1,927.7). Reduction in current reimbursement rates of novel drugs namely VRd, lenalidomide, pomalidomide plus dexamethasone under national insurance program and societal cost of transplant by

50%, would make VRd plus AHSCT and VTd plus AHSCT cost-effective at an incremental cost of ₹ 40,671 (US$ 534) and ₹ 97,639 (US$ 1,281) per QALY gained respectively.

Further, first-line treatment options of metastatic renal cell carcinoma were also assessed for their cost-effectiveness. In this study, we aimed to analyse the most commonly used treatment strategies (both single-agents: sunitinib & pazopanib; and combination therapies: Nivolumab/Ipilimumab & Pembrolizumab/Lenvatinib) for metastatic renal cell carcinoma in India. We found that sunitinib is the most cost-effective treatment option with an average cost of ₹ 143,269 ($ 1,939) per QALY lived at a willingness to pay (WTP) threshold of 1-time per capita GDP of India. Sunitinib at current reimbursement rates (₹ 10,000 per cycle) has a 94.6% probability of being cost-effective at a WTP threshold of 1-time per capita GDP (₹ 168,300). Moreover, Pazopanib is a dominated strategy as it offers similar health outcomes at a higher overall cost. Our findings support the current inclusion of sunitinib under India's publicly financed health insurance scheme.

In addition to this, we have also compared the cost-effectiveness of three therapeutic regimens, i.e., chlorambucil plus prednisolone (CP), bendamustine plus rituximab (BR) and ibrutinib for the treatment of chronic lymphocytic leukaemia (CLL) in India. As compared to most affordable regime comprising of CP as first line followed by BR as second line therapy, none of the other therapeutic regimens were cost effective at one time per capita gross-domestic product of India. The scenario analysis, excluding the impact of second-line therapy, also points to a similar conclusion and reports chlorambucil based regimen followed by BR as a cost-effective first-line treatment for CLL in India.

Another economic evaluation was conducted to determine the most cost-effective first-line TKI (Imatinib/Dasatinib/Nilotinib) for the treatment of newly diagnosed CML-chronic phase (CP) patients in India. It was found that Imatinib incurred an average cost of ₹ 64,323 ($ 855) per QALY lived which is cost-effective at the current WTP threshold of 1-time per capita GDP of India. Both, Dasatinib and Nilotinib are not cost-effective at the current WTP threshold of 1-time per capita GDP in the Indian context. Dasatinib has and Nilotinib have a 27.7% and 2.9% probability of being cost-effective respectively, at the current WTP threshold of 1-time per-capita GDP of India. A 21% reduction in the reimbursement rate of Dasatinib (from ₹ 5,500 to ₹ 4,345) will make it a cost-effective treatment option as compared to Imatinib.

Further, we have evaluated the cost effectiveness of concomitant temozolamide with radiation and maintenance temozolamide for 6 months for treatment of Glioblastoma Multiforme **(**GBM) in India. We used a Markov model to evaluate the lifetime costs and consequences of treating GBM with radiation alone versus radiation with adjuvant temozolamide. We concluded that Temozolamide is not cost effective for treatment of GBM patients in India. This evidence should be used while framing guidelines for treatment and price-regulation.

Another health technology assessment was done in context of cost-effectiveness of Trastuzumab for management of breast cancer in India. Addition of the HER2-targeted mono-clonal antibody trastuzumab to chemotherapy in adjuvant treatment has been shown to improve disease- free survival (DFS) by 50% and overall survival (OS) by 30% among human epidermal growth factor receptor (HER)-2 positive early and advanced breast cancers. However, trastuzumab is an expensive drug. It was reported to have been used in only 8.6% of eligible patients, half of whom were enrolled in a clinical trial. The low rate of trastuzumab use raises the important question of whether public resources should be used to make this treatment routinely accessible in India. This question is highly relevant because of the recently announced ambitious Indian health insurance program, Ayushman Bharat, which includes coverage of chemotherapy for cancer treatment under the Prime Minister's Jan Aarogya Yojana (PMJAY) component. We used a Markov model to estimate the incremental cost and benefits of using trastuzumab (for 1 year, 6 months, or 9 weeks) as compared with chemo-therapy alone using a societal perspective. Use of trastuzumab for 1 year is not cost effective in India at the current price. At the current price, 1-year trasutuzumab use has just a 4% to 57% probability of being cost-effective. However, trastuzumab use for 9 weeks is cost effective and should be included in clinical guidelines and reimbursement policies. A price reduction of 15% to 35% increases the probability of 1-year trastuzumab use being cost effective, to 90%.

Currently, cost-effectiveness analysis comparing zoledronic acid (3-monthly), zolerdronic acid (4-weekly) and denosumab (4-weekly) for prevention of skeletal related evemts among metastatic breast cancer patients is in progress.

As part of the **second objective**, primary data was collected from a nationally representative sample of cancer patients on out-of-pocket expenditure and HRQOL, which will help to develop a national database of patient costs and quality of life among cancer patients in India – '*National Cancer database for Costs and Quality of Life* –

CaDCQoL'. This database would serve to build an open-access data repository to derive estimates of cancer-related medical care costs borne by the patients, indirect costs due to loss of productivity and HRQOL by type of cancer, stage or severity, as well as by treatment approach. This evidence would be useful for outcome valuation in the HTA analyses for 42 anti-cancer drugs for 28 cancers in India.

Primary data collection

A cross-sectional study was being conducted to recruit cancer patients at purposively selected seven public health care facilities providing cancer care in India. A multi-stage stratified sampling technique was followed to recruit cancer patients. In the first stage, the states/regions were selected on the basis of epidemiological transition level (ETL) of top 10 cancers in India. The ETL state groups were defined on the basis of the trends of top 10 cancer types responsible for the highest proportion of cancer disability adjusted life years (DALYs) in India. Among high ETL states, Chandigarh (Punjab) and Tamil Nadu were randomly selected. Similarly among middle and low ETL states, Delhi & Maharashtra and Assam were selected respectively. The selection of these states also ensures geographical representation of the country.

At the second stage, seven health-care facilities were purposively selected in order to choose hospitals in these states which cater to largest volume of oncology patients. The selected seven health care facilities were Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh; Government Medical College and Hospital (GMCH), Chandigarh; B. Booroah Cancer Institute (BBCI), Guwahati, Assam; Christian Medical College (CMC), Vellore, Tamil Nadu; Adyar Cancer Institute, Chennai, Tamil Nadu; Tata Memorial Centre (TMC), Mumbai, Maharashtra and All India Institute of Medical Sciences (AIIMS), New Delhi. At the third stage, probability proportional to size (PPS) method was used to select patients from each of the disease management groups in these selected health care facilities.

The patients diagnosed with any type of cancer irrespective of age and gender seeking hospitalized and non-hospitalized treatment for any stage at selected health care facilities were prospectively recruited in the study. The three types of cancer patients were recruited in outpatient setting viz. newly diagnosed (who have been recently diagnosed with cancer), on-treatment (patients who were on some form of active cancer treatment like chemotherapy/radiotherapy etc.) and follow-up cases (patients whose treatment has

been completed and were on maintenance therapy). The inpatient department included cancer wards, high-dependency unit (HDU), intensive care unit (ICU) etc. Newly admitted cancer patients who have been hospitalized overnight (last 24 hours) due to cancer were recruited prospectively in inpatient setting. Each patient was followed up on a daily basis till discharge for capturing information on expenses incurred during last 24 hours. The HRQOL was assessed on the day of the recruitment.

The outcomes measured were mean per visit OOPE incurred on non-hospitalized treatment of cancer, mean OOPE incurred per episode of hospitalization, mean OOPE for non-hospitalized treatment and hospitalization by type of treatment, disease severity, line of treatment, stage of cancer, presence of adverse effects. The indicators of financial toxicity in terms of catastrophic health expenditures (CHE), impoverishment and distress financing due to cancer treatment were also computed. Similarly, HRQOL of cancer patients by primary site of cancer, type of treatment, disease stage, line of treatment, response to treatment, presence/absence of aderse events/complications etc.

The total annual direct OOPE on cancer treatment was estimated as INR 3,49,497 (6047.95) [INR 57,553 (2935.37) for hospitalisation and INR 3,33,408 (5947.41) for non-hospitalised treatment]. The stratified analysis was also done to elicit the cancer-site specific estimates on OOPE. It was found that the maximum expenditure was incurred on kidney and ureter cancer for both non-hospitalized treatment [INR 13,017] and hospitalization [INR 70,429]. The cancer category with the lowest OOPE was testicular cancer [INR 5,793] among non-hospitalized cancer cases and penile cancer [INR 9394] for hospitalisation. The overall prevalence of CHE among cancer patients was found to be 84% due to non-hospitalised treatment and 28.5% due to cancer-related hospitalisation. Approximately 67% patients were impoverished due to non-hospitalised treatment and 17% due to hospitalisation.

For calculating the indirect cost, total hours forgone by patients on various activities were converted into work days and relevant standardised wage rates [National Sample Survey 2011-16, (68th round) – 'Household Consumer Expenditure' and 'Employment and Unemployment'] were applied to estimate the loss of productivity. Daily wage rates were stratified by (i) area of residence and gender, and (ii) level of education. Indirect cost was also calculated by using annual household expenditure as proxy for their annual income. For generating cost estimates of caregivers, daily wage rates were calculated based on

the income reported by them. The product of total hours forgone and daily/monthly wage rates represented the indirect cost.

Indirect cost data were elicited from a total of 2,576 patients out of a sample size of 9,787 cancer patients. Majority patients were females (n=1519, 58.96 %) and 41.03% were males (n=1057). The graduate and post-graduate patients were found to incur highest indirect OOPE [mean: INR 11,038 (95% CI: 10,384-11,693) as compared to patients with lower educational status [mean: INR 2,014 (95% CI: 1943-2086). Loss of productivity was highest among urban males [INR 6,750] and the least among rural females [mean: INR 1750]. On considering the annual consumption expenditure as an indicator of per-capita income, the overall mean indirect OOPE was estimated as INR 7,489 (95% CI: 7246-7732) with a median loss of productivity of INR 6,273 (IQR: 6323) with 50% of the population ranging between INR 3,468 and INR 9,791. The indirect cost incurred by caregivers was found to be INR 39,379 (95% CI: 39304 – 39453). An overall indirect OOPE due to loss of wages (patient plus caregiver) was computed as INR 8,802 [standard error=134.8).

To ensure continuous protocol compliance throughout the data collection, daily monitoring of the data collection was being undertaken at PGIMER and individual telephonic feedback was provided to interviewers. The PGIMER, Chandigarh served as the nodal centre to carry-out the study activities including supervision and monitoring of data collection, training of staff recruited at respective states, development of tools & information manual, data cleaning and data analysis of primary data. Additionally, PGIMER was responsible for conduct of HTAs (N=8) for value based pricing of 42 anticancer drugs along with the analysis of insurance claims data to assess the impact of price regulation on insurers. The recruitment and data-collection at the respective states was undertaken by the partner institutes in the respective states. The data collection in PGIMER was undertaken by PGIMER Chandigarh itself. The data collection was undertaken at 6 partner institutes and 12,148 patient interviews (9,787 OPD and 2,361 IPD) were conducted.

Furthermore, keeping in view the increasing disease burden and lack of affordable cost of treatment due to cancer, the National Pharmaceutical Pricing Authority (NPPA) released a gazette to ensure the affordability of 42 essential anti-cancer drugs in India. The **third objective** of the study is to evaluate the impact of this price regulation policy implemented across various cancer institutes in India, using the interrupted time series

approach. This procedure of segmented time series regression analysis helps to *undertake the statistical comparison of time trends before and after intervention. The* primary outcome indicator for evaluating the impact of the policy is the market share of 42 anti-cancer drugs. The market share of a drug is measured in terms of sales volumes (percentage based). The month-wise data on sales volume and value of all the concerned anticancer drugs was obtained from the Pharmatrac from January 2015 to December 2020. To employ the ITS approach, the entire duration was divided into two parts namely pre intervention and post intervention period. The price regulation policy was made legally effective from 8th March 2019. Hence the period before Mar-2019 (August, 2017 to February, 2019) was considered as pre-intervention period and post intervention period includes the data on sales volume and value after Mar-2019. The pharmatrac data analysis has been carried out by Public Health Foundation of India (PHFI), New Delhi in collaboration with PGIMER, Chandigarh. Findings from the analysis for 18 cancer medicines for which NPPA notified ceiling prices in 2016 and 2017, 8 medicines witnessed both a sudden and sustained increase in sales in the post-intervention period, 5 medicines were observed to have witnessed a sudden increase in sales followed by as sustained decline, 4 medicines witnessed a sudden and sustained decline in sales and 1 medicine was observed to have witnessed a sudden decline followed by a sustained increase in sales. The methodology and findings are presented in detail in the last chapter of the current report.

The **fourth objective** of the study is to assess the impact of price regulation on payers (government and insurance providers). Claims data of a state-specific health insurance scheme of Punjab state namely Mukh Mantri Cancer Rahat Kosh, was analyzed. The difference in the claim amount before and after price regulation was assessed. The period before Mar-2019 (January 2018 to March 2019) was considered as pre-intervention period and post intervention period included the data on insurance claims after March 2019 (April, 2019 to December, 2021). On analysing 10,586 insurance claims paid under the Mukh Mantri Cancer Rahat Kosh), it was found that patients claimed a good portion (average 78%) of the total available cover of ₹ 150,000/-. Cost of medications formed approximately 14% of the total claim amounts which is a noteworthy figure. National Pharmaceutical Pricing Authority (NPPA) put a 30% trade margin cap on retail of 42 crucial anti-cancer drugs in February 2019. The drugs selected for price regulation were the ones which posed a remarkably higher burden on insurance claim payers. This measure of NPPA brought about a statistically significant reduction in the amounts of

claims filled for medications by the cancer patients. These results convey that the government's efforts for reducing the economic burden of cancer-care by keeping the trade margin at a rational level, are definitely yielding momentous outcomes, although further refinement of the endeavour is recommended.

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Chandigarh

Study Highlights

- The present study aims to assess the value based pricing of anti-cancer drugs in India. The major findings of various cost-effectiveness analyses conducted are below:
- **Cost-effectiveness of Novel agent regimens for Transplant-Eligible Newly Diagnosed Multiple Myeloma patients in India**
  - Survival outcomes for multiple myeloma have improved dramatically since the introduction of novel therapeutic agents. While these drugs are highly effective in improving survival outcomes and quality of life in patients with multiple myeloma, they come at a significant cost.
  - We assessed the cost-effectiveness of bortezomib-based triplets or quadruplet drug regimens in isolation and followed by autologous hematopoietic stem cell transplantation (AHSCT) for the treatment of newly diagnosed multiple myeloma (NDMM) in the Indian context.
  - Among the five non-dominated strategies, VRd has a lowest incremental cost of ₹ 2,20,093 (US$ 2,888) per QALY gained compared to VTd alone followed by VRd plus AHSCT [₹3,14,530 (US$ 4,128) per QALY gained] in comparison to VRd alone. **None of the novel treatment sequences were found to be cost-effective at the current WTP threshold of ₹1,46,890 (US$1,927.7).**
  - At the current WTP threshold, VRd plus AHSCT and VTd plus AHSCT has 6.9% and 3.7% probability to be cost-effective, respectively. **Reduction in current reimbursement rates of novel drugs namely VRd, lenalidomide, pomalidomide plus dexamethasone under national insurance program and societal cost of transplant by 50%,** would make **VRd plus AHSCT and VTd plus AHSCT cost-effectiv**e at an incremental cost of ₹ 40,671 (US$ 534) and ₹ 97,639 (US$ 1,281) per QALY gained respectively.

- **Cost-effectiveness of first-line treatment options of metastatic renal cell carcinoma in India**
  - Currently, there are several treatment options available to a newly diagnosed metastatic renal cell carcinoma patient in India. In a developing country such

as India, factors such as the cost of the treatment plays a vital role in the decision-making while choosing the most appropriate therapy.

- In this study, we aimed to analyse the most commonly used treatment strategies (both single-agents: sunitinib & pazopanib; and combination therapies: Nivolumab/Ipilimumab & Pembrolizumab/Lenvatinib) for metastatic renal cell carcinoma in India.
- Pazopanib incurs higher cost and statistically insignificant health benefits as compared to sunitinib, and is hence dominated. Among the three non-dominated options, pembrolizumab/lenvatinib and nivolumab/ipilimumab incur an incremental cost of ₹ 3.9 million ($ 53,497) and ₹ 115.8 million ($ 1,568,137) per QALY gained respectively which are not cost-effective when compared with India's current WTP of 1-time per capita GDP (₹ 168,300). **Sunitinib incurs an average cost of ₹ 143,269 ($ 1,939) per QALY lived** which is a cost-effective treatment strategy in the Indian context when compared to the cost-effectiveness threshold of 1-time per capita GDP.
- Therefore, **we support the current inclusion of sunitinib under India's publicly financed health insurance scheme.**

∞ **Cost effectiveness analysis of different combination therapies for the treatment of Chronic Lymphocytic Leukaemia in India**

- We have compared the cost-effectiveness of three therapeutic regimens, i.e., chlorambucil plus prednisolone (CP), bendamustine plus rituximab (BR) and ibrutinib for the treatment of chronic lymphocytic leukaemia (CLL) in India.
- As compared to most affordable regime comprising of CP as first line followed by BR as second line therapy, **none of the other therapeutic regimens were cost effective** at one time per capita gross-domestic product of India.
- The scenario analysis, excluding the impact of second-line therapy, also points to a similar conclusion and reports **chlorambucil based regimen** followed by BR **as a cost-effective first-line treatment for CLL in India.**

∞ **Cost-effectiveness of first-line Tyrosine-kinase inhibitors in the treatment of newly diagnosed Chronic Myeloid Leukaemia patients in India**

- The tyrosine kinase inhibitor (TKI) imatinib was approved in 2001 to treat incident chronic myeloid leukemia in chronic phase (CML-CP) and has been

shown to produce a high cumulative incidence of complete cytogenetic responses (CCyR). Imatinib is also associated with improved survival.

- In the past decade, second-generation TKIs such as Dasatinib and Nilotinib have demonstrated efficacy for treating incident CML-CP and were therefore granted approval for the first-line treatment of CML-CP globally. The second-generation TKIs produce more rapid molecular responses than imatinib at standard doses of 400 mg daily, however five-year OS does not differ between the three TKIs (6–8).
- We aimed to determine the most cost-effective first-line TKI for the treatment of newly diagnosed CML-chronic phase (CP) patients in India.
- **Imatinib** incurred an average cost of **₹ 64,323** ($ 855) per QALY lived which **is cost-effective** at the current WTP threshold of 1-time per capita GDP of India.
- Dasatinib patients incurred an incremental cost of ₹ 2,37,583 ($ 3,159) per QALY gained as compared to Imatinib treatment arm. Further, Nilotinib incurred an incremental cost of ₹ 6,499,642 ($ 86,431) per QALY gained as compared Dasatinib treatment arm. **Both, Dasatinib and Nilotinib are not cost-effective** at the current WTP threshold of 1-time per capita GDP in the Indian context.
- Dasatinib has a 27.7% probability of being cost-effective at the current WTP threshold of 1-time per-capita GDP of India. Whereas, there is 2.9% probability for nilotinib to be cost-effective in the Indian context.
- **A 21% reduction in the reimbursement rate of Dasatinib (from ₹ 5,500 to ₹ 4,345) will make it a cost-effective** treatment option as compared to Imatinib at the current WTP threshold of 1-time per capita GDP in the Indian context.

∞ **Cost-effectiveness of Ribociclib and Palbociclib in the second-line treatment of Hormone receptor-positive, HER2 negative metastatic breast cancer among the post-menopausal Indian women**

- The combination of CDK4/6 inhibitors (ribociclib and palbociclib) and Endocrine therapy (Fulvestrant) has proven to improve survival outcomes among the Hormone-receptor positive, HER2 negative metastatic breast cancer patients.

- In this study, we evaluated the cost-effectiveness of ribociclib/palbociclib combination therapy, Fulvestrant monotherapy, single-agent Paclitaxel and single-agent Capecitabine in the Indian context from two different point of views: Scenario I – as per the prevailing market prices of the drugs; and Scenario II – as per the reimbursement rates set up by the publicly financed national-level health insurance scheme.
- The use of **ribociclib/palbociclib is not a cost-effective treatment option** in the Indian context. A **78% and 72% respectively reduction in the price of Fulvestrant monotherapy in both the scenarios, is required to make it the most cost-effective.**

∞ **Cost-Effectiveness Analysis of Bevacizumab Plus Chemotherapy Versus Chemotherapy Alone for the Treatment of Advanced and Metastatic Cervical Cancer in India**

- The present study was designed to assess the cost effectiveness of incorporating bevacizumab with the standard chemotherapy for the treatment of patients with advanced and metastatic cervical cancer in India.
- Using a disaggregated societal perspective, lifetime horizon and 3% discount rate, a Markov model was developed for estimating the costs and health outcomes in a hypothetical cohort of 1000 patients of advanced and metastatic cervical cancer treated with either standard chemotherapy alone or in combination with bevacizumab.
- Effectiveness data for each of the treatment regimen was assessed using estimates from previously undertaken Gynecologic Oncology Group (GOG) 240 trial. Data on disease specific mortality in metastatic cervical cancer, health system cost and out of pocket (OOP) expenditure was derived from Indian literature. Multivariable probabilistic sensitivity analysis was undertaken to account for parameter uncertainty.
- Over the lifetime of a patient with advanced and metastatic cervical cancer, bevacizumab along with standard chemotherapy results in a gain of 0.275 (0.052 – 0.469) life years and 0.129 (0.032 – 0.218) quality adjusted life years (QALYs) per patient, at an additional cost of US$ 3,816 (2,513- 5,571) per patient as compared to standard chemotherapy alone. This resulted in an incremental cost of US$ 19,080 (7,230- 52,434) per LY gained and US$ 34,744

(15,782- 94,914) per QALY gained with the use of bevacizumab plus standard chemotherapy.

- It was concluded that **addition of bevacizumab to the standard chemotherapy is not cost-effective** for the treatment of advanced and metastatic cervical cancer in India at a threshold of 1-times per capita gross domestic product.

∞ **Cost Effectiveness of Temozolamide for Treatment of Glioblastoma Multiforme in India**

- Glioblastoma Multiforme (GBM) has poor outcomes following surgery and radiation. Adjuvant temozolamide along with radiation therapy has been shown to improve survival.
- In this analysis, we have evaluated the cost effectiveness of concomitant temozolamide with radiation and maintenance temozolamide for 6 months for treatment of GBM in India. We used a Markov model to evaluate the lifetime costs and consequences of treating GBM with radiation alone versus radiation with adjuvant temozolamide.
- Temozolamide resulted in an increase in 0.59 (0.53 – 0.66) LY and 0.33 (0.29 – 0.40) QALY per person respectively, at an incremental cost of INR 74,196 (57,050 – 93,885).
- Overall, the use of temozolamide incurs an incremental cost of INR 212,020 (128,347 – 428902) per QALY gained, **which has a 4.7% probability to be cost effective at 1-time per capita GDP threshold.** A reduction in price by 90% is likely to increase the probability of its use being cost effective to 80%.
- We concluded that **Temozolamide is not cost effective** for treatment of GBM patients in India. This evidence should be used while framing guidelines for treatment and price-regulation.

∞ **Cost Effectiveness of Trastuzumab for Management of Breast Cancer in India**

- Breast cancer is the most common cancer among women in India and accounts for 27% of all cancers in that country.
- Addition of the HER2-targeted mono-clonal antibody trastuzumab to chemotherapy in adjuvant treatment has been shown to improve disease- free survival (DFS) by 50% and overall survival (OS) by 30% among human

epidermal growth factor receptor (HER)-2 positive early and advanced breast cancers.

- However, trastuzumab is an expensive drug. It was reported to have been used in only 8.6% of eligible patients, half of whom were enrolled in a clinical trial.
- The low rate of trastuzumab use raises the important question of whether public resources should be used to make this treatment routinely accessible in India. This question is highly relevant because of the recently announced ambitious Indian health insurance program, Ayushman Bharat, which includes coverage of chemotherapy for cancer treatment under the Prime Minister's Jan Aarogya Yojana (PMJAY) component.
- We used a Markov model to estimate the incremental cost and benefits of using trastuzumab (for 1 year, 6 months, or 9 weeks) as compared with chemo-therapy alone using a societal perspective.
- **Use of trastuzumab for 1 year is not cost effective in India** at the current price. At the current price, 1-year trasutuzumab use has just a 4% to 57% probability of being cost-effective.
- However, **trastuzumab use for 9 weeks is cost effective** and should be included in clinical guidelines and reimbursement policies. A price reduction of **15% to 35% increases the probability of 1-year trastuzumab use being cost effective, to 90%.**

∞ **Assessment of economic burden and health-related quality of life among cancer patients in India**

- Data on OOPE was collected from a total of **9,897** patients recruited at outpatient settings of seven public and semi-private health care facilities across five states of the country. Among these patients, 2,736 patients reported at least one episode of hospitalisation.
- In addition, a total of 2361 hospitalized cancer patients were interviewed to elicit expenditures incurred during each of their stay at hospital.
- The annual cost of non-hospitalised treatment for each patient was calculated as the product of OOPE incurred per-visit and mean number of visits per month multiplied by a factor of 12. **Per visit OOPE on non-hospitalized cancer treatment was estimated as INR 8,053.**

- For hospitalisation, annual mean direct OOPE was calculated by taking into account the total expenditure incurred on all episodes of cancer-related hospitalisation during last one year. Annual consumption expenditure was taken as proxy for annual income to compute indicators of financial toxicity (catastrophic health expenditure and impoverishment). A threshold of 40% of non-food expenditure was considered to calculate catastrophic health expenditure (CHE).
- The total **annual direct OOPE on cancer treatment was estimated as INR 3,49,497** (6047.95); INR 57,553 (2935.37) for hospitalisation and INR 3,33,408 (5947.41) for non-hospitalised treatment. For both hospitalisation and non-hospitalised treatment, **highest OOPE was incurred by patients belonging to richest wealth quintile** [INR 12,260 (394.5) for non-hospitalized treatment and INR 84,400 (6446.8) for hospitalization] and lowest by the poorest income groups [INR 4,839 (198.2) for non-hospitalized treatment and INR 32,250 (3476.7) for hospitalization].
- **Patients who were not insured incurred the highest OOPE** [INR 10,092 (278.5) for non-hospitalized treatment and INR 81,596 (6090.6) for hospitalization].
- Furthermore, maximum OOPE was found to be incurred on diagnostics [INR 14653 (1455.8] and lowest for combination therapy [INR 6,637 (332.8)] among patients seeking non-hospitalized cancer treatment.
- The stratified analysis according to primary cancer site suggested that the maximum expenditure was incurred on kidney and ureter cancer for both non-hospitalized treatment [INR 13,017] and hospitalization [INR 70,429]. The cancer category with the lowest OOPE was testicular cancer [INR 5,793] among non-hospitalized cancer cases and penile cancer [INR 9394] for hospitalisation.
- **Significantly higher OOPE was found to be incurred on hospitalization in private hospitals [INR 79, 342 (5382.8)] as compared to public hospitals [INR 39,784 (2945.4)]**.
- Moreover, **OOPE increased with increasing duration of hospital stay**, ranging from INR 17,131 for one day hospitalization to INR 76,273 for more than 5 days of hospitalization.
- The major source of financing the cancer treatment was salary or savings (74.3% and 67%, respectively). The second most common source was

borrowing money without interest from relatives/friends for outpatients (16.2%) and health insurance for inpatients (14.3%).

- The overall **prevalence of CHE among cancer patients was found to be 84% due to non-hospitalised treatment and 28.5%** due to cancer-related hospitalisation.
- **Approximately 67% patients were impoverished due to non-hospitalised treatment and 17% due to hospitalisation.**
- **CHE was found to be higher among patients who visited private hospitals (36.8%) for hospitalization as compared to public hospitals (21.8%).** Also, prevalence of CHE was found to be increasing with increase in the duration of hospitalisation **(13.1% for one-day hospitalisation and 34.6% for more than five days of admission).**
- The **prevalence of CHE** (34.1%) and impoverishment (18.8%) **due to hospitalization** was found to be **highest among non-insured cancer patients.** On the contrary, **patients insured through publically financed health insurance schemes** like national flagship insurance program-Ayushman Bharat Jan Aarogya Yojana, AB-PMJAY (CHE=19.7% and impoverishment=9.3%), state-sponsored insurance schemes (CHE=27.1% and impoverishment=18.4%) aqnd social security schemes (CHE=22.5% and impoverishment=12.1%), **are less likely to experience CHE and impoverishment.**
- Similarly, cancers patients (seeking non-hospitalized treatment) who were **not covered under any health insurance schemes, faced higher CHE (85.7%) and impoverishment (70.4%) rates.** Also, patients covered under publically financed health insurance schemes such as AB-PMJAY, state-sponsored health insurance schemes, private health insurance, social security schemes and patient aided programmes (NGOs/Philanthropists/Charitable trusts), experience alarmingly high rates of CHE (ranging from 76.1% to 85.6%) and impoverishment (55.3% to 66.6%) due to non-inclusion of non-hospitalized treatment under health benefit packages.
- Further, it was found that patients belonging to poorest wealth quintiles faced higher CHE (91.7%) as compared to richest quintile (75.7%) due to non-hospitalized treatment. Similar trends were observed in impoverishment rates (91% among poorest and 52.1% among richest).

- The odds of CHE (0.108) and impoverishment (0.018) due to non-hospiltized treatment were found to be lowest among richest income groups as compared to poorest income groups. Similarly, the poorest income groups faced higher odds of CHE and impoverishment (odds for CHE=0.329 and odds of impoverishment=0.086 for richest versus poorest).

∞ **Estimation of indirect cost due to loss of productivity**

- For calculating the indirect cost, total hours forgone by patients on various activities were converted into work days and relevant standardised wage rates [National Sample Survey 2011-16, (68th round) – 'Household Consumer Expenditure' and 'Employment and Unemployment'] were applied to estimate the loss of productivity. Daily wage rates were stratified by (i) area of residence and gender, and (ii) level of education. Indirect cost was also calculated by using annual household expenditure as proxy for their annual income. For generating cost estimates of caregivers, daily wage rates were calculated based on the income reported by them. The product of total hours forgone and daily/monthly wage rates represented the indirect cost.
- Indirect cost data were elicited from a total of 2,576 patients out of a sample size of 9,787 cancer patients. Majority patients were females (n=1519, 58.96 %) and 41.03% were males (n=1057). The graduate and post-graduate patients were found to incur highest indirect OOPE [mean: INR 11,038 (95% CI: 10,384-11,693) as compared to patients with lower educational status [mean: INR 2,014 (95% CI: 1943-2086). Loss of productivity was highest among urban males [INR 6,750] and the least among rural females [mean: INR 1750]. On considering the annual consumption expenditure as an indicator of per-capita income, the overall mean indirect OOPE was estimated as INR 7,489 (95% CI: 7246-7732) with a median loss of productivity of INR 6,273 (IQR: 6323) with 50% of the population ranging between INR 3,468 and INR 9,791.
- The indirect cost incurred by caregivers was found to be INR 39,379 (95% CI: 39304 – 39453).
- An overll indirect OOPE due to loss of wages (patient plus caregiver) was computed as INR 8,802 [standard error=134.8) .

∞ **Impact assessment of price regulation on sales/volumes of anticancer drugs in India: Pharmatrac data analysis**

- Utilising nationally representative private sector medicine sales data and robust econometric methods, this study is the first study to the best of our knowledge to report the impact of both price and trade margin regulation polices on the anti-cancer drug market.
- The most notably effect observed was an immediate as well as sustained decline in the sales volume of 6 (35%) of the 17 price regulated medicines and 5 (19%) of the 26 trade margin of regulated medicines under study in the post-intervention period in comparison to the pre-intervention period.
- An immediate increase followed by a sustained decline in sales volume was observed for 3 (18%) price regulated medicines and 10 (38%) trade margin regulated medicines under study in the post intervention period.
- 7 (41%) medicines under price regulation and 2 (8%) medicines under trade margin regulation witnessed both an immediate and sustained increase in sales in the post-intervention period.
- 1 (6%) medicine under price regulation and 9 (35%) medicines under trade margin regulation witnessed an immediate decline followed by a sustained increase in sales in the post-intervention period.

∞ **Impact assessment of price regulation on insurance claims: Analysis of state-specific insurance scheme-'Punjab Cancer Raahat Kosh Yojana'**

- On analysing 10,586 insurance claims paid under the Mukh Mantri Cancer Rahat Kosh (Chief Minister Cancer Relief Fund), it was found that patients claimed a good portion (average 78%) of the total available cover of ₹ 150,000/-.
- Cost of medications formed approximately 14% of the total claim amounts which is a noteworthy figure.
- National Pharmaceutical Pricing Authority (NPPA) put a 30% trade margin cap on retail of 42 crucial anti-cancer drugs in February 2019. The drugs selected for price regulation were the ones which posed a remarkably higher burden on insurance claim payers. This measure of NPPA brought about a statistically significant reduction in the amounts of claims filled for medications by the cancer patients.

- The difference in the sums claimed for cancers whither the concerned drugs are and are not employed, declined after price regulation. However, this difference in difference was not found to be statistically significant.
- These results convey that the government's efforts for reducing the economic burden of cancer-care by keeping the trade margin at a rational level, are definitely yielding momentous outcomes, although further refinement of the endeavour is recommended.

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∞ **Administrative timelines**: The research protocol of the study was approved by the Technical Appraisal Committee (TAC) of HTAIn in its meeting held on. The first annual instalment of the financial assistance was received on 25th March 2020. The project started on 1st June 2020, and the total duration of the project is 24 months. However, the duration of data collection is 14 months. The second installament. The second annual instalment was received on 13th September 2021. The third instalment was received on 30th December 2021 for the purpose of extending of data collection (approved by technical appraisal committe). The project activities were ceased on 31st May 2022.

Chapter-1: Need of Health Technology Assessment on Cancer

High and increasing health care cost is one of the major public health challenges in India.[1, 2] As households remain the major source of financing health care, the extent of impoverishment and indebtedness due to high out-of-pocket expenditure (OOPE) is on the rise. Importantly, the average OOPE for cancer patients is 2.5 times that for other diseases.[3, 4] Although reduction of catastrophic health expenditure (CHE) has been integrated into Sustainable Development Goals, unaffordable hospital bills and exorbitantly priced chemotherapeutic agents used in treatment of cancer has been the cause of financial distress for around 22 lakh cancer patients in India.[5] The Government has a dual responsibility of protecting patients' interests, and allowing domestic industry to flourish in a level-playing field with the multinationals. In this case, one possible solution for ensuring reasonable maximum retail price (MRP) is keeping the trade margin at a rational level along the supply chain. Trade margin is the difference between the price at which the manufacturers sell to trade and the price to patients, i.e., MRP. Therefore, on 27th February, 2019, National Pharmaceutical Pricing Authority (NPPA) had put 42 anti-cancer drugs under 30% trade margin cap.[6] Consequently, manufacturers and hospitals have revised MRP of these drugs (all strengths and dosage forms, whether individual or in combination, irrespective of dosage strength, dosage form and /or route of administration), which was effective from 8th March, 2019, based on the Trade Margin (TM) formula. This ambitious step of government has the potential of putting long-lasting impact on the cancer-care arena of India comprising of patients, pharmaceutical industry, insurance providers and price regulators. This being the case, the present study aims to assess the impact of price regulation of anti- cancer drugs on cancer patients, industry, insurers and regulators.

As a matter of fact, the prevalence of cancer was conventionally much evident in developed nations, but in recent years, it has increased substantially in developing countries as well. The estimates from Global Burden of Disease study suggest that about 70 percent of all cancer deaths are now concentrated among low- and middle-income countries.[7] However, cancer research and treatment are one of the most challenging fields in biomedical sciences and oncologists have been struggling to ensure greater survival chances among cancer patients. In general, there is a consensus that about 60 percent of cancer deaths can be prevented with improved preventive (removing the

causes of disease so theta exposure to risk is minimal) and screening (test or procedure used to detect disease) facilities.[8, 9] Given the fact that much of the cancer survival is associated with early diagnosis, access to state-of-the-art medical technology is a prominent policy concern for low-and middle-income countries. The problem increases manifold for developing nations such as India that has poor geographical coverage of medical services and negligible financial protection in health.

The financial burden associated with cancer treatment can force patients and households to acute misery and even insolvency.[3, 4, 10] While catastrophic expenditure on cancer inpatient treatment is highest among all NCDs, poor health financing mechanisms and heavy reliance on out-of-pocket healthcare payments compels several cancer patients to resort to distressed means for treatment financing.[11] In fact, previous studies on India suggest that about 60 and 32 percent households resort to borrowings and contributions (from friends and relatives) respectively for cancer hospitalization.[4]

It has been noted that due to prevalent inequalities, out of pocket expenditure on medicines is the single largest contributor to pushing families beyond poverty threshold in the country. Thus, ensuring affordable drugs is a necessary pre-requisite for bringing down the overall healthcare expenses and to achieve the overall goal of affordable healthcare for all. The Competition Commission of India (CCI) in its policy note titled 'Making Market Work for Affordable Healthcare' (October 2018) has observed that the pharmaceutical sector is characterized by information asymmetry and supplier-induced demand that significantly circumscribes consumer choice, a condition necessary for well-functioning markets.[12] In the absence of agency with the consumer, various industry practices flourish which do not allow markets to work effectively and efficiently. One major factor that contributes to high drug prices in India is the unreasonable high trade margin.[6] The high margins are in form of incentive and an indirect marketing tool employed by drug companies. Considering the high trade margin in sale of drugs leading to high out of pocket expenses on healthcare, the Government thereby, sought to undertake the matter of price control through a 'trade margin rationalization approach'. Therefore, in order to bring in regulation of drugs in the 'non-scheduled' segment the Government capped the prices of selected anti- cancer drugs, identified by the Ministry of Health and Family Welfare (MoHFW) as being essential for the treatment of this disease.[6]

It is worthwhile to describe here the process of controlling the prices of drugs in India. The prices of drugs in India are controlled by the Drugs (Prices Control) Order (DPCO) which is issued by the government of India to regulate and set the prices of essential drugs and their formulations.[13] National Pharmaceutical Pricing Authority (NPPA) is the umbrella body which is responsible for regulating and fixing prices of essential drugs, expanding the national list of essential medicines (NLEM), and regulating the price increase of non-essential medicines which are not under the DPCO.[13]

There are 2 broad mechanisms to control the prices of drugs in India, market based and cost-based. Currently, the DPCO uses the market-based pricing mechanism where-in the ceiling price is calculated by taking the simple average of prices of brands which have more than 1% of market share total market turnover of the respective drug. Another method is cost-based pricing which accounts for the cost of active pharmaceutical ingredient, cost of excipients, cost of labour and overheads, cost of packaging and also the cost of duties applicable. Further, additional to this cost, the profits are added. Though the market-based method is currently in practice, the topic of which method being better is highly debated.[14] It is often argued that there is no relation between the set price and the actual cost of the drug when the ceiling price is set via the market approach as it considers the price set by the competitors only. Whereas, with cost-based approach, the multinational companies might resort to the mechanism of transfer pricing. Transfer pricing refers to maximising the cost of buying the active pharmaceutical ingredient (the only cost which can be manipulated) so as to show least profits which helps them escaping the tax payments to the government.[14]

Apart from regulating the scheduled drugs via the above-mentioned mechanisms, the NPPA also regulates and reviews the increase in prices of the non-scheduled drugs and has the right to bring certain drugs under price control which are highly priced and of major public health importance. One such initiative by our government has been to bring certain medical devices and drugs under price capping via capping over the trade margin.[15] Trade margin refers to the difference between the price at which the drug is sold by the manufacturers to the distributors and the price at which it is available to the patients. A recent example of this reform being the capping of trade margin for anti-cancer drugs.[6]

Apart from these reforms, access to drugs and diagnostics still remains very low in our country due to very high cost of drugs. 'Compulsory licensing' was one of the reforms introduced in our country under Trade Related Intellectual Property Right (TRIPS) Flexibilities to tackle the high burden diseases, the treatment for which is very expensive and thus not accessible. This flexibility allows to manufacture the generic versions of patented drugs which leads to a very high drop in prices.[16] Though such mechanisms are available, the use of compulsory licensing has been very limited in India.

In this regard, one approach that may facilitate the identification of an optimal list price for retail sale and compulsory licensing would be through the application of decision analytic modeling techniques. The basic premise of such decision analyses evaluations is to compare the costs and consequences of a new drug to determine if it offers the best value for money relative to the standard of care.[17] Such analyses are usually undertaken after the unit cost of the drug has been set following regulatory approval. However, these may have an additional and perhaps more valuable role in estimating or negotiating the price of the drug based on societal value thresholds. These techniques have been used in this capacity for the evaluation of numerous biologics, including novel oncologic agents assessed by The National Institute of Health and Care Excellence (NICE) for the United Kingdom (UK).[18, 19] This approach can also be used to estimate a more affordable price of a drug for the Indian healthcare setting.

The use of thresholds based on per capita GDP in combination with decision modeling to establish a value-based price for a drug is an interesting approach, because it sets the foundation for improving patient access. To illustrate the application of this drug pricing strategy, decision analyses modeling is being used in the current study to estimate the price of anti- cancer drugs that would provide the best value for money at the given standards of care.

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Study Objectives

1. To assess the cost-effectiveness of 42 anti-cancer drugs used in the treatment of 28 types of cancers in India.
2. To assess the economic burden and health-related quality of life among cancer patients in India.
3. To capture the change in sales (quantity & value) and market share of 42 anti-cancer drugs in retail market across India before and after price control.
4. To examine the change in claim amount for treatment of 28 cancers after price regulation of 42 anti- cancer drugs.

SECTION-A: Cost-effectiveness analysis and value-based pricing of Anti-cancer Drugs in India

Cost-effectiveness and value-based pricing of anti-cancer drugs in India

Table 1: List of anticancer drugs assessed for their cost-effectiveness

Sr. No.	Cancer	Drug/ Regimen	Comparator
1.	Chronic Lymphocytic Leukaemia	Bendamustine	Irutinib
2.	Chronic Myeloid Leukemia	Imatinib	Nilotinib or Dasatinib
3.	Multiple Myeloma	Bortezomib (in three drug combination:VRD-Bortezomib+ Lenalidomide+ Dexamethsone)	VTD (Bortezomib/ Thalidomide/ Dexamethasone)
4.	Multiple Myeloma	Bortezomib (in three drug combination: VTD-Bortezomib+ Thalidomide+ Dexamethsone)	VCD (Bortezomib/Cyclophosphamide/ Dexamethasone)
5.	Multiple Myeloma	Autologous stem cell transplantation	Bortezomib (in three drug combination: VCD-Bortezomib+ Cyclophosphamide+ Dexamethsone
6.	Multiple Myeloma	Autologous stem cell transplantation	Combination of bortezomib, Lenalidomide and dexamethasone
7.	Breast cancer with bone metastasis	Denosumab	Zoledronic Acid
8.	Early breast cancer	Trastuzumab (3 months)	Trastuzumab (6/12 months)
9.	Advanced, recurrent and metastatic Cervical Cancer	Bevacizumab with Paclitaxel and Carboplatin	Paclitaxel and Carboplatin alone
10.	Advanced, recurrent and metastatic renal cell carcinoma	Sunitinib	Pazopanib
11.	Glioblastoma Multiforme	Temozolamide	Radiation alone
12.	ER+Ve, Her 2 negative Metast-atic BrCancer	CDK-4/6 inhibitors plus Fulvestrant	Fulvestrant alone

Chapter 2: Cost-effectiveness of Novel agent regimens for Transplant-Eligible Newly Diagnosed Multiple Myeloma patients in India

Introduction

Multiple myeloma (MM) is the second most frequent haematological malignancy (~15%), accounting for nearly 20% of all haematological cancer-related deaths [1–3]. As per GLOBOCAN data from the International Agency for Research on Cancer (IARC), there were an estimated 114,000 new cases of MM globally in 2012 [4]. More recent estimates suggested 159,985 newly diagnosed MM worldwide (i.e. about 0.9% of all cancers and 1.1% of all cancer deaths) in 2018 [5]. Data from 27 population-based cancer registries under the National Cancer Registry Programme in India suggested that MM accounted for 1.19% (95% CI: 1.14–1.24%) of all cancers.

The therapeutic landscape of MM has changed significantly over the past few years with the introduction of novel agents like bortezomib, lenalidomide and thalidomide. These drugs are increasingly used in combinations to improve the outcomes among newly diagnosed multiple myeloma (NDMM) patients [6-7]. The improvements were marked when using the novel agents as induction therapy followed by autologous hematopoietic cell transplantation (AHSCT) [6, 8-9]. The initial therapy for transplant-eligible NDMM patients consists of 3–6 cycles of induction therapy followed by AHSCT and maintenance therapy [8-9]. If the patient progresses following transplant, the patient is switched to salvage therapy. The initial induction therapy usually comprises combination of three drugs consisting of corticosteroids (dexamethasone or prednisone) combined with novel agents-bortezomib, a proteasome inhibitor and immunomodulatory drugs such as thalidomide/lenalidomide [10]. More recently, monoclonal antibodies, such as daratumumab is approved as an upfront therapy in combination with the above mentioned agents and elotuzumab, and bispecifics as salvage therapies, approved by the US Food and Drug Administration (FDA) [11]. The heterogeneity of these drug classes and non-overlapping mechanisms of action have allowed their use in combination to achieve more significant responses [12-13].

Due to these advanced therapeutic combinations and standard use of AHSCT, the cost of care of MM has increased significantly in the last two decades. The cost of novel agent

combinations and their usage as induction therapy prior to AHSCT is substantially higher compared to conventional chemotherapy regimens that were earlier used to treat MM patients. The cost per treatment sequence depends on the dose per cycle and the number of cycles administered. Additionally, there is a considerable variation of drug prices due to different pricing regulations and the availability of generics in the market. Since the number of treatment options for NDMM have increased substantially, it is vital to compare the costs and consequences of different induction regimens.

To the best of our knowledge, there is no published cost-effectiveness analysis that compares different novel drug agents for induction therapy with or without AHSCT among transplant eligible NDMM patients. A recent systematic review by Fu et al in 2019 suggested that only four studies have evaluated the cost-effectiveness of regimens based on novel agents, including bortezomib, thalidomide and lenalidomide [14]. Among them, three studies have included only the transplant-ineligible MM population [15-17], while one cost-benefit analysis compared the novel agents against conventional chemotherapy but did not include a transplant scenario [18]. Furthermore, a single study from India has compared the cost-effectiveness of AHSCT versus conventional chemotherapy [19]. However, this study did not compare the novel agents for chemotherapy.

To bridge this gap in evidence, we undertook the present analysis to evaluate the cost-effectiveness of seven treatment sequences namely (1) Bortezomib, lenalidomide, dexamethasone (VRd) alone (2) Bortezomib, thalidomide, dexamethasone (VTd) alone (3) Bortezomib, cyclophosphamide, dexamethasone (VCd) alone (4) VRd followed by AHSCT (5) VTd followed by AHSCT (6) VCd followed by AHSCT (7) Daratumumab plus VRd (DVRd) followed by AHSCT for treating transplant eligible NDMM patients in India.

Methodology

Model Structure

A comprehensive Markov model was constructed in Microsoft Excel to estimate health and economic outcomes of novel drug regimens for the treatment of transplant eligible NDMM patients using real world clinical data on effectiveness and cost of drugs under comparison in this study. As shown in Figure 1, the model structure comprised of three mutually exclusive health states namely progression free survival (PFS), progressive disease (PD) and death. Health states were modelled according to revised international staging system (RISS) staging for multiple myeloma, i.e., Stage-I, Stage-II and Stage-III

[20]. Apart from it, two absorbing health states were also included, i.e. death from multiple myeloma in PD state and death from natural causes in both PFS and PD states.

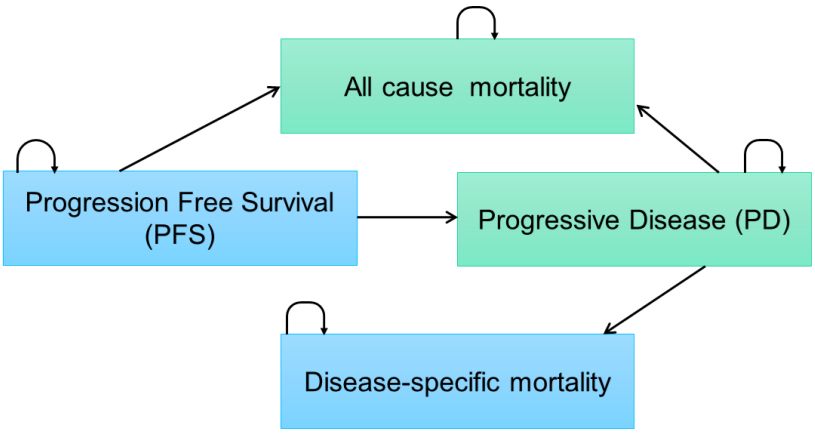

Figure 1: Model structure

The model starts with patients at 50 years of age, the median age of diagnosis for MM in India [19]. All patients were assumed to enter the model in PFS state according to stage wise distribution of MM in India and immediately commenced treatment after being diagnosed with MM [21].The Markov cycle length was considered as one month, which is consistent with standard MM treatment protocol world over [22]. Clinical, cost and effectiveness parameters were used to model the lifetime costs and consequences for a hypothetical cohort of 1000 NDMM patients, for each of the seven treatment scenarios, using societal perspective. Future costs and consequences were discounted at 3% for future time preferences of cost and utility, in line with the Indian reference case methodological guidance [23]. A lifetime horizon was considered in order to capture all costs and consequences over lifetime. We did not include the indirect cost due to productivity losses. The cost-effectiveness was assessed in terms of incremental cost effectiveness ratio (ICER) for all treatment scenarios. We have followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to report the findings [24].

Treatment sequences

Seven treatment scenarios were modelled. (1) VRd - Bortezomib (1.3 mg/m^2 subcutaneously on Day 1, 8, 15 & 22 in a 28-day cycle) plus lenalidomide (25 mg orally on days 1- 21 of each 28-day cycle) and dexamethasone (40mg orally on days 1, 8, 15, 22 in a 28-day cycle); (2) VTd - Bortezomib (1.3 mg/m^2 subcutaneously on Day 1, 8, 15 & 22 of a 28-day cycle) plus thalidomide (100-200 mg orally daily of each 28-day cycle) and dexamethasone (40mg orally on days 1, 8, 15, 22 in a 28-day cycle); (3) VCd - Bortezomib (1.3 mg/m^2 subcutaneously on Day 1, 8, 15 & 22 in a 28-day cycle) plus cyclophosphamide (300 mg/m^2 weekly of each 28-day cycle) and dexamethasone (40mg orally on days 1, 8, 15, 22 of a 28-day cycle (4) VRd followed by high dose melphalan 140-200mg/m^2 supported by AHSCT (5) VTd followed by high dose melphalan 140-200mg/m^2 supported by AHSCT (6) VCd followed by high dose melphalan 140-200mg/m^2 supported by AHSCT (7) Daratumumab (16 mg/kg intravenously on days 1, 8, 15 and 22 of cycles 1 to 2 and day 1 and 15 of cycles 3 to 6 and 6) followed by high dose melphalan 140-200mg/m2 supported by AHSCT [22, 25].

All patients were administered six cycles of induction therapy every 28 days using different chemotherapeutic novel drug agents during PFS state in transplant arms. The induction therapy was followed by AHSCT and maintenance therapy (lenalidomide 10 mg for 21 days every 28-day cycle) until the progression or death. The patients who progressed during induction therapy were given two cycles of KPd i.e. carfilzomib (20 mg/m^2 on day 1, 27 mg/m^2 on day 2 and 36 mg/m^2 on days 8, 9, 15 and 16 of a 28-day cycle), pomalidamide (4 mg for 21 days in a 28-day cycle) and dexamethasone (40 mg once a week per 28-day cycle) followed by transplant and maintenance therapy until progression or death in VRd plus transplant scenario. In VCd and VTd transplant scenarios, 2 cycles of VRd were administered if the patient progressed during induction (1-6 cycles) followed by AHSCT and maintenance therapy until progression or death. Further, the patients who progressed during 1-3 years and after 3 years of maintenance therapy post-transplant were given KPd and VPd i.e. Bortezomib (1.3 mg/m^2 subcutaneously on Day 1, 8, 15 & 22 in a 28-day cycle), pomalidamide (4 mg for 21 days in a 28-day cycle) and dexamethasone (40 mg once a week per 28-day cycle) respectively, for upto-12 cycles in all transplant arms.

In non-transplant arms, patients were administered 9-12 cycles of induction therapy every 28 days during PFS state followed by maintenance therapy. In the event of

progression during induction or maintenance therapy, KPd was administered for up-to 12 cycles. During maintenance, the patients received lenalidomide 10 mg orally on days 1 to 21 every 28 days until death, across all triple drug combination arms (VRd, VTd, VCd with/without AHSCT) [27]. However, in case of DVRd plus AHSCT treatment arm, the patients either received lenalidomide alone 10 mg orally on days 1 to 21 every 28 days or in combination with daratumumab 16 mg/kg IV every 8 weeks until progression or death [26].

Valuation of consequences

A literature review was conducted to identify relevant clinical evidence on effectiveness of novel three- and four-drug combination regimens namely VRd, VTd, VCd and DVRd in isolation (without AHSCT), and followed by high dose melphalan 140-200mg/m2 supported by AHSCT for the treatment of transplant eligible NDMM. In order to mimic the real-world scenario, we used Indian data on progression free survival (PFS) and overall survival (OS) for VRd plus AHSCT, VTd plus AHSCT and VCd plus AHSCT treatment arms [25]. The PFS Kaplan Meir (KM) curves obtained via published literature for each drug combination were digitized using Engauge (version 4.1) software [27] and individual patient data (IPD) were pooled (S1 appendix, Figure-1). After pooling PFS data, parametric curves were fitted assuming the following distributions: exponential, Weibull, log-logistic, log-normal, generalized gamma and gompertz. The best fitting distribution was chosen based on statistical information criteria, visual inspection of the curve and clinical plausibility [26]. The survival functions were used to estimate monthly transition probabilities from the initial PFS state. The KM curves and fitted parametric curves for each treatment arm for PFS are given in supplementary appendix II (S2 appendix, Figure 1, 2 and 3).

However, there was no Indian data available on PFS and OS among patients who did not undergo transplant stratified by the induction regimen. We calculated a gradient for PFS between patients who underwent ASCT versus those who did not, among transplant eligible patients on mixed induction therapy [28] (S appendix I, Figure-4). This gradient was used to derive the probability to be in PFS state stratified by induction regimen among patients who did not undergo AHSCT. Furthermore, there was no published Indian data reporting PFS and OS for DVRd plus AHSCT arm. We have therefore used estimates reported in the GRIFFIN trial [29].

Measurement of QALYs

The outcomes were assessed in terms of life-years (LYs) and QALYs. The probability to be in PFS state for all treatment arms was obtained using published literature [25, 28].The rates were converted to transition probabilities using standard methods [30]. Age specific all-cause mortality rates were obtained from the Indian Sample Registration System (SRS) lifetables [31]. Disease mortality rate for PD state for all treatment arms was obtained from published Indian literature as given in Table 2 [25, 28].

Stage wise utility scores were obtained from the nationally representative study (CaDCQoL) being undertaken to develop a database of costs and health-related quality of life (HRQoL) [21]. Primary data were collected from 320 MM patients selected from 6 Indian states, who were interviewed using EQ-5D-5L tool to measure the HRQoL (Table 2). The Indian tariff values were used to calculate the index utility score [23].

Cost of treatment of Newly Diagnosed Multiple Myeloma

The comparative cost-effectiveness was assessed in terms of incremental cost per QALY gained i.e. incremental cost-effectiveness ratio (ICER). The costs were estimated from societal perspective for all treatment arms. The cost of treatment in the PFS state for non-transplant arms included the drug acquisition cost, management of AEs (grades 3-4), and the cost of routine follow-up. Routine follow-up cost included cost per outpatient consultation in oncology department, cost of day-care visit for induction therapy, and cost of routine laboratory investigations and diagnostic tests (Table 1). In the transplant scenarios, the cost of AHSCT was also added. The costs were applied separately in each cycle using the treatment protocol obtained from the subject experts and standard treatment guidelines as per Indian Council of Medical Research (ICMR) consensus document on the management of MM [22]. In the PD state, the cost of outpatient consultation, routine laboratory and diagnostic tests, drug acquisition cost for second-line therapy and maintenance therapy were included. It was assumed that the maintenance therapy would be given to the patients in PD state till death.

We have used reimbursement rates under publicly financed national insurance program to elicit the societal cost of VRd, VTd, VCd, lenalidomide (for use in maintenance therapy) and PomDex (pomalidomide and dexamethasone for use in salvage therapy for patients who received frontline VRd in PD state) [32]. The reimbursement rates are inclusive of chemotherapeutic agents, recurring investigations, day care / inpatient charges,

supportive care and professional charges. Supportive care per cycle, such as use of antiemetics, pre-medication, post chemo prophylaxis etc. are all included in the package cost. In addition to this, we included direct non-medical expenditure (including travelling, boarding/lodging, food, informal payments etc.) using primary data collected based on the CADCQoL database [21].

However, for carfilzomib and daratumumab which are not included under any publicly financed health insurance scheme, we have used market prices. [Table 1] The cost of day-care for administration of injection carfilzomib and daratumumab was obtained from published literature and applied in the model considering the average number of injections required per cycle for each of these drugs [19, 31]. To account for the cost of diagnostic services for NDMM in cycle zero, we used the provider payment rates under the Central Government Health Scheme (CGHS) – a publicly financed national insurance scheme [33]. All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 76.2 [34].

Sensitivity analyses

Univariate sensitivity analysis was also undertaken to assess the effect that each parameter has on ICER. A multivariable probabilistic sensitivity analysis (PSA) was undertaken to estimate the effect of joint parameter uncertainty [35]. Under PSA, all cost parameters were assigned gamma distribution, while utility values and probabilities/proportions were assigned beta distribution. The value of standard error (SE) was used to create a distribution around the point estimate of a parameter. In cases where SE was not reported, a variation of 50% and 10% on either side of the base value was used for cost and clinical parameters respectively. The median value of ICER along the 2.5th and 97.5th percentile was calculated using 999 Monte Carlo simulations. The per capita GDP of India of ₹146,890 (US$ 1,927.7) for the year 2021-22 was used to compare ICERs to make recommendations about cost-effectiveness [36].

Ethical approval

Ethical approval was obtained from Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research, India with reference number IEC-03/20202-1565.

Table 1: Cost parameters for assessing the cost-effectiveness of novel agent combination therapy

Cost Parameters	Cost per cycle in ₹ (95% CI)	Cost per cycle in US$ (95% CI)	Source	Distribution
Drug Costs				
VRd Bortezomib 1.3 mg/m^2 Lenalidomide 25 mg Dexamethasone 40 mg	17,800 (8,900-26,700)	233.6 (116.8-350.4)	Reimbursement rate [32]	γ
VTd Bortezomib 1.3 mg/m^2 Thalidomide 100 mg Dexamethasone 40 mg	15,000 (7,500-22,500)	196.8 (98.4-295.3)	Reimbursement rate [32]	γ
VCd Bortezomib 1.3 mg/m^2 Cyclophosphamide 300 mg/m^2 Dexamethasone 40 mg	14,600 (7,300-21,900)	191.6 (95.8-287.4)	Reimbursement rate [32]	γ
Pom Dex Pomalidomide 4 mg Dexamethasone 40 mg	7,200 (3,600-10,800)	94.5 (47.2-141.7)	Reimbursement rate [32]	γ
Tab. Lenalidomide (10-25 mg)	4,800 (2,400-7,200)	62.9 (31.5-94.5)	Reimbursement rate [32]	γ
Inj. Carfilzomib 60 mg	8,000 (4,000-12,000)	104.9 (52.5-157,5)	Market Price	γ
Inj. Daratumumab 400 mg vial	1,40,000 (70,000-2,10,000)	1,021.7 (510.8-1532.6)	Market Price	γ
Health system cost				
Day care visit	1,038 (826-1238)	14.1 (11.2-16.9)	[37]	γ
Bed-day hospitalisation in general ward	10,107 (5053.5-15160.5)	132.6 (66.3-198.9)	[38]	γ
Bed-day hospitalisation in HDU	8,683 (4341.5-13024.5)	113.9 (56.9-170.9)	[38]	γ
Autologous hematopoietic cell transplant	160,027 (80013.5-240040.5)	2,100 (1050.1-3150.1)	[38]	γ
Haemodialysis	1500 (750-2250)	19.7 (9.8-29.5)		γ
Out-of-Pocket Expenditure (OOPE)				
Direct non-medical expenditure*	2,458 (1229-3687)	32.2 (16.1-48.3)	Primary data analysis	γ
Hospitalization	1,5000 (7,500-22,500)	197 (98-295)	Primary data analysis	γ
Autologous hematopoietic stem cell transplant	193,000 (96,500-2,89,500)	2,533 (1,266-3,799)	[38]	γ
Cost of diagnostics (Package rates)				
Complete blood count	135 (67.5-202.5)	1.8 (0.9-2.8)	[33]	γ
Liver function test	225 (112.5-337.5)	3.1 (1.5-4.6)	[33]	γ

Kidney function test	225 (112.5-337.5)	3.1 (1.5-4.6)	[33]	γ
Serum protein electrophoresis	220 (110-330)	3.0 (1.5-4.5)	[33]	γ
Urine protein electrophoresis	47 (23.5-70.50	0.6 (0.3-1)	[33]	γ
Beta 2 microglobulin	100 (50-150)	1.4 (0.7-2)	[33]	γ
Bone marrow aspiration	440 (220-660)	6.0 (3-9)	[33]	γ
Bone marrow biopsy	1060 (530-1590)	14.4 (7.2-21.7)	[33]	γ
Skeletal survey	949 (474.5-1423.5)	12.9 (6.5-19.4)	[33]	γ
Immunoglobulin G (IgG)	250 (125-375)	3.4 (1.7-5.1)	[33]	γ
Immunoglobulin A (IgA)	250 (125-375)	3.4 (1.7-5.1)	[33]	γ
Immunoglobulin M (IgM)	250 (125-375)	3.4 (1.7-5.1)	[33]	γ
Triiodothyronine (T3)	64 (32-96)	0.9 (0.4-1.3)	[33]	γ
Thyroxine (T4)	64 (32-96)	0.9 (0.4-1.3)	[33]	γ
Thyroid stimulating hormone (TSH)	90 (45-135)	1.2 (0.6-1.8)	[33]	γ
24 hour urine protein, sodium, creatinine	50 (25-75)	0.7 (0.3-1)	[33]	γ
Electrocardiography	50 (25-75)	0.7 (0.3-1)	[33]	γ
Haemoglobin A1c (Hb A1c)	130 (65-195)	1.8 (0.9-2.7)	[33]	γ
Lactate dehydrogenase (LDH)	100 (50-150)	1.4 (0.7-2)	[33]	γ
Serum free light chain	3500 (1750-5250)	47.7 (23.8-71.5)	[33]	γ

*Tab: Tablet; Inj.: Injection; OOPE: Out-of-Pocket Expenditure; HDU-High dependency Unit ;*Including the OOPE on travel, boarding/lodging, informal payments and others (excluding the user fees, drugs and diagnostics)*

Table 2: Model input parameters for assessing the effectiveness of novel agent combination therapy

Input variable	VRd plus AHSCT	VTd plus AHSCT	VCd plus AHSCT	Overall transplant	Overall non-transplant	DVRd plus AHSCT
Progression free survival (PFS) [25,27,28]						
• **Lambda**	4.461	4.027	0.001	4.443	0.001	
• **Gamma**	0.025	-0.073	0.454	-0.013	0.454	PFS at 36 months= 78%
• **Distribution**	Lognormal	Lognormal	Weibull	Lognormal	Weibull	
Overall survival (OS) [25,27,28]						
• **Median (in months)**	82	97.5	84	120	49	OS at 36 months= 93.8%
• **95% CI**	(41.5-122.5)	(30.5-164.5)	(60-108.1)	(81.3-158.6)	(42.2-56.1)	
Utility scores [21]						
• **Stage 1**	0.751 (0.624-0.877)					
• **Stage 2**	0.722 (0.660-0.785)					
• **Stage 3**	0.584 (0.396-0.772)					

Results

We estimated that a MM patient incurs a lifetime cost of ₹ 7,41,438 (US$ 9,730), ₹ 6,25,023 (US$ 8,202) and 6,15,735 (US$ 8,080) when treated with VRd, VTd and VCd alone respectively (Table 3). The lifetime cost incurred by a MM patient was estimated to be ₹ 11,61,905 (US$ 15,248), ₹ 10,50,819 (US$ 13,790), ₹ 10,25,824 (US$ 13,462) and ₹ 27,74,235 (US$ 36,407) when treated with VRd, VTd, VCd and DVRd in induction phase followed by AHSCT respectively.

A MM patient treated with VRd, VTd, VCd alone has an overall mean survival of 4.98, 4.11, and 4.08 LYs respectively. After factoring in the quality of life, this would translate into 3.01, 2.48 and 2.46 QALYs respectively. However, VRd, VTd, VCd and DVRd induction therapy followed by AHSCT yielded better survival outcomes (7.23, 6.14, 5.85 and 10.51 LYs respectively. This translates into 4.35, 3.70, 3.53 and 6.30 QALYs with VRd, VTd, VCd and DVRd induction followed by AHSCT. [Table 3]

Cost-effectiveness

Among the seven treatment sequences, VCd alone arm has lowest cost and health benefits as compared to four treatment sequences namely VTd alone, VRd alone, VRd plus AHSCT and DVRd plus AHSCT. Secondly, we found that VTd plus AHSCT and VCd plus AHSCT arm are extendedly dominated (ED) by combination of two alternative treatments. The ICER of DVRd plus AHSCT arm [₹ 824,969 (US$ 10,826)] is 5.6 times the per-capita GDP of India and hence not cost-effective at the currently recommended willingness to pay (WTP) threshold of per capita GDP. Among the five non-dominated strategies, VRd has an incremental cost of ₹ 2,20,093 (US$ 2,888) per QALY gained compared to VTd alone followed by VRd plus AHSCT, with an incremental cost of ₹ 3,14,530 (US$ 4,128) per Q

Probabilistic Sensitivity Analysis

At the current WTP threshold of one-time per capita GDP (₹ 146,890) of India, VRd alone and VRd plus AHSCT has 38.1% and 6.9% probability to be cost-effective, respectively.

Price threshold analysis

On reducing the current reimbursement rates under national insurance program by 50% i.e. from ₹ 17,800 to ₹ 8,900 for VRd, ₹ 7200 to ₹ 3600 for pomalidomide plus dexamethasone, ₹4800 to ₹ 2400 for lenalidomide and societal cost of transplant from ₹3,53,027 to ₹1,76,513, VRd plus AHSCT (against VTd plus AHSCT) becomes cost-effective at an ICER value of ₹ 40,671 (US$ 534) followed by VTd plus AHSCT treatment at an incremental cost of 97,639 (US$ 1281) per QALY gained (against VCd plus AHSCT) which is much below current WTP threshold of India. [Table 5]

Table 3: Per person lifetime cost and health outcomes in seven treatment arms

Outcome Variable	VRd alone	VTd alone	VCd alone	VRd plus AHSCT	VTd plus AHSCT	VCd plus AHSCT	DVRd plus AHSCT
LYs							
• **Undiscounted**	5.56 (4.14-6.48)	4.52 (3.63-5.31)	4.49 (3.61-5.29)	8.54 (6.28-10.65)	7.16 (5.35-9.01)	6.79 (5.12-8.49)	12.86 (10.63-15.18)
• **Discounted**	4.98 (3.75-5.77)	4.11 (3.32-4.81)	4.08 (3.31-4.77)	7.23 (5.41-8.89)	6.14 (4.67-7.61)	5.85 (4.47-7.24)	10.51 (8.82-12.21)
QALYs							
• **Undiscounted**	3.37 (2.21-4.40)	2.73 (1.88-3.63)	2.71 (1.88-3.73)	5.14 (3.47-7.13)	4.32 (2.79-6.02)	4.10 (2.75-5.76)	7.72 (5.68-11.24)
• **Discounted**	3.01 (1.99-3.94)	2.48 (1.70-3.29)	2.46 (1.71-3.38)	4.35 (2.97-5.97)	3.70 (2.42-5.14)	3.53 (2.39-4.87)	6.30 (4.61-9.04)
Per-person lifetime cost (in ₹)							
• **Undiscounted**	8,00,817 (5,82,091-9,99,659)	6,66,981 (4,99,382-8,16,660)	6,57,799 (4,93,074-8,21,470)	12,89,025 (9,68,879-16,16,869)	11,52,003 (8,62,407-14,08,672)	11,20,658 (8,51,084-13,76,212)	31,13,159 (25,49,239-38,79,952)
• **Discounted**	7,41,438 (5,43,545-9,19,070)	6,25,023 (4,69,741-7,65,704)	6,15,735 (4,64,652-7,63,384)	11,61,905 (8,91,746-14,35,527)	10,50,819 (7,93,169-12,74,141)	10,25,824 (7,87,270-12,46,349)	27,74,235 (22,53,488-33,18,393)

LY: Life-years; QALYs: Quality-adjusted Life-years; ₹: Indian Rupee

Table 4: Costs, outcomes and cost- effectiveness of various novel strategies for treatment of NDMM at current reimbursement rates in India

Strategy	Costs in ₹ (US$)	Effect (QALYs)	ICER (Cost/QALY)	Status
VCd alone	6,15,735 (US$ 8,080)	2.46	-	Non-dominated
VTd alone	6,25,023 (US$ 8,202)	2.48	4,19,920	Non-dominated
VRd alone	7,41,438 (US$ 9,730)	**3.01**	**2,20,093**	Non-dominated
VRd plus AHSCT	11,61,905 (US$ 15,248)	**4.35**	**3,14,530**	Non-dominated
DVRd plus AHSCT	27,74,235 (US$ 36,407)	6.30	824,969	Non-dominated
VCd plus AHSCT	10,25,824 (US$ 13,462)	3.52	**-**	**Extendedly dominated**
VTd plus AHSCT	10,50,819 (US$ 13,790)	3.70	-	**Extendedly dominated**

Table 5: Costs, outcomes and cost- effectiveness of various novel strategies for treatment of NDMM at revised reimbursement rates in India

Strategy	Costs in ₹ (US$)	Effect (QALYs)	ICER (Cost/QALY)	Status
VRd alone	5,24,113 (US$ 6,878)	3.01	-	Non-dominated
VCd plus AHSCT	7,02,648 (US$ 9,221)	3.52	3,46,015	Non-dominated
VTd plus AHSCT	7,19,689 (US$ 9,445)	3.70	**97,639**	Non-dominated
VRd plus AHSCT	7,45,975 (US$ 9,790)	**4.35**	**40,671**	Non-dominated
DVRd plus AHSCT	22,65,069 (US$ 29,725)	6.30	7,77,264	Non-dominated
VCd alone	5,27,109 (US$ 6,917)	2.46	-	Dominated
VTd alone	5,35,989 (US$ 7,034)	2.48	-	Dominated

Discussion

The present analysis is the first to assess the economic impact of different novel treatment sequences alone or with AHSCT for the treatment of NDMM in India. We have used a markov model which is plausible based on the current understanding of the disease progression and its outcomes. As far as possible, country-specific estimates on clinical effectiveness in terms of OS and PFS as well as cost of care were used in the model. Lifetime costs associated with treatment of MM in all seven alternate therapies were estimated and compared with gains in terms of OS and PFS.

Overall, more LYs and QALYs are gained among the therapeutic interventions which include a transplant following induction therapy, as compared to no transplant (1.7-2.3 increase in LYs and 1.07-1.34 increase in QALYs was observed). However, this was associated with lifetime increase in cost varying from ₹ 4,10,089 to 4,20,466 (US$ 5,382 to US$ 5,518). Overall, we found that VRd alone has lowest incremental cost of ₹ 2,20,093 (US$ 2,888) per QALY gained followed by VRd plus AHSCT, with an incremental cost of ₹ 3,14,530 (US$ 4,128) per QALY gained. At current willingness to pay threshold, VRd alone and VRd plus AHSCT has only 38.1% and 6.9% probability to be cost-effective, respectively. Thus, none of the strategies are cost-effective at current level of reimbursement rates in India. However, with 50% reduction in current reimbursement rates of lenalidomide, VRd, pomalidomide plus dexamethasone and cost of AHSCT, VRd plus AHSCT would be a cost-effective strategy with an incremental cost of ₹ 40,671 (US$ 534) per QALY gained, followed by VTd plus AHSCT treatment [₹ 97,639 (US$ 1,281) per QALY gained].

Model Validation

The findings of our model are in concurrence with the existing clinical and epidemiological evidence for all seven treatment arms. The 5 year survival in VRd plus AHSCT was estimated as 65.2% which is consistent with the estimates reported by Khattry et al 2018 (63%). The median PFS in VRd plus AHSCT treatment arm was found to be 85 months in the present model which is comparable to median PFS of 69.5 (95% 53.3-85.7) months as given in the published literature [25]. The median OS in our model for VRd alone arm was estimated to be 60 months. This finding is consistent with Kumar et al (2021) which reported a median OS of 49.2 months (95% CI: 42.2-56.1) for MM

patients on mixed induction therapy who did not undergo transplant [25]. A study by Sidana et al 2021 and Kumar et al 2021 reported the median PFS of 44.6 and 50 (34.7-65.3) months respectively among MM patients on VCd induction therapy prior to AHSCT, whereas we estimated a median PFS of 57 months in the VCd plus AHSCT arm [25,39]. Similarly, median OS of 69 months estimated for VTd plus AHSCT arm is also comparable to reported estimates of 97.5 (95% 30.5-164.5).

Additionally, an Indian study by Prinja et al 2017 estimated 5.5 LYs and 4.4 QALYs among MM patients who underwent transplant which is comparable to our study findings (7.23 LYs and 4.35 QALYs) [19]. The overall survival is slightly higher in our study because of the use of novel drug regimens prior to transplant, which are proven to be associated with better health outcomes as compared to conventional chemotherapy. Another study by Garrison et al reported an overall survival of 4.2 LYs among NDMM patients with the use of bortezomib based triple drug combination therapy (VMP- bortezomib, prednisone and melphalan) which is consistent with our study findings [15].

We estimated an overall survival ranging between 5.8-7.3 years among NDMM patients on high dose novel induction therapy prior to AHSCT. This concurs with the available evidence which suggests that a newly diagnosed with MM is expected to live for an average of 5–7 years, with some exceptions where patients can live longer than 10 years [40-41]. The four drug combination induction therapy (DVRd) prior to AHSCT yielded maximum survival of 10.5 years. However, for non-transplant arms, overall survival was estimated in the range of 4 to 4.9 years using different novel agents (VRd/VCd/VTd) which is in line with 4.9 life years gained with conventional chemotherapy without transplant [19]. The present study recommends AHSCT for improving the survival as well as quality of life among NDMM patients in India. However, none of the treatment scenarios are cost-effective at current reimbursement rates, which is consistent with previously published evidence on comparison of high-dose melphalan plus AHSCT with Conventional chemotherapy which showed that high-dose melphalan plus AHSCT was cost-ineffective for MM patients [19]. However, none of studies compared the cost-effectiveness of different induction regimens with and without AHSCT. Therefore, our study narrows the gap in evidence.

Policy Implications

Ayushman Bharat-Pradhan Mantri Jan Aarogya Yojana (AB-PMJAY) [42], which is the flagship health insurance scheme in India, reimburses the use of novel agents such as VRd, VTd, pomalidomide & dexamethasone and lenalidomide maintenance for MM patients as part of their Health Benefit Package (HBP) 2.0 [32]. Our analysis supports this policy measure to incorporate the reimbursement of these drugs in the package for the treatment of MM. However, these reimbursement rates need to be revised. The triple drug-VRd induction therapy prior to AHSCT [₹ 40,671 (US$ 534) per QALY gained] would be the most cost-effective treatment regime for NDMM patients upon reducing the current reimbursement rates under national insurance program by 50% i.e. from ₹ 17,800 to ₹ 8,900 for VRd, ₹ 7200 to ₹ 3600 for pomalidomide plus dexamethasone, ₹ 4800 to ₹ 2400 for lenalidomide and societal cost of transplant from ₹ 3,53,027 to ₹ 1,76,513.

We would further recommend the inclusion of carfilzomib drug regimen in the HBP 2.0 for the treatment of MM patients in India. Furthermore, drugs like daratumumab may also be considered for inclusion under publicly financed health insurance schemes in order to further improve the survival as well as quality of life of MM patients in India. Since there is significant heterogeneity in market prices drugs such as carfilzomib, dartumumab etc., there is an urgent need to place certain price regulations in place so as to make these drugs more accessible and affordable to MM patients.

Limitations

There are certain limitations of this analysis. Firstly, we have not used the actual data on PFS for non-transplant arms i.e. VRd, VTd and VCd alone. A gradient was calculated using PFS curves for transplant and non-transplant (although transplant eligible) treatment arms so as to obtain the probability to be in PFS state according to induction regimen for non-transplant arms. However, we do not currently have robust country specific data for such subgroup analysis. Secondly, we have used estimates from GRIFFIN trial for DVRd plus AHSCT arm as there was no published Indian data reporting PFS and OS for DVRd plus AHSCT arm. Thirdly, we did not consider the cost of grade 1-2 AEs which might have slightly underestimated the costs. Lastly, we also did not consider the indirect costs due

to loss of productivity incurred by the patients as well as the caregivers. This was in agreement with Indian HTA guidelines, [23] and to avoid duplication [43].

Conclusion

Our study provides an insight and supports the evidence that the novel agent based induction regimens followed by AHSCT for treating MM, improves survival and quality of life, but are not cost-effective at current level of WTP threshold in India. The present study recommends the revision (reduction by 50%) of reimbursement package rates of VRd, pomalidomide plus dexamethasone and lenalidomide under the world's largest health insurance scheme i.e. AB-PMJAY [42]. Furthermore, the cost of transplant also needs to be reduced by 50% to make VRd plus AHSCT a cost-effective treatment strategy for India. The study insights can be used for clinical decision-making, guideline development, reimbursement decisions, and price negotiations.

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Chapter 3: Cost-effectiveness of first-line treatment options of metastatic renal cell carcinoma in India

Introduction

Approximately, 3% of all the adult cancers are renal cell carcinomas (RCC), and 85% of all kidney tumours are RCCs (1). In India, the incidence of RCC is reported to be about 2 per 100,000 for males and 1 per 100,000 for females (2). It's more common in the geriatric population with the median age of presentation ranging from 50-60 years with clear cell carcinoma being the commonest histological type accounting for nearly 70-80% of RCC cases (3–5).

In India, patients present with an advanced disease due to lack of screening and reporting (5,6). Until the last decade, the pharmacological treatment options for metastatic RCC (mRCC) were limited to immunomodulatory cytokines interleukin (IL)-2 and interferon-α (IFN-α) (7). The targeted therapies such as the Tyrosine-kinase Inhibitors (TKIs) (namely, Sunitinib, Pazopanib, Lenvatinib etc.), mammalian Target of Rapamycin (mTOR) inhibitors (Everolimus) and Anti-angiogenesis therapy (Bevacizumab) are the mainstay for the treatment of mRCC globally (8).

The Indian National Cancer Grid (NCG) (9), National Comprehensive Cancer Network (NCCN) (8) and Evidence-based Management (EBM) guidelines (10) recommend using TKIs such as Sunitinib, Pazopanib as the first-line therapy for favourable risk mRCC patients. Their high price makes them unaffordable for the majority of Indian patients. However, the introduction of low-cost generics has provided some relief to the patients. Moreover, India's government-funded health insurance program – the *Ayushman Bharat Pradhan Mantri Jan Aarogya Yojana* (PM-JAY) has recently included TKIs (such as sunitinib, cabozantinib and sorafenib) for the treatment of mRCC in its health benefit package (HBP) (11). This has helped in reducing the financial hardship faced by many Indian mRCC patients.

The Immune checkpoint inhibitors (ICIs) such as pembrolizumab and nivolumab in combination with TKIs have shown significant improvement in both progression-free survival (PFS) and overall survival (OS), with fewer toxicities as compared to the

conventional sunitinib monotherapy (12,13). However, the ICIs are expensive in the Indian and global markets. Cost-effectiveness analysis can help physicians and payers, particularly in low-middle-income countries like India, to choose appropriate therapies that offer the maximum value for money.

Published economic evaluation studies comparing TKIs (sunitinib and pazopanib), have reported that pazopanib is a cost-effective treatment option as compared to sunitinib (14–16). However, these studies have similar efficacy evidence but different country-specific cost estimates (14–17). Moreover, the clinical trials and systematic reviews show insignificant difference in the PFS and OS between sunitinib and pazopanib (18,19). There is also a dearth of studies providing a comparative analysis of newly approved drugs making it difficult to make an informed decision. Two studies compared all the first-line treatment options for mRCC and concluded that pembrolizumab/axitinib is a cost-effective treatment option in the context of the United States (20,21). However, these studies used a higher willingness to pay (WTP) threshold, which is not useful in developing countries like India. Thus, these differences in the context of these studies makes it difficult to generalize the evidence. We, therefore, aim to bridge this evidence gap, by evaluating the cost-effectiveness of various treatment options for the treatment of newly diagnosed mRCC patients in India.

Methodology

Overview of the Analysis

We undertook the present cost-effectiveness analysis using a societal perspective as per the methodological guidelines for conducting economic evaluation provided by India's health technology assessment (HTAIn) Agency (22). We compared 4 options for the treatment of newly diagnosed previously untreated mRCC patients in India – sunitinib, pazopanib, combination of pembrolizumab/Lenvatinib, and nivolumab/ipilimumab. A lifetime horizon was used to measure the health care costs and consequences in the different treatment arms. All future costs and outcomes were discounted at the rate of 3% (22). We followed the methodological guidelines as provided by the 'Indian Reference Case' for conducting economic evaluations (22). The study findings are reported as per the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (23).

Model structure

A Markov state-transition model was developed in Microsoft Excel to estimate the lifetime costs and consequences for mRCC patients (Figure 1). The overall target population for the economic evaluation included adults with previously untreated, advanced or metastatic RCC. The model consisted of three mutually exclusive health states: PFS, progressive disease (PD) and death. A 6-weekly cycle length was considered based on the treatment schedule for sunitinib which is given daily for 4 weeks, followed by 2 weeks off as per the dosage schedule in the COMPARZ trial (24).

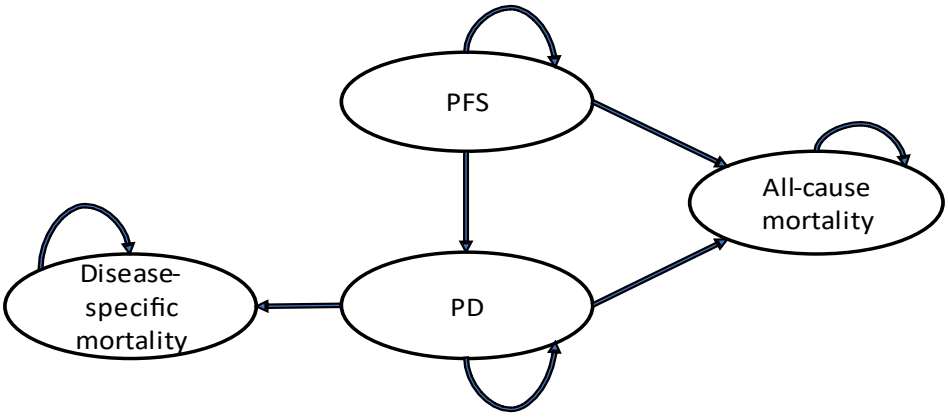

Figure 1: Schematic diagram for the Markov state transition model. PFS: Progression-Free State; PD: Progressive Disease

Once in PD health state, the patients are put on the same second-line targeted therapy or palliative care management irrespective of the type of first-line therapy. No disease-specific mortality was assumed in the PFS state, whereas in the PD state, deaths both from mRCC and all-cause were assumed. The patient enters the model at age of 55 years, which is the median age of presentation of mRCC in India (4,5).

Treatment arms and scenarios

Four treatment arms were modelled: (1) Sunitinib (50 mg orally once daily for 4 weeks followed by 2 weeks without treatment); (2) Pazopanib (800 mg orally once daily); (3) Pembrolizumab (200 mg intravenously 3-weekly) plus Lenvatinib (20 mg orally once

daily); and (4) Nivolumab (240 mg intravenously 2-weekly) plus Ipilimumab 50 mg (4 doses intravenously once every 6 weeks).

Valuation of consequences

The outcomes were assessed in terms of life-years (LYs) and Quality Adjusted Life-Years (QALYs). The probabilities to stay in the PFS health state were estimated for each cycle for all the arms. The PFS survival data for the sunitinib was extracted using a web-based digitiser software from the Kaplan-Meier curve (KM curve) using the CLEAR trial (25). We used the CLEAR trial as it is the most recently published randomized clinical trial comparing two different treatment regimens with sunitinib. The probabilities were estimated using the published standard extrapolation technique (26). The PFS data from the KM curve was extracted to generate pseudo-individual patient-level data (IPD). This reconstructed IPD was then fitted to five standard parametric models (exponential, Weibull, Gompertz, log-normal and log-logistic). A suitable distribution was selected based on visual inspection and the goodness of fit (Akaike and Bayesian information criteria). The log-normal distribution was the best fit for the sunitinib arm [Supplementary Figure 1]. The PFS data for the other arms, i.e., Pazopanib, Pembrolizumab/Lenvatinib and Nivolumab/Ipilimumab was estimated by applying hazard ratios from the published systematic reviews and network meta-analysis (19,27). Age-specific all-cause mortality rates were obtained from the Sample Registration System (SRS) lifetables (28). The disease-specific mortality in the PD state was assumed to be the same for all treatment arms as all the patients underwent the same second-line therapy. The probability of death was obtained from the published Indian literature which aimed to determine the efficacy of second-line treatment among mRCC patients (29). The detailed input parameters are shown in Table 1.

Baseline utility values for PFS and PD health state were obtained from the published literature (30). The study also provided disutility values for each of the AEs related to the treatment. These disutility values were applied to the base value and the utility scores were computed for different Aes associated with the treatment of mRCC (Table 2) (30). The data on incidence of Aes related to treatment was obtained from published literature [Supplementary Table 1] (12,24,31).

Table 1: Input parameters to determine the effectiveness of the different treatment arms

Input variable	Parameter	Distribution	Source
Median age of presentation of mRCC in India	55 years	-	(4,5)
Discount Rate	3%	Beta	(22)
Survival model of PFS for Sunitinib	• Shape = 2.20667 • Scale = 0.076447	Log-normal	(25)
HR (vs sunitinib)			
Pazopanib	1.05 (0.9 – 1.22)	Beta	(19)
Pembrolizumab/ Lenvatinib	0.39 (0.31 – 0.49)	Beta	(27)
Nivolumab/ Ipilimumab	0.89 (0.75 – 1.05)	Beta	(27)
Disease-specific mortality			
PD to death	0.078 (0.05 – 0.10)	Beta	(29)
Age-specific mortality (6-weekly probability)			
55-59	0.00165 (0.00126 – 0.00191)	Beta	(28)
60-64	0.00237 (0.0019 – 0.00297)	Beta	(28)
65-69	0.00361 (0.00298 – 0.00461)	Beta	(28)
70-74	0.00558 (0.00454 – 0.0072)	Beta	(28)
75-79	0.00842 (0.0068 – 0.011)	Beta	(28)

80+	0.01458 (0.0109 – 0.0189)	Beta	(28)
Health-related quality of life scores			
PFS with AEs	0.75	Beta	(30)
PFS without AEs	0.76	Beta	(30)
PD	0.66	Beta	(30)

mRCC: metastatic renal cell carcinoma; PFS: Progression-free survival; HR: Hazard Ratio; PD: Progressive disease; AEs: Adverse events

Cost of treatment of Metastatic Renal Cell Carcinoma

The costs were estimated from a societal perspective for all the treatment arms. We did not consider the productivity losses incurred by the patient and their caregivers due to the treatment as per existing Indian reference case for health technology assessment (22).

The cost of treatment in the PFS state for the sunitinib arm included the reimbursement rate as per the HBP under the PMJAY scheme. The reimbursement rate includes chemotherapeutic agents, recurring investigations, day-care charges, supportive care, and doctor and nursing charges. In addition, the direct non-medical out-of-pocket expenditure (OOP) (including travel, boarding/lodging, food, informal payment etc) were added to estimate the societal cost. For the other three treatment arms which are not included in the PMJAY, drug acquisition costs; direct non-medical OOP expenditure (including the user fees), cost of management of grade 3-4 AEs and the follow-up was incorporated. Routine follow-up costs include cost per outpatient consultation, cost of day-care visit, laboratory investigations and diagnostic tests (Table 2). Separate incidence rates for each grade 3-4 AEs were applied using the published literature (12,24,31). We assumed that the cost of routine laboratory and diagnostic tests was applied after every 3 months as per the standard treatment guidelines (32).

For PD, we included the cost of outpatient consultation, laboratory and diagnostic tests, as well as second-line therapy. We assumed that the patients would be given second-line therapy for 9 months, after which the patient would be on palliative management. The second-line therapy included oral administration of sorafenib, axitinib and everolimus as

per the standard treatment guidelines (32) (Supplementary Appendix I). We used the reimbursement rates for sorafenib and market prices for the rest of the drugs.

Health system costs of outpatient consultation and day-care visit were elicited using data from published studies (33,34) and the nationally representative 'National Health System Cost Database'(NHSCD). (35) The OOPE estimates were derived from primary data collected as a part of the larger multi-centric 'National Cancer Database for Cost and Quality of Life' (CaDCQoL) (34). We used the reimbursement rates (11); generic & market prices (36) and procurement rates of the Rajasthan Medical Service Corporation (RMSC) (37), for estimating expenditures on drugs. For diagnostic services, we used the provider payment rates from a publicly financed national insurance scheme for central government employees i.e. Central Government Health Scheme (CGHS) (38). All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 73.9 for the year 2021 (39).

The comparative cost-effectiveness was assessed in terms of incremental cost per QALY gained. A WTP threshold equal to per capita gross domestic product (GDP) of India was used to assess the cost-effectiveness as per the guidelines for health technology assessment in India (22,40). The per capita GDP of India for the year 2021 was ₹168,300 ($ 2,277.4). (41)

Table 2: Input cost parameters

Input Parameter	Cost per cycle (in ₹)	Cost per cycle (in $)	Distribution	Source
Per cycle cost of drug (6-weekly cycle)				
Sunitinib 50mg	10,000 (5,000-15,000)	135 (68-203)	Gamma	(11)
Pazopanib 400mg	17,631 (8,815-26,446)	238 (119-358)	Gamma	Generic rate
Pembrolizumab 200mg	480,000 (240,000 – 720,000)	6,495 (3,247-9,743)	Gamma	(36)
Lenvatinib 10mg	21,168 (10,584-25,402)	286 (143-344)	Gamma	Generic rate

Nivolumab 240mg	432,000 (216,000-648,000)	5,845 (2,922-8,769)	Gamma	(36)
Ipilimumab 50mg	220,000 (110,000 – 330,000)	2,977 (1,488-4,465)	Gamma	(36)
Sorafenib 400mg	9,500 (4,750-11,400)	128 (64-154)	Gamma	(11)
Everolimus 5mg	29,186 (14,593-43,779)	394 (197-592)	Gamma	(36)
Axitinib 5mg	12,000 (6,000 – 14,400)	162 (81-194)	Gamma	(36)
Health system cost				
Out-patient consultation	266.2 (186.4-346.1)	3.6 (2.5-4.6)	Gamma	(35)
Day care visit	1,038 (826-1238)	14.1 (11.2-16.7)	Gamma	(33)
Out-of-Pocket Expenditure (OOPE)				
Per Out-patient consultation*	2,774 (1,387-4,161)	37 (19-56)	Gamma	(34)
Per Out-patient consultation**	2,421 (1,210-2,905)	33 (16-39)	Gamma	(34)
Per cycle cost of management of adverse effects				
Diarrhoea	25 (12-37)	0.34 (0.16-0.5)	Gamma	(37)
Hypertension	5 (2.5-7.3)	0.07 (0.03-0.1)	Gamma	(37)
Nausea/Vomiting	7 (3-10)	0.09 (0.04-0.13)	Gamma	(37)
Decreased Appetite	13 (6-19)	0.18 (0.08-0.26)	Gamma	(37)
Hand-foot Syndrome/ Palmer-planter dysesthesia	583 (291-975)	7.9 (3.9-13.2)	Gamma	(37)
Abdominal Pain/ Arthralgia	141 (70-212)	1.9 (0.9-2.9)	Gamma	(37)
Rash	262 (131-393)	3.5 (1.7-5.2)	Gamma	(37)
Stomatitis/ Mucosal Inflammation	235 (117-352)	3.2 (1.6-4.8)	Gamma	(37)
Leukopenia	2,198 (1099-3297)	30 (15-45)	Gamma	(37)
Thrombocytopenia	2,000 (1000-3000)	27 (14-41)	Gamma	(11)
Anaemia	2,000 (1000-3000)	27 (14-41)	Gamma	(11)
Transaminitis	197 (98-295)	2.7 (1.3-4.0)	Gamma	(37)
Asthenia	23 (12-35)	0.3 (0.2-0.4)	Gamma	(37)

Hypothyroidism	5 (2.6-7.8)	0.1 (0.03-0.1)	Gamma	(37)
Constipation	84 (42-126)	1.1 (0.5-1.7)	Gamma	(37)

**Including the OOP expenditure on travel, user fees, boarding/lodging, food, informal payments and others (excluding the drugs and diagnostics) – direct expenditure (for pazopanib, pembrolizumab/Lenvatinib and nivolumab/ipilimumab arms)*

*** Including the OOP expenditure on travel, boarding/lodging, food, informal payments and others (excluding the drugs, diagnostics and user fees) – direct non-medical expenditure (for sunitinib, axitinib and sorafenib patients)*

Sensitivity and Threshold Analysis

A probabilistic sensitivity analysis (PSA) was undertaken to test the parameter uncertainty for each scenario. Under PSA, we used gamma distribution for cost parameters and beta distribution for parameters related to effectiveness, risk of complications, overall survival, and utility scores. For the rest of the parameters in the model, we used uniform distribution. Uncertainty ranges for input parameters were computed from the standard error estimates from the primary data, or data available in the literature. Wherever the measures of dispersion were unavailable, a variation of 20% for clinical parameters; 30% variation for mortality risks, utility scores and treatment patterns; and 50% variation for cost parameters was assumed on either side of base parameter values. Model results were simulated 1000 times and the median value (ICER) along with 95% confidence interval was generated for base estimates using the percentile method.

Extended dominance analysis was undertaken in which each treatment arm was compared against the next best alternative to assess the comparative cost-effectiveness between various treatment arms.

Results

Costs and outcomes

We estimated that an mRCC patient incurs a lifetime cost of ₹ 273,846 ($ 3,706), ₹ 348,537 ($ 4,716), and ₹ 9.7 million ($ 131,858) and ₹ 6.7 million ($ 90,481) for sunitinib, pazopanib, pembrolizumab/lenvatinib and nivolumab/ipilimumab treatments, respectively. The overall mean LYs lived with sunitinib, pazopanib,

pembrolizumab/lenvatinib and nivolumab/ipilimumab were 2.70, 2.63, 3.79 and 2.78 respectively. In terms of utility measures, this translates into 1.91, 1.86, 2.75 and 1.97 QALYs respectively (Table 3).

Table 3: Base-case results for treatment of metastatic Renal Cell Carcinoma

Outcomes	Sunitinib	Pazopanib	Pembrolizumab/ Lenvatinib	Nivolumab/ Ipilimumab
Costs (95% CI)				
Total Lifetime costs (in ₹)				
• **Undiscounted**	291,152 (235,669-367,800)	368,628 (287,161-540,855)	11,089,983 (6,938,0510-17,110,607)	6,969,356 (4,336,779-10,024,677)
• **Discounted**	273,846 (223,678-342,190)	348,537 (272,885-502,445)	9,744,330 (6,153,746-14,977,909)	6,686,526 (4,183,488-9,592,982)
Effectiveness (95% CI)				
LYs				
• **Undiscounted**	2.9 (2.3-3.6)	2.8 (2.4-3.6)	4.3 (3.8-4.8)	3.0 (2.5-3.5)
• **Discounted**	2.7 (2.2-3.4)	2.6 (2.2-3.6)	3.8 (3.4-4.2)	2.8 (2.3-3.3)
QALYs				
• **Undiscounted**	2.1 (1.6-2.6)	2.0 (1.6-2.6)	3.1 (2.7-3.6)	2.1 (1.7-2.5)
• **Discounted**	1.9 (1.5-2.4)	1.9 (1.5-2.4)	2.7 (2.4-3.1)	2.0 (1.6-2.3)

LY: Life-years; CI: Confidence Intervals; QALYs: Quality-Adjusted Life-years; ICER: Incremental cost effectiveness ratio

Cost-effectiveness

According to Table 4, pazopanib incurs higher cost and statistically insignificant health benefits as compared to sunitinib, and is hence dominated. Among the three non-dominated options, pembrolizumab/lenvatinib and nivolumab/ipilimumab incur an incremental cost of ₹ 3.9 million ($ 53,497) and ₹ 115.8 million ($ 1,568,137) per QALY gained respectively which are not cost-effective when compared with India's current WTP of 1-time per capita GDP (₹ 168,300). Sunitinib incurs an average cost of ₹ 143,269 ($ 1,939) per QALY lived which is a cost-effective treatment strategy in the Indian context when compared to the cost-effectiveness threshold of 1-time per capita GDP.

Table 4: Cost-effectiveness of different treatment strategies for mRCC in India

Treatment strategy	Cost in ₹ ($)	QALYs	Incremental cost per QALY gained in ₹ ($)	Interpretation
Sunitinib	273,846 (3,706)	1.91	-	ND
Nivolumab/ Ipilimumab	6,686,526 (90,481)	1.97	115,885,317 (1,568,137)	ND
Pembrolizumab/ Lenvatinib	9,744,330 (131,858)	2.75	3,953,457 (53,497)	ND
Pazopanib	348,537 (4,716)	1.86	-	D

QALY: Quality-adjusted Life-Years; ND: Non-dominated; D: Dominated

Sensitivity Analysis

Sunitinib, at the current reimbursement rate (₹ 10,000), has nearly 95% probability to be cost-effective at the current WTP threshold of 1-time per capita GDP (₹ 168,300) of India. Similarly, the probability of pembrolizumab/lenvatinib to be cost-effective as compared to nivolumab/ipilimumab was 19.9%. A 33% reduction in the current price of pembrolizumab (from ₹ 480,000 per cycle to ₹ 321,600 per cycle) is required to make it a cost-effective treatment option as compared to nivolumab/ipilimumab (Figure 2). However, even with a 95% reduction in the current price, nivolumab/ipilimumab is not a cost-effective treatment option as compared to sunitinib.

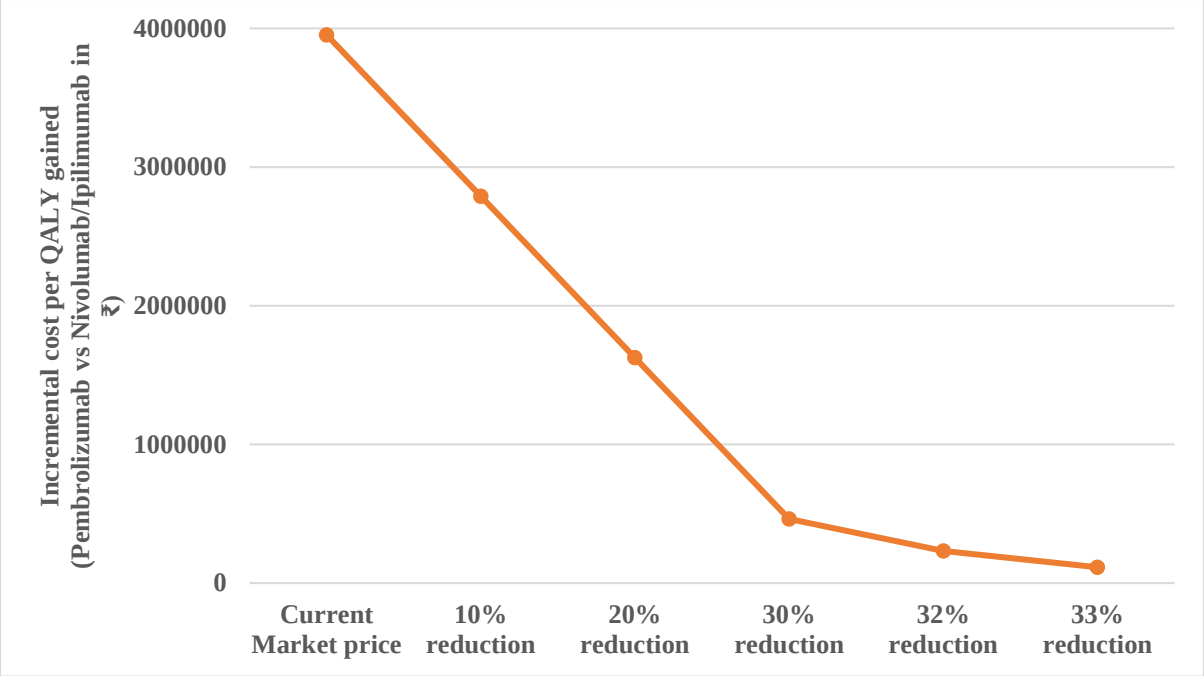

Figure 2: Price threshold Analysis: Pembrolizumab

Discussion

Our study compared four different options for the first-line treatment of metastatic RCC in the Indian context. We concluded that sunitinib is the most cost-effective treatment option. Although, the combination of pembrolizumab/lenvatinib provides the maximum health benefits, it is not a cost-effective treatment strategy at current prices. In contrast to other countries, the cost of pazopanib is higher in India as compared to sunitinib. As a result, pazopanib is a dominated treatment strategy for first-line mRCC patients in India as it offers similar health outcomes at a higher overall cost. Therefore, this significantly higher cost of pazopanib bends the results in the favour of sunitinib. Table 5 shows the comparative assessment of our findings in context of other model-based cost-effectiveness studies.

Table 5: Comparison of costs and outcomes for pazopanib and sunitinib

Studies	Intervention	Comparator	Incremental LY gained/person	Incremental QALY gained/person	Incremental cost per QALY gained (in I$*)	Conclusion
Capri et al. (17)	Pazopanib	Sunitinib	0.057	0.06	-147,904	Pazopanib is cost-effective
Delea et al. (16)	Pazopanib	Sunitinib	0.053	0.09	-75,867	Pazopanib is cost-effective
Present Study	Sunitinib	Pazopanib	0.07	0.06	-56,429	Pazopanib is dominated

LY: Life-years; QALY: Quality-adjusted life-years; I$: International dollar

**The 2021 World Bank Group conversion rates have been used to depict the costs in International Dollars* (42)*. The exchange rate used for Italy and India was 0.66 and 22.06 respectively.*

According to the literature, the use of immunotherapy provides better health outcomes in terms of PFS and OS than sunitinib and pazopanib (19,27,43). Our study corroborates the above-mentioned finding that the immunotherapy and TKI combination provides more LYs and QALYs as compared to single-agent TKIs. However, at current prices, the Pembrolizumab/Lenvatinib and nivolumab/ipilimumab combinations are expensive for the developing countries like India as compared to the incremental health benefits attributable to them. Therefore, these drugs are not cost-effective at current prices.

Model validation

The findings of our model are in concurrence with existing clinical and epidemiological evidence available in the Indian as well as the global context. The median PFS (mPFS) and OS (mOS) in our model for Sunitinib (mPFS: >9 months; mOS: 27 months) and Pazopanib (mPFS: <9 months; mOS: 27 months) is consistent with the current Indian literature. Two Indian studies estimated the mPFS for sunitinib patients to be 11.4 months and 9 (3-45) months respectively which is consistent with our model estimates (44,45). Similarly, the mOS for the sunitinib arm is reported to be 22.6 months and 28.2 months respectively which is in line with our study findings (44,46). There is a significant lack of evidence

with respect to the other two arms (i.e., pembrolizumab/lenvatinib and nivolumab/ipilimumab) in the Indian context however, a single-centre study from India reported 1-year OS among patients treated with Immunotherapy (pembrolizumab or nivolumab)-TKI (axitinib or lenvatinib) combination to be 92%. This corroborates with our study outcomes that estimate the 1-year OS to be 88.8% and 85.1% among the pembrolizumab/lenvatinib and nivolumab/ipilimumab arms respectively (47).

A recently published study comparing all the frequently used first-line treatment regimens estimated 2.13 (2.99 LYs), 2.61 (3.44 LYs) and 2.42 (3.21 LYs) QALYs in sunitinib, pembrolizumab/Lenvatinib and nivolumab/ipilimumab treatment arms respectively (20). This is in line with our study results which estimated 1.9 (2.7 LYs), 2.75 (3.7 LYs) and 2.0 (2.8 LYs) in sunitinib, pembrolizumab/ipilimumab and nivolumab/ipilimumab arms respectively. In our study, pazopanib was estimated to incur fewer progression-free LYs (1.26 LYs) than sunitinib which incurred 1.3 progression-free LYs. Many studies that compare sunitinib and pazopanib have also reported more progression-free LYs (1.17 and 1.15 respectively) (14–16).

Strengths & Limitations of the analysis

We would like to highlight a few merits of our study. Firstly, this study is the first to examine the cost-effectiveness of the treatment options for metastatic renal cell carcinoma in the Indian context. Secondly, we included all the possible first-line treatment options available, making the analysis comprehensive and close to real-world practices. Thirdly, we have obtained OOPE estimates from the primary data being collected as a part of an ongoing multicentric study for assessing the economic burden among cancer patients in India (34). Fourthly, we incorporated the reimbursement rates set up under India's publicly funded national health insurance scheme wherever available to make our analysis policy-relevant (11,48). Lastly, we used the survival data from published Indian studies to make our results representative in the Indian context.

However, there are certain limitations to this analysis. Firstly, we used a 4/2 regimen instead of a 3/1 regimen for the sunitinib treatment as the literature considers the former regimen and there would not be major cost differences between the two. Secondly, we did not consider the cost of grade 1-2 AEs which has resulted in a slight underestimation of costs. However, since none of the immunotherapeutic treatments is cost-effective, the

exclusion of such costs further strengthens our conclusions. Thirdly, we did not take into account the indirect costs due to loss of productivity incurred by the patients as well as the caregivers which are in line with Indian HTA guidelines which do not recommend the inclusion of indirect costs in the base case (22). Lastly, we did not perform separate subgroup analysis according to the favourable, intermediate, and poor risk categories in our study due to the lack of robust Indian evidence on the same.

We performed the analysis from the societal perspective and have not presented the costs separately from the health system and patients' perspective. This is in line with the methodological principles outlined by the HTAIn. Inclusion of a treatment in a largely publicly financed insurance program such as PMJAY may lower the overall cost due to economies of scale. However, we did consider a wide variation in prices during the PSA, which did not alter the overall conclusions on cost-effectiveness. Hence, our study results are robust to these variations in contextual factor of healthcare financing and delivery.

Conclusion & Policy Implications

From this analysis, we can conclude that at the current reimbursement rate, sunitinib is the cost-effective option for treatment of mRCC in India. The immunotherapeutic agents (such as Nivolumab, Pembrolizumab etc.) provide significant clinical benefits, but they are very expensive drugs to be considered cost-effective for use in the Indian context. Therefore, further consideration should be made to promote the manufacturing and introduction of low-cost generics and regulate the price of these expensive drugs to make it cost-effective and affordable for Indian patients. Finally, the screening strategies for early-stage detection of mRCC (along the lines of screening for breast, oral and cervix cancer etc.) should be implemented to reduce the economic and clinical burden of the disease in India.

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Chapter 4: Cost effectiveness analysis of different combination therapies for the treatment of Chronic Lymphocytic Leukaemia in India

Introduction

Chronic lymphocytic leukaemia (CLL) accounts for around 5% of all leukaemia cases, and approximately 6195 deaths annually in India. (1)(2)Though the incidence of CLL, with 4.1 cases per million in India, is lower thanin western regions of the world, it is diagnosed almost ten years earlier with the worst performance status and requires an aggressive course for treatment.(2)

Chlorambucil, a drug no longer in practice in developed nations, is still commonly prescribed in India for the treatment of CLL.(1)(3) Chlorambucil has shown decent clinical effectiveness and was also used to be the first-line treatment for CLLglobally before the introduction of newer drugs - bendamustine and ibrutinib.(4) As compared to chlorambucil, both bendamustine(Median PFS; 21.6 months vs. 8.3 months; $P < 0.0001$) and ibrutinib (70% versus 12% at 5 years) have significantly highprogression-free survival (PFS).(5)(6)When compared between themselves, ibrutinib has relatively higher PFS (87% versus 74% at 2 years; $p < 0.001$) than bendamustine.(7)Though these newer drug regimens lead to improved survival, they are also associated with higher costas well as high incidence of side effects.(5)(6)(7)Study from India shows that the six-monthly expenditure for CLL treatment with Ibrutinib ($ 12,000) and bendamustine ($ 2300) is around 200 times and 40 times higher than chlorambucil-based regimen ($ 60), respectively.(1)

With continuous new advancements in drug technology for CLL treatment along with limited budgets in the health sector, it becomes crucial to assess thecost-effectiveness of newer interventionsalong with their health benefits.Regarding anti-CLL drugs, no economic evaluations are reported from India or even the South-East Asia Region (SEAR). All the existing literature on cost-effectivenessof these drugs has been reported from the context of developed countries.(8)(9)(10)(11)However, none of thesestudieshasdirectly compared the threedrugs in question, i.e.,chlorambucil, bendamustine and ibrutinib.

Recently,India's National Pharmaceutical Pricing Authority (NPPA) hasundertaken a price regulation of about 42 anticancer drugs that includes various anti-CLL drugs.(12) Considering the same, the Health Technology Assessment India (HTAIn) commissioned the present study to assess the cost-effectiveness and value-based pricing ofthese drugs. In view of limited generalizability of theevidence from the developed nations, the present study was undertaken toassess the cost-effectivenessof three treatment regimes, i.e., chlorambucil plus prednisolone (CP), bendamustine plus rituximab (BR), and ibrutinib for the treatment of CLL in India

Methodology

Model Overview

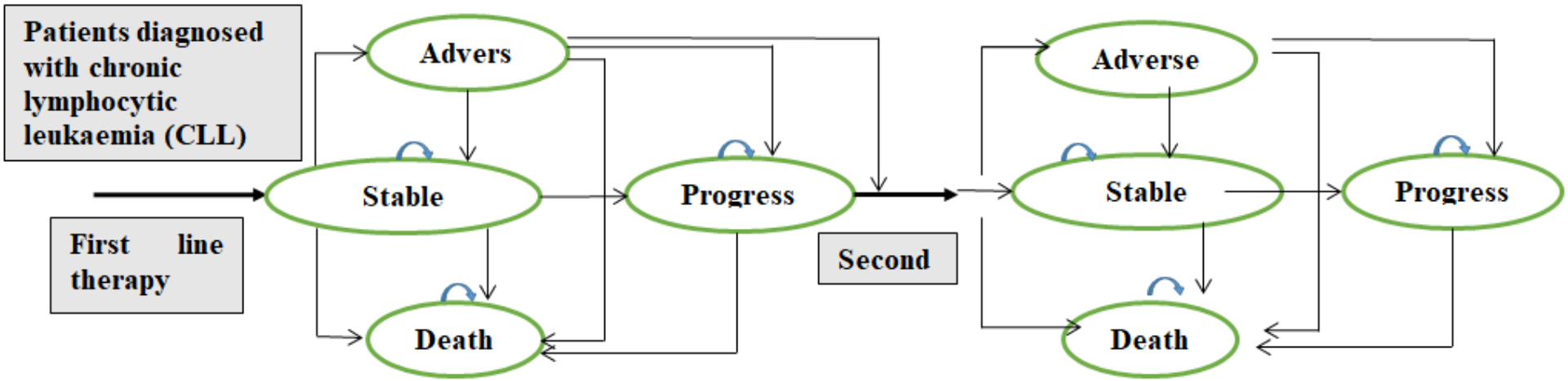
A Markov model was developed to estimate costs and health outcomes in a hypothetical cohort of 1000 CLL patients followingtreatment with different therapeutic regimens.The analysis was based on a disaggregated societal perspective which included health system costs and out of pocket (OOP) expenses.(13) We excluded the indirect cost both due to productivity losses and premature mortality. A lifetime horizon with a discount rate of 3% was used per India's HTA guidelines.(13) Health outcomes were assessed in term of life years (LY) quality-adjusted life years (QALY).

The Markov model (Fig. 1), representing various health states of CLL patients following diagnosis and undertaking first line of treatment for CLL, was developed. During the duration of treatment, patients were presumed to develop severe adverse events (AE-1) or mild side-effects.(1)(5)(6)(7) Those patients with severe AE-1 were assumed todiscontinue the treatment and either receive the second-line therapy, face a probability of dying (cause specific or all-cause mortality), develop progression, or move back to receive the initial first-line therapy following treatment of AE-1.(1)(5)(6)(7)Mild side effectswere assumed to bepharmacologically managed alongside the treatment. Based on the clinical responsefollowing first-line treatment, patients were assumed to be eitherin stable/disease-free, defined as the progression-free state (PFS-1), or could develop progressive disease (PD-1). Those patients in the PFS-1 state further faced a probability of developing the progressive disease (PD-1) or dying from the all-cause mortality. Lastly, patients in PD-1 state were either assumed to die because of the disease-specific/all-

cause mortality or were assumed to receive the second line therapeutic regimen. As per clinical guidelines, the patients with progressive disease are noteligible to receive treatment.(14) So as per the expert opinion, 50% of patients who developed PD-1 were assumed to wait for six months, and the remaining 50% wait for 12 months before receiving the second line of treatment.(14)

Patients on second-line therapy had a similar clinical course, as followed during the first-line treatment. However, we did not assume any third-line therapy for patients with adverse events (AE-2) and progressive disease (PD-2).Patients from these stages were finally assumed to either progress or die from disease/cause-specific death or all-cause mortality.We included grade 3 or higher infection with pneumonia and atrial fibrillation as severe adverse events. Further, neutropenia and thrombocytopenia were modelled as mild side effects. Based on the standard treatment guidelines on treatment duration with chlorambucil and bendamustine, the cycle length was assumed to be of six months. (14)The model was assumed to start at 60 years of age, which is the mean age at diagnosis with CLL in India.(1)

Fig. 1: Markov Model



Treatment arms

Based on clinical consultation, we modelled four treatment arms as the base case. The first arm 'A' comprised CP as first-line therapy and BR as a second-line therapy. Similarly, the second arm 'B' constituted CP as first-line therapy and IBR as second-line therapy. The third arm 'C' consisted of BR as first-line therapy and IBR as second-line therapy. Lastly, in the fourth arm 'D', IBR was considered first-line therapy followed by BR as the second-line therapy.

In addition to the four primary treatment arms, three scenario analyses were undertaken. Under these scenarios, CP, BR and IBR were each given as first-line therapy with no additional second-line treatment. The primary purpose of the scenario analysis was to directly compare and assess the cost effectiveness of the three drugs in question, while excluding the impact of the second-line therapy. Dosage of chlorambucil and prednisolone was taken as 10 mg/$m^2$and of 60 mg/m^2respectively for five days in a 28-day cycle, for 6 cycles.(1)The dose for Bendamustine estimated as 90 mg/m^2 on day 1 and 2,along with rituximab at 375 mg/m^2in a 28-day cycle, for 6 cycles.(1) Ibrutinib was administered at a dose of 420 mg daily.(6)(7) Dosage was considered the same for the first and second line of treatment.

Clinical effectiveness and transition probabilities

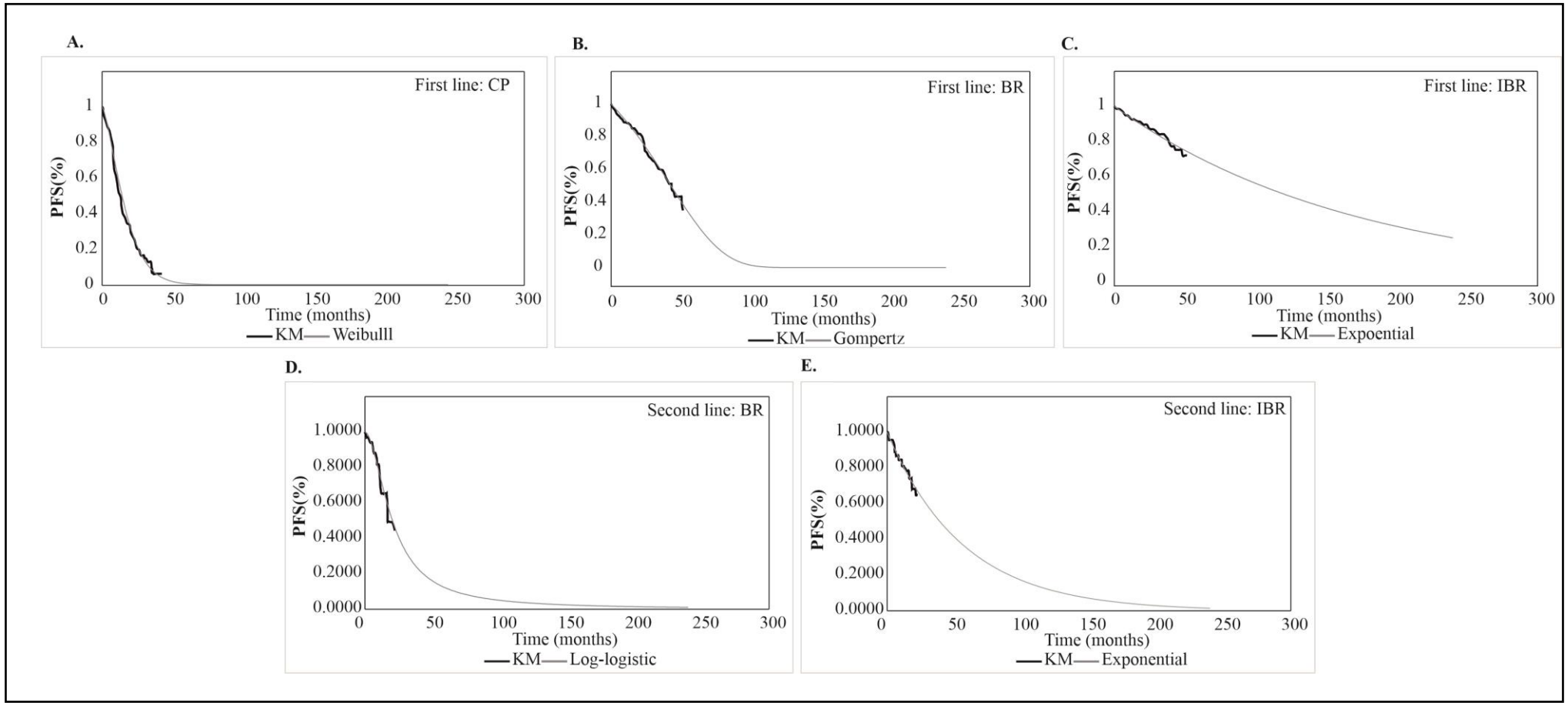
The data on progression and occurrence of adverse events with administration of each drug (both forfirst-lineand second-line) was obtained from variousrandomized controlled trials (RCT)as shown in table 1.The probability ofprogressionwas calculated using the PFS survival curves reported in thesetrials.(4)(7)(15)The PFS curves from each trial were extrapolated using standard methods.(16)Individual patient-level data was created using an online tool from the published PFS curves.(17) This patient-level data was then extrapolatedusing different parametric models (Gompertz, Weibul, Log-logistic, etc.)in STATA.(16)(17) The preferred model was selected using the Akaike's Information Criterion (AIC) and Bayesian Information Criterion(BIC), and on the visual comparison of published Kaplan-Meier and fitted survival curves.(16) Table 1 shows the results of fitting parametric survival curves of the time to progression (TTP). Fig. 2 shows the empirical and fitted survival curves for TTP for each of first line and second line

therapy.The time dependentsix-monthly transition probabilities of moving from PFS-1 to PD-1 were derived for all first-line therapies. Data on disease specific mortality was assessed from a study that had reported survival up till 10 years following treatment initiation. Based on the fact thataround 80% of the CLL patients died at 10 years, parametric survival functions were not applied and an actual probability of dying from the published curve was used.

A constant transition probability was used for the post progression i.e., PFS-2 to PD-2 for second-line therapies. Likewise, a constant probability of disease specific mortality was assumed. This approach was justified as the incorporation of time dependent probability of moving from PFS-2 to PD-2 or progressive disease to death would have greatly increased the complexity of the model.

The probability of death from adverse events was calculated using the data from Institute for health metrics and evaluation (IHME),Global burden of Disease Study.(18)The data on thepercentage of patients discontinuing the treatmentfollowing adverse events was used to calculate the probability from AE-1 to PFS 2 (Table 1).(4)(15)(19)The CLL specific mortality was specifically assessed from an Indian study, that had reported survival rate following first line treatment of CLL.(3)All-cause mortality rates were assessed from Sample Registration System (SRS) life tables of India- 2014-2018.

Fig. 2: Comparison of empirical and fitted progression free survival curves



*CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; IBR: Ibrutinib; KM: Kaplan Meier; PFS:Progression free survival

Table 1: Model input parameters

Parameter	Estimate	Range/ SE	Source
PFS for CP as first line therapy	Weibull; 0.016834 = 0.3373993	0.004638 = 0.064348	Hillmen et al(4)
PFS for BR as first line therapy	Gompertz; 0.008776 =0.0259679	0.002134 =0.009710	Woyach et al(7)
PFS for IBR as first line therapy	Exponential; 0.0057715	0.001004	Woyach et al (7)
PFS for BR as second line therapy	Log-logistic; 3.021232 = -0.6195551	0.224552 =0.2577661	Ghia et al(15)
PFS for IBR as second line therapy	Exponential; 0.0176984	0.003539	Xiaojun et al(19)
Incidence of severe adverse events with CP as first-line therapy	27	2.755	Hillmen et al(4)
Incidence of adverse events with BR as first line therapy	31	3.163	Woyach e al(7)
Incidence of adverse events with IBR as first line therapy	54	5.510	Woyach et al(7)
Incidence of adverse events with BR as 2nd line therapy	5	0.510	Ghia et al(15)
Incidence of adverse events with IBR as 2nd line therapy	23	2.346	Xiaojun et al(19)
Proportion of patients receiving 2nd line therapy following adverse events with CP as 1st line therapy	0.099	0.010	Hillmen et al(4)
Proportion of patients receiving 2nd line therapy following adverse events with BR as 1st line therapy	0.17	0.017	Ghia et al(15)
Proportion of patients receiving 2nd line therapy following adverse events with IBR as 1st line therapy	0.024726	0.002523	Xiaojun et al(19)
Annual disease specific mortality rate with CLL	0.148913	0.015195	Gogia et al(3)
Age-specific all-cause annual mortality rates, years			
60-65	0.0907	0.009	SRS life tables

65-70	0.01346	0.013	
70-75	0.2006	0.020	
75-80	0.2969	0.029	
80-85	0.4503	0.045	
Case fatality rate for pneumonia	0.1265	0.012	GBD, 2019
Case fatality rate for atrial fibrillation	0.003	0.0004	GBD, 2019
Health state utility values			
Progression free state (PFS-1) following first line therapy	0.806	0.082	a
Progressive disease (PD-1) following first line therapy	0.64873	0.066	a
Progression free state (PFS-2) following second line therapy	0.69788	0.071	a
Progressive disease (PD-2) following second line therapy	0.57993	0.059	a
Stable disease plus atrial fibrillation following first line therapy#	0.65286	0.066	Sullivan et al(22)
Stable disease plus pneumonia following first line therapy#	0.332072	0.033	Galante et al(24)
Stable disease plus atrial fibrillation following second line therapy#	0.565283	0.057	Sullivan et al(22)
Stable disease plus pneumonia following second line therapy	0.287527	0.029	Galante et al(24)

*CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; IBR: Ibrutinib; PD: progressive disease; PFS: Progression free state; SE: Standard error, CLL: Chronic Lymphocytic Leukaemia

#: The utility values were calculated separately for adverse event atrial fibrillation and pneumonia which along with utility values of CLL, using multiplicative methods

a: obtained based on the primary data collection, as part of the Cancer Database for Cost and Quality of Life (CaDCQoL)

Utility scores

Utility values for progression-free and post-progression health states were obtained based on the primary data collection from 242 cervical cancer patients fromsix large cancer hospitals across India, as part of the Cancer Database for Cost and Quality of Life (CaDCQoL).(21) The patients were administered the EQ-5D-5L tool, and India specific tariff values were used for estimating the utility score for the health states (Table 1). The

utility value for adverse events i.e., atrial fibrillation and pneumonia, wasassessed from the published literature (22)(23)(24)

Costs

As mentioned above, we included both the health systems costs and patient-level OOP expenditure incurred during the length of CLL treatment. Health systems costsaccounted for outpatient consultation, diagnostic tests, day-care.(Table-2) Further,OOP expenditure included the direct non-medical expenses incurred on travel boarding/lodging, food and user fees during the treatment(Table 2).The unit health system cost of day-care was assessed from a previous costing study from India.(25)The unit cost of outpatient consultation and diagnostic tests were assessed from the reimbursement rates of India's national social health insurance, i.e., the Central Government Health Scheme (CGHS).(26)Due to a lack of information on the cost of immunoglobinheavy chain gene (IGVH) mutational tests, markets prices of the same were used. (26) The data on OOP expenditure and quality of life utility values were analysis of primary data being collected as part of National Database on cost and QOL for cancer in India.(21) The cost for treating neutropenia and thrombocytopeniawas calculated usingdisaggregated from National Health System Cost Database and normative guidelines. The cost of treatment for atrial fibrillation and pneumonia was assessed using theprovider payment rates of *PradhanMantri Jan ArogyaYojana (PM-JAY)*.(27) Market prices of ibrutinib, bendamustine, chlorambucil and other drugs (used in the analysis) were used in the present analysis.(28)(29)(30)(31)(32) The cost of the drugs was calculated based on the quantity of drug required as per the average weight and height of Indian population from the report of expert group on nutrient requirements for Indians, 2020.(33)

The information on the type and quantity of various health services (outpatient consultation, day-care, etc.), including diagnostic tests undertaken before and during the CLL treatment, was assessed using the standard treatment guidelines, International workshop on chronic lymphocytic leukemia (iwCLL) guidelines, and the clinician's expert opinion.(14) The quantities were then multiplied by the unit cost of respective health services to estimate the total cost of CLL treatment. Finally, the total cost comprised of initial baseline cost incurred during the diagnosis process (includes diagnostics and

outpatient consultations), delivery of therapeutic regimen (consisting of the price of drugs and day-care cost), managing complications and adverse effects and follow-up sessions. All the cost estimates belong to the year 2020. Cost estimates are presented in United States Dollar ($). A conversion rate for the year 2020 of 1 $ = ₹74.13 was used.(34)

Table 2: Costs parameters

Parameter	Estimate ($)	Standard error	Source
Health system cost			
Outpatient consultation (per visit)	2.02	0.40	(26)
Day-care (per visit)	14.00	2.84	(25)
CBC (per test)	1.88	0.37	(26)
Flow-cytometry (per test)	32.34	6.79	(39)
Serum chemistry panel (per test)	19.81	4.03	(26)
Chest X ray (per test)	0.80	0.16	(26)
IGVH mutational status (per test)	101.17	20.63	(40)
Serum b2-microglobulin (per test)	1.40	0.28	(26)
Abdominal ultrasound (per test)	4.35	0.89	(26)
FISH test (per test)	6.74	1.37	(26)
Cost of peripheral smear (per test)	0.60	0.12	(26)
Price of drugs			
Ibrutinib(per mg)	1.714	0.349	(28)
Bendamustine(per mg)	18.11	3.695	(29)
Rituximab (per mg)	52.99	12.242	(30)
Chlorambucil (per mg)	16	3.265	(31)
Prednisolone (per mg)	0.082	0.016	(32)
Out of pocket expenditure (Monthly)			
Direct non-medical expenses	34.31	7	Primary data
Cost of managing adverse events (Unit cost)			
Neutropenia	109.98	22.43	Normative costing

Thrombocytopenia	2.91	0.59	Normative costing
Atrial fibrillation	24.28	4.95	(41)
Pneumonia	24.28	4.95	(41)

*₹: Indian Rupee; $: United States Dollar; CBC: Complete Blood Count; IGVH: immunoglobin heavy chain gene; FISH: Fluorescence in situ hybridization

Sensitivity analysis

A multivariable probabilistic sensitivity analysis (PSA) was undertaken for estimating the effect of joint parameter uncertainty. Under PSA, all cost parameters were assigned gamma distribution, while utility values and probabilities/proportions were assigned beta distribution. A 40% and 20% variation on either side of the base value was used for cost and clinical parameters, respectively. Based on 999 Monte Carlo simulations, median value of incremental cost-effectiveness ratio (ICER) along with 2.5th and 97.5th percentile was computed and reported. GDP per capita of $ 1965 for India in year 2020 was considered as the threshold of cost effectiveness.

Threshold Analysis

A threshold analysis was undertaken to understand the effect of varying the costs of drugs on theresults.Cost of Bendamustine, Rituximab and Ibrutinibwas decreased by 20%, 50% and 80% and the respective deterministic ICERs were compared.

Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research, India, with reference number IEC-03/20202-1565.

Results

Base case results

An absolute number of LYs and QALYs lived by a patient following treatment for CLL varied from 5.63 (4.98-6.24) to 12.57 (12.27-12.87) and 3.8 (3.22-4.46) to 9.71 (7.77-11.04), respectively, among the treatment arms included in the base case analysis (Table 3). Similarly, lifetime costs ranged from $ 4356 (3517-5441) to $ 48901 (35419- 65173) incurred on the treatment of CLL patients among the four therapeutic regimens. Compared to arm A, a CLL patient gained0.7 (0.37-1.11) to 5.9 (4.28-7.17) QALYs at an additional cost of $ 9449 (5496-14660) to $ 44,545 (31,404-60,973) following treatment with the other three treatment arms (Table 4).This resulted in an ICER ($ per QALY gained) of $ 14,071 (7474-24983), $ 4652 (3052-6837) and $ 7669 (5011-11,701) with treatment arm B, C and D, respectively, as compared to arm A. Further, the resulting ICERs were $ 1149 (440-2095) and $ 6906 (4497-10988) when treatment arms C and D were compared against arm B. Lastly, the use of treatment arm D as compared to arm C resulted in an ICER of $ 9948 (6287-16568). The cost-effectiveness plane (supplement material; Fig S1) showed that all the four treatment arms were non-dominant.

Scenario analysis

Based on model output, an absolute number of LYs and QALYs lived by a CLL patient varied from 4.19 (3.57-4.82) to 11.42 (11.17-11.69) and 2.94 (2.3-3.62) to 8.96 (7.12-10.28), respectively, following treatment with the three treatment regimes (i.e., E, F, and G) included in the scenario analysis (Table 3). A total lifetime cost of $ 1573 (1222-1984), $ 4981 (3924-6324) and $ 41342 (29118-56493) was incurred with arms E, F and G, respectively. Further, over the lifetime of CLL patients, strategies F and G led to a gain of 1.56 (1.06- 2.03) to 6.02 (4.41- 7.22) QALYs at an additional cost of $ 3407 (2486- 4666) and $ 39,768 (27,510- 54,979), respectively, compared to arm E (Table 4). This resulted in an ICER of $ 2237 (1452- 3401) and $ 6711 (4423-10,245) following treatment with arm F and G compared to arm E. Lastly, arm F compared to arm G resulted in an ICER of $ 8291 (5249-12,969). All the three treatment arms were non-dominant as shown in supplement material; fig S2.

Table 3: Discounted probabilistic median absolute outcomes of the treatment arms included in the base case and scenario analysis

Strategy	First line regimen	Second line regimen	Cost per person in $	Life years lived per person	QALYs lived per person
A	CP	BR	4356 (3517-5441)	5.63 (4.98-6.24)	3.8 (3.22-4.46)
B	CP	IBR	13,805 (9798-18,997)	6.57 (5.86-7.25)	4.51 (3.81-5.23)
C	BR	IBR	15,804 (12,090-20,602)	7.3 (6.93-7.72)	6.3 (5.39-7.11)
D	IBR	BR	48,901 (35,419-65,173)	12.57 (12.27-12.87)	9.71 (7.77-11.04)
E	CP	-	1573 (1222-1984)	4.19 (3.57-4.82)	2.94 (2.3-3.62)
F	BR	-	4981 (3924-6324)	6.09 (5.7-6.53)	4.5 (3.72-5.16)
G	Ibr	-	41,342 (29,118-56,493)	11.42 (11.17-11.69)	8.96 (7.12-10.28)

* Figures in parenthesis indicate 2.5th and 97.5th percentile; CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; IBR: Ibrutinib; $: United States Dollar; QALY: Quality adjusted life years;

Table 4 A: Discounted probabilistic incremental outcomes of the treatment arms included in the base case analysis

Incremental outcomes	Treatment arms	Comparison group		
		versus A	**versus B**	**versus C**
Incremental life years	B	0.93 (0.53-1.35)	-	Same as C versus B
	C	1.67 (0.99-2.35)	0.73 (0.23-1.24)	-
	D	6.93 (6.49-7.38)	5.99 (5.39-6.58)	5.26 (4.83-5.65)
Incremental QALYs	B	0.7 (0.37-1.11)	-	Same as C versus B
	C	2.49 (1.87-3.13)	1.78 (1.2-2.31)	-
	D	5.9 (4.28-7.17)	5.2 (3.51-6.44)	3.41 (2.27-4.26)
Incremental cost	B	9449 (5496-14660)	-	Same as C versus B
	C	11,447 (8059-15853)	1998 (865-3264)	-
	D	44,545 (31,404-60,973)	35,096 (25,087-46,766)	33,097 (22,956-45,193)
Incremental cost per QALY gained	B	14,071 (7474-24983)	-	Same as C versus B
	C	4652 (3052-6837)	1149 (440-2095)	-
	D	7669 (5011-11,701)	6906 (4497-10,988)	9948 (6287-16,568)

* Figures in parenthesis indicate 2.5th and 97.5th percentile; CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; IBR: Ibrutinib; $: United States Dollar; QALY: Quality adjusted life years

Table 4 B: Discounted probabilistic incremental outcomes of the treatment arms included in the scenario analysis

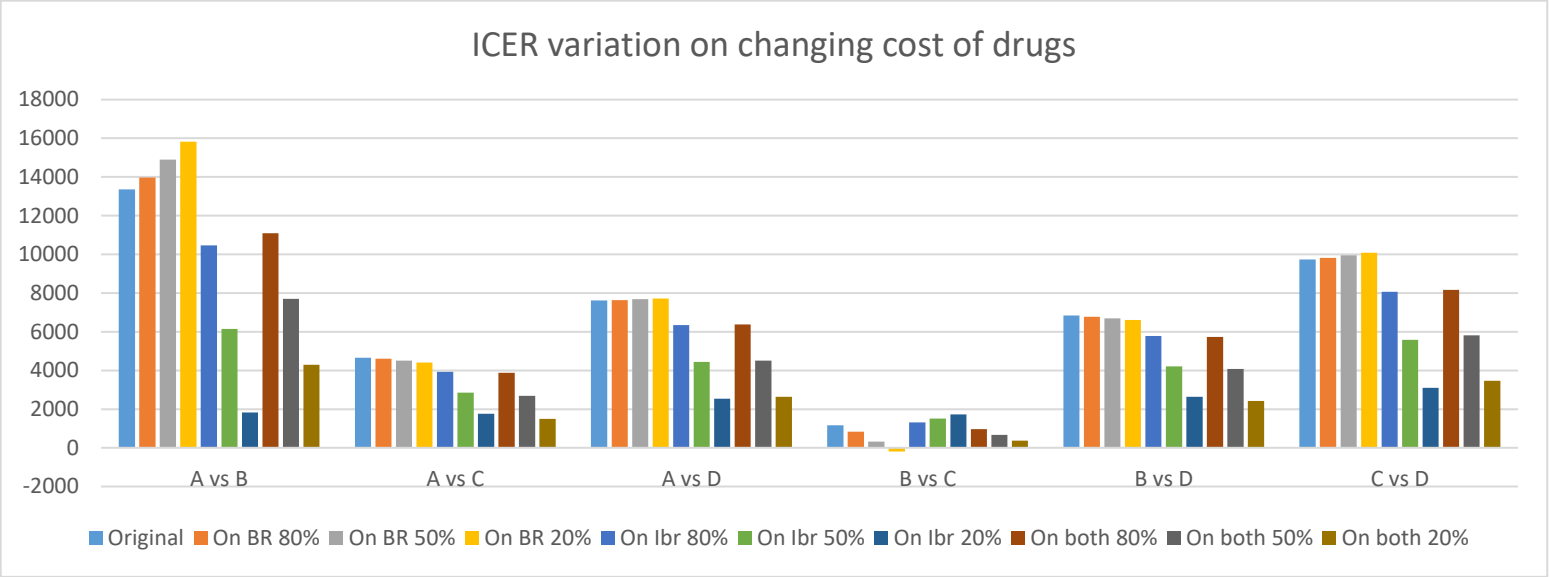
Incremental outcomes	Treatment arms	Comparison group	
		versus E	**versus F**
Incremental life years	F	1.89 (1.44-2.03)	-
	G	7.22 (6.74- 7.68)	5.32 (5.16-5.47)
Incremental QALYs	F	1.56 (1.06- 2.03)	-
	G	6.02 (4.41- 7.22)	4.45 (3.19- 5.29)
Incremental cost	F	3407 (2486- 4666)	-
	G	39,768 (27,510- 54,979)	36,361 (24,410- 51,090)
Incremental cost per QALY gained	F	2237 (1452- 3401)	-
	G	6711 (4423-10,245)	8291 (5249-12,969)

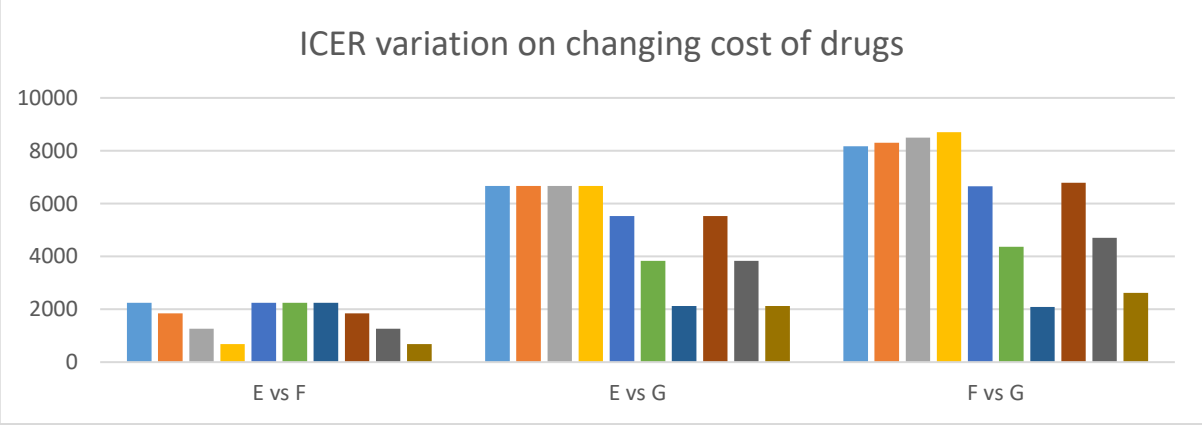
* Figures in parenthesis indicate 2.5th and 97.5th percentile; CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; IBR: Ibrutinib; $: United States Dollar; QALY: Quality adjusted life years

Threshold analysis

On decreasing the cost of Ibrutinib to 20% of current costs, treatment arms B and C become cost effective when compared to arm A.When comparing the single line treatments, on decreasing the costs of Bendamustine and Rituximab to 80% of current costs, arm F is cost-effective versus arm E. (Fig 3)

Fig. 3: Threshold analysis





Discussion

With no previous economic evaluation assessing the cost-effectiveness of anti-CLL drugs, especially from developing nations in the SEAR region, the present study was undertaken to determine the cost-effectiveness of various therapeutic regimens in treatment-naive patients of CLL in India. The results show that newer treatments regimes comprising of first-line bendamustine or ibrutinib are not cost-effective at current market prices in India. Among the various therapeutic regimens for CLL treatment included in the present study, the CP as the first line followed by BR as second-line therapy came out to be cost-effective at one time GDP per capita of India. The scenario analysis, excluding the impact of second-line therapy, also points to a similar conclusion and shows chlorambucil based regimen as a cost-effective first-line treatment in India.

Fludarabine in combination with plus cyclophosphamide and rituximab (FCR) is the standard first line treatment for CLL in the developed countries for patients who can tolerate intense chemotherapy.(36)Though FCR is also prescribed in India, but due to its high toxicity profile and cost of administration, drug regimen comprising of chlorambucil and prednisolone is the standard first line of treatment.(1)(3)Among those ineligible for FCR based regimens, economic evaluations from developed countries have shown bendamustine or chlorambucil to be cost-effective for the treatment of CLL.(8)(11) Astudy by Woods et al.from UK, concludes that bendamustine was cost effectiveas first-line treatment, when compared to chlorambucil based therapy.(8) Similarly, another study from the context of USA also concludes bendamustine as a cost-effective optionas compared to chlorambucil.(10)However, a study from Finland by Soini et al., reported that chlorambucil based therapy provided the best value for money compared to bendamustine.(11)

In contrast to the findings in the above studies, most of the economic evaluations involving ibrutinib, shows it to be notcost effective first line treatment.(9) Specifically, studies by Chen et al.(37) and Barnes et al shows first line ibrutinib for the CLL treatment to be cost-ineffective. (38) Further, a study by Patel et al. comparing first-line ibrutinib versus second line and third line ibrutinib concluded that delaying ibrutinib for later lines is a cost-effective option instead of the first-line use. (9) A cost analysis estimated that ibrutinib, when used as a first line therapy, could increase the total cost of CLL treatment

by around $ 0.3 million compared to second line therapy. Our analysis on a similar lines also shows that ibrutinib, when used as a second line therapy in treatment arm C, provides more value for money as compared to Ibrutinib as a first line therapy in treatment arm D. Thus, our study, along with the findings from previous study support the conclusion that delaying ibrutinib until later lines of therapy may be a reasonable strategy to limit healthcare costs without compromising health outcomes.(9) Patel et al also showed that using Ibrutinib for third line therapy is even more cost effective than keeping Ibrutinib as a second line therapy. Delaying Ibrutinib as a third line therapy can also be studied for its cost-effectiveness in Indian scenario as a future area of research.

Model Validation

The median survival time and survival rate of the arm E, chlorambucil alone for first line treatment was compared with the local epidemiological data from India.(3) Our study reported a median survival time of 42 months and 5-year survival rate of around 25% following treatment with Arm A. These model outcomes corroborate with the findings from an Indian prospective cohort study that reported a median survival time and 5- year survival rates of around 3.5 years and 25% respectively among those in the stage IV CLL.(3)The PFS curves for the patients on treatment with chlorambucil alone as per Hillmen et al presented around 52% patients progression free at 12 months of treatment duration which corroborates with the data in our analysis, which shows that 49% patients are progression-free at 12 months in treatment arm E.(4)

Strength and limitations

The present study is first of its kind that has comprehensively analysed and compared not only the first line anti-CLL drugs, but also assessed the cost effectiveness of various combinations of first line and second line therapies. We used a lifetime horizon that appears to be justified considering longer survival of patients with CLL. We recognize that most of the clinical parameters were assessed from the existing RCTs that had limited follow up periods. This could further lead to uncertainty regarding the long-term outcomes beyond the trial period. We used parametric survival modelling to extrapolate

post-trial time dependent probabilities, where feasible, to increase the accuracy of model outcomes. Furthermore, various sensitivity analyses were performed to measure the impact of parameter uncertainty. To simulate the real world scenario, we also considered discontinuation of first-line therapy due to specific serious AEand modelled both disutility and costs associated with these AE.

The data on quality of life and OOP expenses was assessed from National Cancer Database for Cost and Quality of Life (CaDCQoL) of India, which makes our findings more reliable. Given the nature and availability of cancer treatment in India, we also included direct non-medical cost as well. In India, the cancer treatment is available at regional specialized tertiary care facilities and is not too decentralized. Therefore, such non-medical expenditures on travel, food, accommodation contribute significantly to the total cost of cancer care. Evidence shows direct non-medical expenditures account for around 30% the total direct expenditure on cancer treatment in India.

Conclusion

Among the various therapeutic regimens included in the present study, regime comprising of Chlorambucil plus Prednisolone as first line followed by Bendamustine plus Rituximab as second line therapy is most cost effective for the treatment of CLL In India.

Supplementary material

Figure-S1: Cost effectiveness plane

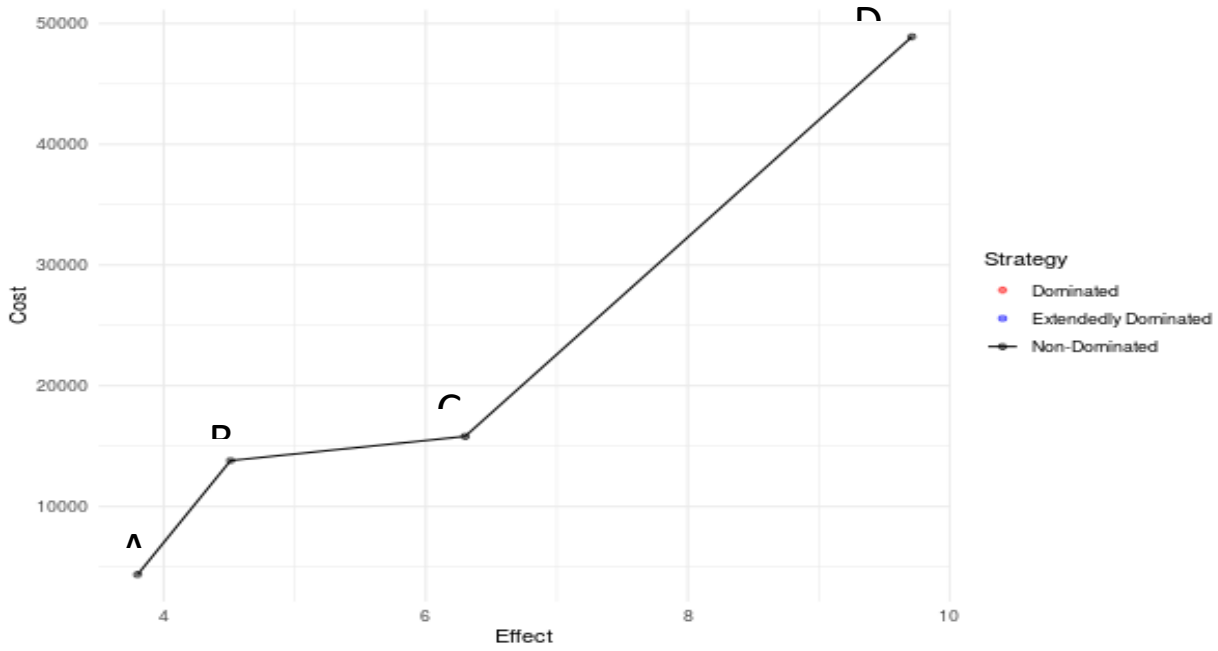
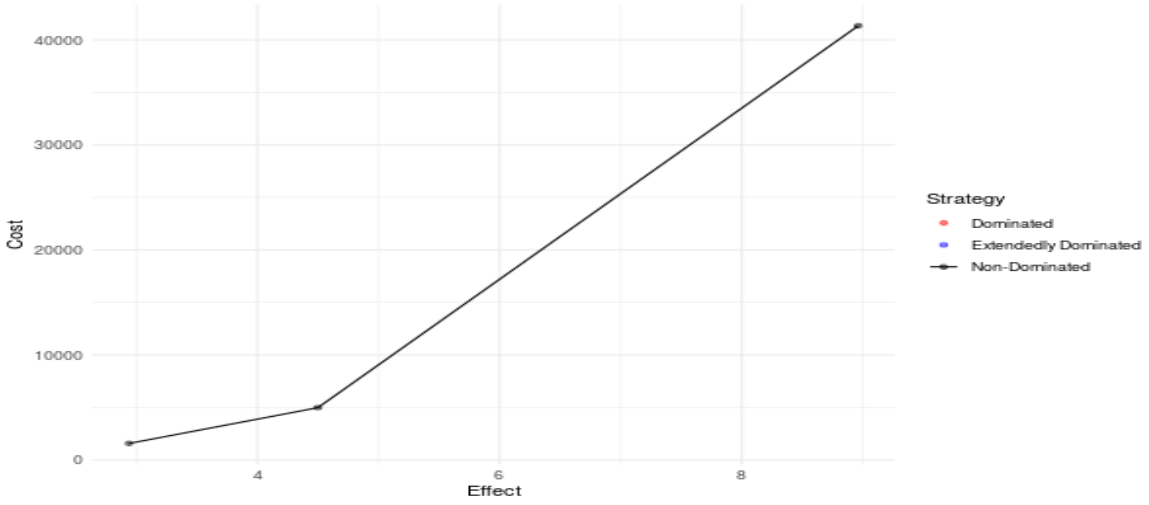


Figure- S2: Cost effectiveness plane



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Chapter 5: Cost-effectiveness of first-line Tyrosine-kinase inhibitors in the treatment of newly diagnosed Chronic Myeloid Leukaemia patients in India

Introduction

Chronic Myeloid Leukaemia (CML) is a clonal myeloproliferative disorder of a pluripotent stem cells. It is the commonest adult leukaemia in India and the annual incidence ranges from 0.8-2.2/100,000 population and 0.6-1.6/100,000 population in females in India (1). Before the advent of targeted therapies, the treatment for CML patients included cytotoxic chemotherapy (hydroxyurea, cytarabine) or Interferon-α. The introduction of tyrosine-kinase inhibitors (TKIs) such as Imatinib, has drastically changed the treatment and natural history of the disease with an improvement in the 5-year survival rate from approximately 20% to over 90% (1,2). The tyrosine kinase inhibitor (TKI) imatinib was approved in 2001 to treat incident chronic myeloid leukemia in chronic phase (CML-CP) and has been shown to produce a high cumulative incidence of complete cytogenetic responses (CCyR) (3,4). Imatinib is also associated with improved survival. After eight years, the overall survival (OS) on the International Randomized Study of Interferon vs imatinib (the IRIS trial) was 85% for patients treated with imatinib, and their freedom from progression to accelerated phase or blast crisis (AP/BC) was 92% (5). In the past decade, second-generation TKIs such as Dasatinib and Nilotinib have demonstrated efficacy for treating incident CML-CP and were therefore granted approval for the first-line treatment of CML-CP globally (6,7). The second-generation TKIs produce more rapid molecular responses than imatinib at standard doses of 400 mg daily, but five-year OS does not differ between the three TKIs (6–8).

Most incident CML-CP patients require life-long, daily TKI-based care. This causes an immense financial burden on the cancer patients and their families. The launch of generic imatinib in the market, reimbursement of imatinib in the health benefit package (HBP) and introduction of Glivec International Patient Assistance Program (GIPAP) have provided some relief to the patients in terms of better health outcomes at lower costs. But, there is still a significant financial burden on the patients incurring immense Out-of-Pocket (OOP) expenditure especially in low-middle income countries such as India (9).

Along with Imatinib, Dasatinib is also a part HBP under India's publicly financed national health insurance scheme – *Ayushman Bharat* Pradhan Mantri Jan Aarogya Yojana (ABPM-JAY) (10). Therefore, the health system spending on incident CML-CP after generic versions of TKIs (Imatinib and Dasatinib) becomes available is the subject of great interest among patients, physicians, and payers. Loss of patent exclusivity opens the market to potential competition from multiple manufacturers. Thus, it becomes important to compare both the costs and consequences associated with different treatment strategies to make informed policy and clinical decisions. In this study, we aimed to determine the most cost-effective tyrosine-kinase inhibitors (Imatinib, Nilotinib and Dasatinib) for newly diagnosed CML-CP patients from a societal perspective in the Indian context.

Methodology

Overview of the Analysis

A Markov cost-effectiveness model was developed to determine the lifetime cost and consequences in newly diagnosed CML patients in chronic phase from the societal perspective in the Indian context. The methodological principles were consistent with the guidelines for conducting economic evaluation provided by India's health technology assessment (HTA) agency (11). We aimed to compared the 3 most commonly used first-line TKIs for the treatment of newly diagnosed CML patients – Imatinib, Dasatinib and Nilotinib. A lifetime horizon was used to measure the health care costs and consequences in the different treatment arms. All future costs and outcomes were discounted at the rate of 3% (11). We followed the methodological guidelines as provided by 'Indian Reference Case' for conducting economic evaluations (11). The study findings are reported as per the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (12).

Model structure

A Markov state-transition model was developed in Microsoft Excel to estimate the lifetime costs and consequences for the newly diagnosed CML patients in India (Figure 1). The model consists of the following 3 health states: (1) Progression-free state; (2) Progressed disease; and (3) death. The model uses monthly cycles with probabilities for the likelihood of a health state transition. A monthly cycle length was considered based

on the follow-up schedule of the three treatment arms. Life expectancy (life years, LYs), quality-adjusted life years (QALYs), and the associated direct medical and non-medical costs were the primary outcomes. Incremental cost-effectiveness ratios (ICERs) were calculated and expressed as cost per additional QALY gained.

All newly diagnosed CML patients in the chronic phase enter the model in the PFS health state, wherein they receive one of the three TKI options. Subsequently, the patient can either stay in PFS or progress to PD or die due to natural cause. It is assumed that 70% of the PD patients are in the Accelerated Phase (AP) and 30% are in the Blast crisis (BC). The patients in PD remain in the same health state until death. The patients are put on subsequent second-line therapy in the PD health state. No disease-specific mortality was assumed in PFS state, whereas in the PD state, deaths both from AP, BC and all-cause were assumed. The patient enters the model at age of 45 years as per the Indian epidemiological evidence, which is almost a decade earlier than the western literature (13).

Treatment arms and scenarios

All newly diagnosed CML-CP patients were assumed to start with one of the following treatments: (1) Imatinib 400mg once daily; (2) Nilotinib 300mg twice daily; and (3) Dasatinib 100mg once daily.

Valuation of consequences

In this present study, the lifetime consequences were measured in terms of LYs and QALYs. The transition probabilities to move from PFS to PD health state was obtained from published studies (7,14,15). The data on 5-year PFS rates was extracted from literature and then converted to monthly transition probabilities using standard methods (16). Age specific all-cause mortality rates were obtained from the Sample Registration System (SRS) lifetables (17). Disease mortality rate for PD state for the Imatinib and Nilotinib arms were obtained from published Indian studies (18,19). For the Dasatinib arm, we obtained the survival data from the respective DASISION clinical trial comparing the long-term efficacy of Dasatinib and Imatinib in CML-CP patients (6). The obtained survival probabilities were then adjusted using a gradient to estimate the probability to die among the patients in PD health state (Accelerated and blast Phase).

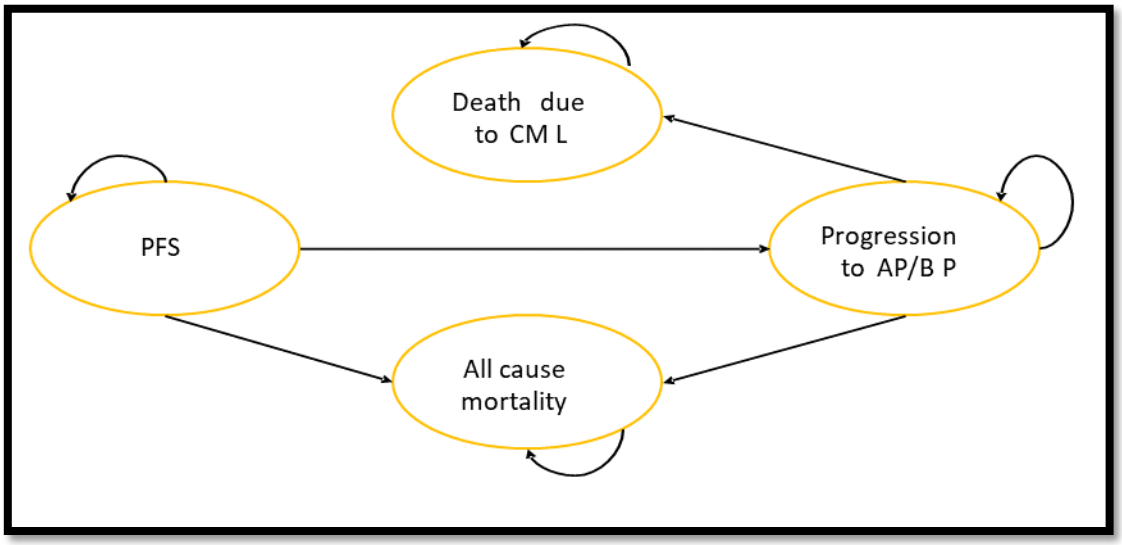

Figure 2: Schematic diagram for the Markov state transition model. PFS: Progression-Free State; PD: Progressive Disease

Table 1: Effectiveness parameters for all the treatment arms

Input variable	Imatinib	Nilotinib	Dasatinib	Source
Clinical Effectiveness				
Probability to move from PFS to PD	0.0048 (0.0038-0.0057)	0.0012 (0.0009-0.0015)	0.0027 (0.0022-0.0032)	(7,14,15)
Probability of dying: Accelerated phase	0.0029 (0.0021-0.0038)	0.0022 (0.0016-0.0029)	0.0017 (0.0012-0.0022)	(15,18,19)
Probability of dying: Blast crisis	0.0075 (0.0053-0.0098)	0.0057 (0.004-0.0074)	0.0044 (0.0031-0.0058)	(15,18,19)
Proportion of PD patients in Accelerated phase	0.70 (0.63-0.77)	0.70 (0.63-0.77)	0.70 (0.63-0.77)	Expert opinion
Proportion of PD patients in Blast crisis	0.30 (0.23-0.37)	0.30 (0.23-0.37)	0.30 (0.23-0.37)	Expert opinion
Utility Parameters				
PFS (without AEs)	0.927 (0.880-0.973)	0.927 (0.880-0.973)	0.927 (0.880-0.973)	Primary data
PFS (with AEs)	0.808 (0.646-0.970)	0.808 (0.646-0.970)	0.808 (0.646-0.970)	Primary data
PD: Accelerated phase (without AEs)	0.891 (0.802-0.980)	0.891 (0.802-0.980)	0.891 (0.802-0.980)	Primary data
PD: Accelerated phase (with AEs)	0.777 (0.621-0.932)	0.777 (0.621-0.932)	0.777 (0.621-0.932)	Primary data

PD: Blast crisis (without AEs)	0.588 (0.470-0.706)	0.588 (0.470-0.706)	0.588 (0.470-0.706)	Primary data
PD: Blast crisis (with AEs)	0.513 (0.410-0.615)	0.513 (0.410-0.615)	0.513 (0.410-0.615)	Primary data

PFS: Progression-free survival; PD: Progressive disease; AEs: Adverse events

Baseline utility values for each health state (PFS and PD, including AP and BC phases) were obtained from the primary data being collected as the part of a multicentric study on out-of-pocket and quality of life of cancer patients in India (20). We used the Indian tariff values to obtain the health state-specific quality of life scores (21). The primary data was obtained from 602 CML patients in different phases. We also incorporated the effect of adverse events due to the treatment in both the PFS and PD health state. The baseline utility values for the CP, AP and BC stages were adjusted using a gradient to estimate the final utility values for each health state with and without AE.

Cost of treatment of CML

In this study, the costs were estimated from a societal perspective for all the treatment arms. Productivity losses incurred by the patient and their caregivers due to the cancer treatment was not taken in account. This is accordance with the guidelines for base case analysis as per the Indian reference case for health technology assessment (11).

We have used the reimbursements rates set up as the part of India's publicly funded national health insurance scheme (ABPM-JAY) for the Imatinib and Dasatinib treatment arms. The reimbursement rate is inclusive of chemotherapeutic agents, recurring investigations, day care charges, supportive care, doctor and nursing charges. In addition, the direct non-medical expenditure (including travel, boarding/lodging, food, informal payment etc) were added to estimate the societal cost. For the Nilotinib arm, the cost of the treatment included the drug acquisition costs, direct patient-level OOP expenditure (including user fees, travel, boarding/lodging, food, informal payment etc.), management of grade 3-4 AEs and cost of routine follow-up was incorporated. Routine follow-up cost included cost per outpatient consultation, cost of day-care visit, routine laboratory investigations and diagnostic tests (Table 1). Separate incidence rates for each grade 3-4 AEs were applied for all the arms using the published literature (15,19,22). There are some important considerations we took into account for cost calculations. Firstly, we assumed that in cycle 0, only the cost of diagnostics and direct OOP expenditure will be

applied and not the cost of the drugs and management of adverse effects among PFS patients. Secondly, the cost of routine laboratory and diagnostic tests were applied after every 6 months as per the standard treatment guidelines (23).

For patients in PD health state, Imatinib was given to first-line Nilotinib and Dasatinib patients and meanwhile, Dasatinib was given to patients who progressed on first-line Imatinib treatment. We, therefore, applied the reimbursement rates as per the HBP. We assumed that the patients will be on the second-line therapy till death as per the standard treatment guidelines.

Health system cost per outpatient consultation was elicited using data from nationally representative 'National Health System Cost Database (NHSCD)' (24). The data on OOP expenditure were estimated from primary data collected as a part of the ongoing larger multi-centric 'National Cancer Database for Cost and Quality of Life (CADCQoL)' (20). The data were collected using standardised questionnaire from patients recruited in outpatient and inpatient setting in cancer centres located in six different Indian states. The data were analysed to compute both direct medical (user fees/procedure charges incurred on outpatient consultation) and non-medical expenditures (travelling, food, boarding/lodging, informal payment, others etc.). We used the reimbursement rates (25) and market prices for estimating expenditures on drugs. For the diagnostic services, we used the provider payment rates from a publicly financed national insurance scheme for central government employees i.e. Central Government Health Scheme (CGHS) (26). All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 75.2 for the year 2022.

Table 2: Input cost parameters

Input Parameter	Cost per cycle (in ₹)	Distribution	Source
Cost of Drugs			
Tab. Imatinib 400mg	1,375 (687-2,062)	Gamma	(25)
Tab. Nilotinib 300mg	18,214 (9,107-27,321)	Gamma	Market price
Dasatinib 100mg	5,500 (2,750-8,250)	Gamma	(25)
OOPE			
OOPE per OPD consultation*	1,677 (834-2,516)	Gamma	Primary data
OOPE: User fees	70 (35-105)	Gamma	Primary data
Total cost of diagnostics before treatment initiation	16,207 (8,103-24310)	Gamma	(26)

OOPE: Out-of-Pocket Expenditure
**Includes the OOP expenditure on travel, food, boarding/lodging, informal payments etc.*

The comparative cost effectiveness was assessed in terms of incremental cost per QALY gained (27). A willingness to pay (WTP) threshold equal to per capita gross domestic product (GDP) of India was used to assess the cost-effectiveness as per the guidelines for health technology assessment in India (20,38). The per capita GDP of India for the year 2020-21 was ₹144,963 (US$ 1,927.7).

Sensitivity and Threshold Analysis

A probabilistic sensitivity analysis (PSA) was undertaken to test the parameter uncertainty for each scenario. Under PSA, we used gamma distribution for cost parameters and beta distribution for parameters related to effectiveness, risk of complications, overall survival and utility scores. For rest of the parameters in the model, we used uniform distribution. Uncertainty ranges for input parameters were computed from the standard error estimates from the primary data, or data available in the literature. Wherever the measures of dispersion were not available, a variation of 20% for clinical parameters; 30% variation for mortality risks, utility scores and treatment patterns; and 50% variation for cost parameters was assumed on either side of base parameter values. Model results were simulated 1000 times and median value (ICER) along 95% confidence interval was generated for base estimates using percentile method.

An extended dominance analysis was undertaken in which each treatment arm was compared against the next best alternative to assess the comparative cost-effectiveness between various treatment arms.

A univariate price threshold analysis was also undertaken at various prices for pazopanib arm so as to determine the rate at which pazopanib is a cost-effective treatment option at a WTP threshold of 1-time per capita GDP (₹ 144,963) for India.

Results

Costs and outcomes

A newly diagnosed CML-CP patient incurred a total lifetime cost of ₹ 746,939 ($ 9,933), ₹ 1,147,877 ($ 15,264), and ₹ 3,590,493 ($ 47,746) for Imatinib, Dasatinib and Nilotinib treatment arms respectively. The overall mean LYs lived with Imatinib, Dasatinib and Nilotinib were 13.98, 15.52 and 15.18 respectively. In terms of utility measures, this translates into 11.61, 13.68 and 13.30 QALYs respectively.

Cost-effectiveness

Imatinib, Dasatinib and Nilotinib were found to be non-dominant treatment strategies for the newly diagnosed CML-CP patients in India. Imatinib incurred an average cost of ₹ 64,323 ($ 855) per QALY lived which is cost-effective at the current WTP threshold of 1-time per capita GDP of India. Dasatinib patients incurred an incremental cost of ₹ 2,37,583 ($ 3,159) per QALY gained as compared to Imatinib treatment arm. Further, Nilotinib incurred an incremental cost of ₹ 6,499,642 ($ 86,431) per QALY gained as compared Dasatinib treatment arm. Both, Dasatinib and Nilotinib are not cost-effective at the current WTP threshold of 1-time per capita GDP in the Indian context.

Table 3: Base-case discounted cost and consequences for different treatment strategies for CML

Outcome variable	Imatinib	Nilotinib	Dasatinib
LYs	13. 98 (13.55-14.42)	15.52 (15.33-15.70)	15.18 (14.92-15.42)
QALYs	11.61 (10.63-12.47)	13.68 (12.90-14.30)	13.30 (12.59-13.93)
Total costs	746,939 (603,282-1,245,220)	3,590,493 (2,393,244-5,274,825)	1,147,877 (880,025-1,861,636)

LYs: Life-years; QALYs: Quality adjusted life-years

Table 4: Cost-effectiveness of different tyrosine-kinase inhibitors for CML-CP patients in India

Treatment strategy (in ₹)	Cost (in ₹)	QALYs	Incremental cost per QALY gained (in ₹)	Interpretation
Imatinib	746,939	11.61	-	Non-dominated
Dasatinib	1,147,877	13.30	237,583	Non-dominated
Nilotinib	3,590,493	13.68	6,499,642	Non-dominated

QALYs: Quality adjusted life-years

Sensitivity and Threshold Analysis

In the probabilistic sensitivity analysis, Dasatinib has a 27.7% probability of being cost-effective at the current WTP threshold of 1-time per-capita GDP of India. Whereas, there is 2.9% probability for nilotinib to be cost-effective in the Indian context (Figure 2).

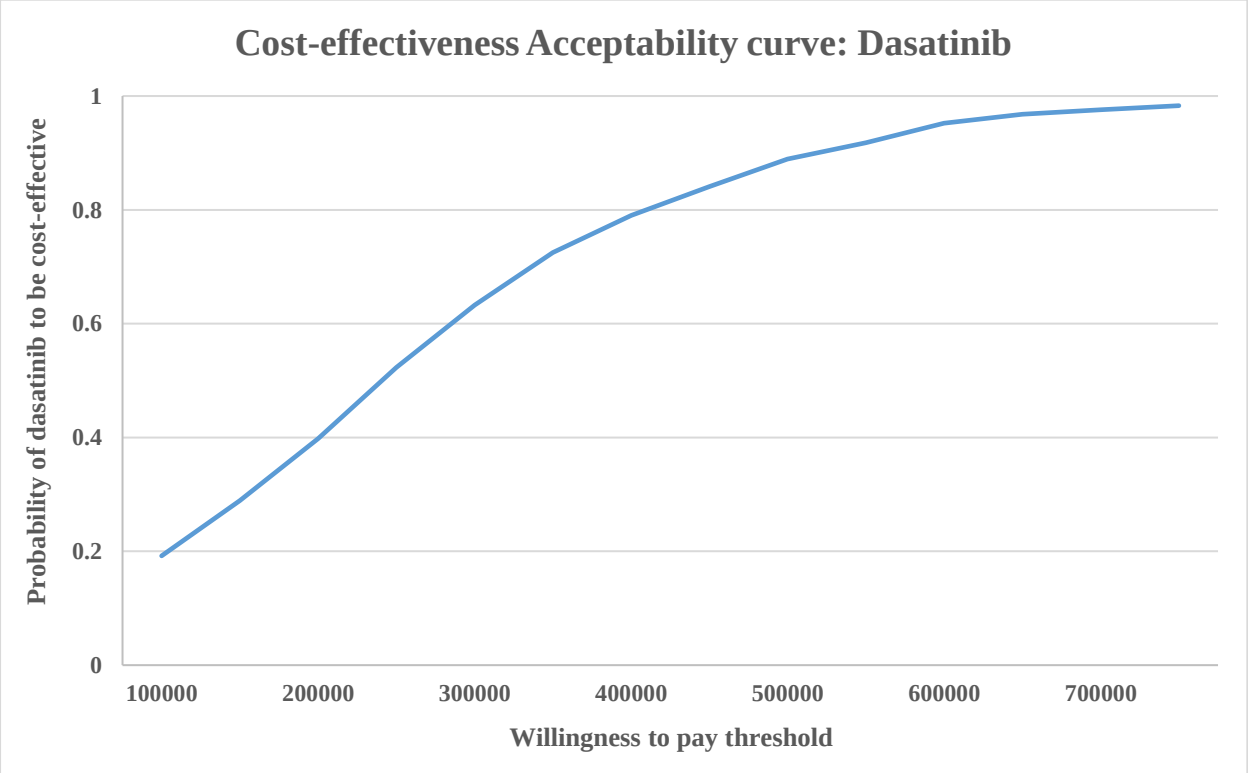

Figure 3: Cost-effectiveness Acceptability curve: Dasatinib

A 21% reduction in the reimbursement rate of Dasatinib (from ₹ 5,500 to ₹ 4,345) will make it a cost-effective treatment option as compared to Imatinib at the current WTP threshold of 1-time per capita GDP in the Indian context (Figure 3).

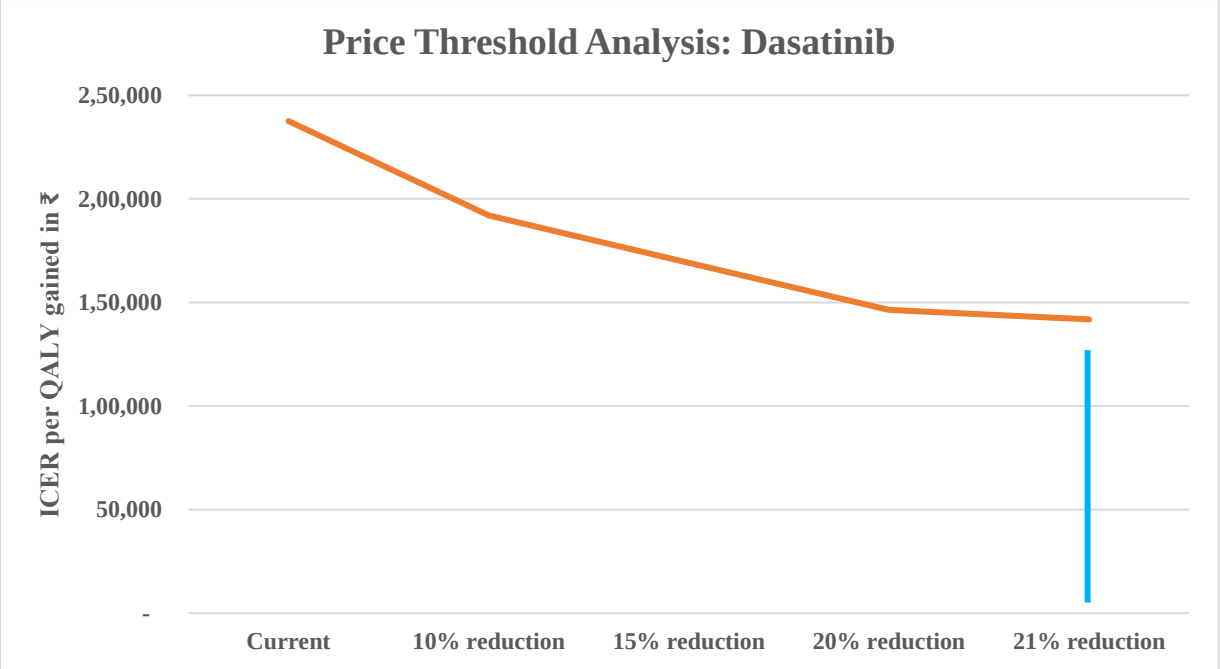

Figure 4: Price threshold Analysis for Dasatinib

Discussion

In this study, we aimed to determine the most cost-effective first-line TKI for the treatment of newly diagnosed CML-CP patients in India. We estimated that Imatinib is the most cost-effective treatment option for CML-CP patients with an average cost of ₹ 64,323 ($ 855) per QALY lived. This is followed by Dasatinib which incurs an incremental cost of ₹ 2,37,583 ($ 3,159) per QALY gained as compared to Imatinib which is not cost-effective in the Indian context. However, a 21% reduction in the reimbursement rate of Dasatinib in the India's publicly financed national health insurance scheme will make it a cost-effective treatment option from the societal perspective for the Indian CML-CP patients.

Model validation

Our study estimates are concurrent with the existing published epidemiological and clinical literature. Our study estimated a 5-year OS among Imatinib arm to be 94.5%. Various retrospective studies report 5-year OS ranging from 88.5-95% in the Indian setting (14,28,29). The 5-year PFS for Imatinib patients is estimated to be 73.1% in our study which is in line with the 72% 5-year EFS reported in another Indian retrospective study (28).

Similarly, in our study, we estimated that LYs gained in Imatinib, Nilotinib and Dasatinib arms to be 13.98, 15.52 and 15.18 respectively. These findings are concurrent with those reported by Shin M et al. which estimated 14.52, 15.13 and 15.18 LYs among Imatinib, Nilotinib and Dasatinib patients respectively (30). Similarly, Romero M et al. report 14.91 and 15.21 LYs among Dasatinib and Nilotinib patients respectively (31).

We would like to mention certain highlights of this study. Firstly, this is the first study in the context of developing country like India, which compares both the costs and consequences associated with the three most commonly used TKIs (i.e., Imatinib, Dasatinib and Nilotinib) in a single analysis. Secondly, we used the primary data with regard to both costs and quality of life from an ongoing multicentric CADCQoL database which makes the results highly useful and representative for India (20). The study also makes use of Indian tariff values to obtain the QoL scores with respect to the stage of the disease (i.e., Chronic, Accelerated or Blast Phase) (21).

There are certain limitations in this analysis. Firstly, due to lack of availability of published Indian literature for Nilotinib and Dasatinib treatment arms, we considered the 5-year PFS rates reported in their respective randomised controlled trials. Secondly, we assumed a constant probability for a patient to transition from PFS to PD health state instead of time-specific monthly transition probabilities and extrapolating the survival curves. This was done due to lack of availability such PFS curves in the Indian context. Finally, we only took into account the treatment naïve and newly diagnosed CML patients in chronic phase. We did not consider subgroups such as imatinib-resistant, patients diagnosed in advanced stages, relapsed CML patients etc. Further research can be done to incorporate these important subgroups wherein further dose modifications and treatment strategies need to be opted.

Conclusions & Policy Implications

In this study, we tried to determine the most cost-effective first-line treatment for the newly diagnosed CML-CP patients in India from a societal perspective. We can safely

conclude that Imatinib is the most cost-effective first-line treatment option in the Indian context as per the reimbursement rate under India's publicly financed national health insurance scheme. Furthermore, Dasatinib provides better health outcomes than Imatinib and a 21% reduction in the current reimbursement rate would make it a cost-effective treatment option for the Indian CML patients.

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Chapter 6: Cost Effectiveness of Bevacizumab Plus Chemotherapy for the Treatment of Advanced and Metastatic Cervical Cancer in India – A Model-Based Economic Analysis

Introduction

Cervical cancer is the 4th and 2nd most common cancer affecting women globally, and in low and middle income countries (LMICs) respectively.(1)(2) South East Asia Region (SEAR) contributes to around 33% of the global cases and mortality caused by cervical cancer; India alone accounts for around 65% of this burden.(1)(2) Most of the cervical cancer cases in India are diagnosed in locally advanced stage (83% FIGO stage II–IVA).(3) Nearly 15% to 61% of affected women will develop recurrence or metastasis usually within the first 2 years of completing the treatment.(4)

Patients with advanced (recurrent and persistent) and metastatic cervical cancer usually have a poor prognosis with 1-year survival rate between 10-15%.(5) Presently, doublet chemotherapy of cisplatin and paclitaxel is recognized to be the standard of care for the management of these patients.(6) However, as a result of acquired resistance associated with the prior exposure of the platinum-based chemo-radiotherapy for locally advanced disease, response rates with cisplatin-based therapy are poor.(7) Recently, an antiangiogenic humanized monoclonal antibody drug bevacizumab, an inhibitor of vascular endothelial growth factor (VEGF), has shown to improve the survival of patients with advanced cervical cancer.(6) The only randomized controlled trial i.e., Gynecologic Oncology Group (GOG) 240 trial, has shown that the addition of bevacizumab to the chemotherapy significantly improves both the progression free survival (8.2 months versus 6.0 months), as well as overall survival (17 months versus 13.3 months) in advanced and metastatic cervical cancer patients.(8) The trial also showed that use of bevacizumab was associated with toxicities like hypertension, thromboembolism and gastrointestinal or genitourinary fistulas.

A new drug with increased effectiveness may also be associated with increase in health care cost. The cost of incorporating bevacizumab to standard chemotherapy is around 13 times higher than that of chemotherapy alone.(7) With limited budgets allocated to

health care sector, it becomes essential to ascertain whether the incremental cost is worth the potential health gains with a newer drug. Previous economic evaluations undertaken in the United States (US) reported that incorporating bevacizumab with routine chemotherapy for treatment of advanced and metastatic cervical cancer is not cost-effective.(7)(9)

In terms of analytical approach, one of these studies used a static model that did not take into account the transition among various health states.(9) The Markov model used in other study did not include all the necessary health states that could influence the outcome of the study.(7) In view of the methodological limitations of previous economic evaluations,(7)(9) and limited generalizability of the US evidence, we undertook the present study to assess the cost effectiveness of bevacizumab plus standard chemotherapy as compared to chemotherapy alone for the treatment of advanced and metastatic cervical cancer in India.

Methodology

Model overview

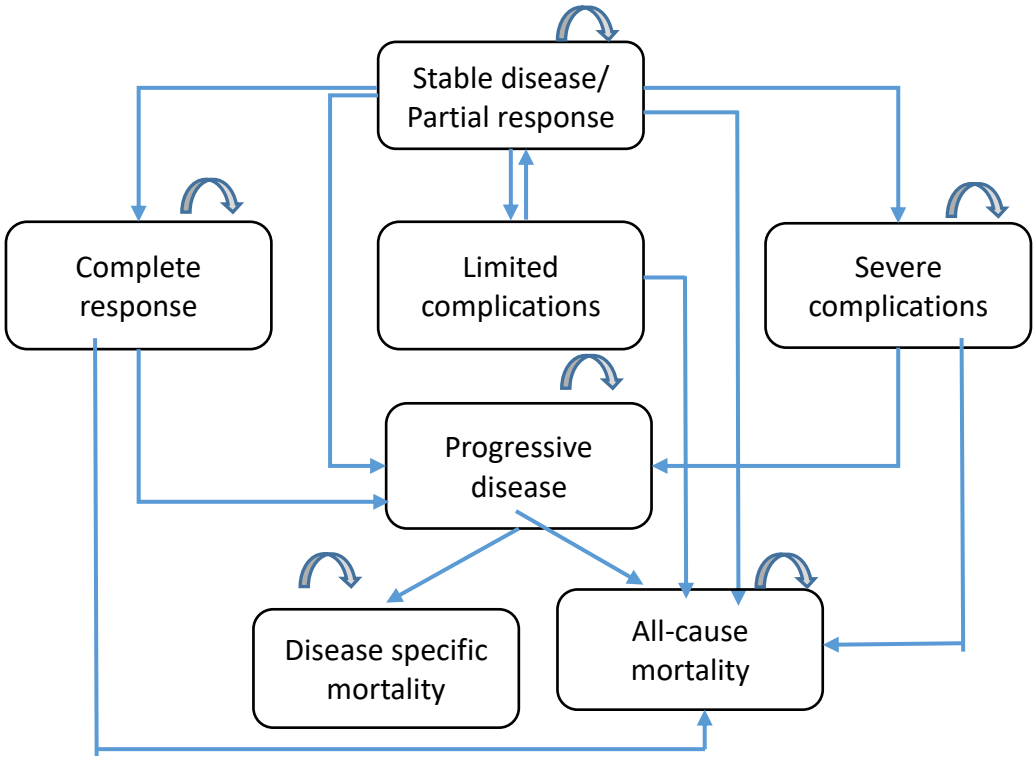
A Markov model was developed for estimating the lifetime costs and health consequences in a hypothetical cohort of 1000 patients in advanced and metastatic cervical cancer treated with either chemotherapy alone or chemotherapy in combination with bevacizumab. In cases of chronic diseases where patients move through different health states, like complete response, limited complications, severe complications, before entering progressive disease or death, a Markov model allows a possibility to move between different health states and is much better suited than a decision tree which is more suitable for acute conditions with unidirectional movement. Secondly, since the overall survival is short, and there are several other health states such as severe complications, a partitioned survival model does not offer any significant advantage. The Markov model also allows us to estimate costs and utilities using a hypothetical cohort when individual patient level data is not available. Similar methods have been used in cost-effectiveness analyses for cervical cancer interventions.(7)(10) The health outcomes were evaluated in terms of life years (LY) and quality adjusted life years (QALY) lived. All the future costs and consequences were discounted at a rate of 3%.(11)(12) The present analysis was based on a disaggregated societal perspective in which both the health

system cost and patient level out of pocket expenditure (OOPE) was incorporated.(13) We did not include the indirect cost due to productivity losses. The cost effectiveness was assessed in terms of incremental cost effectiveness ratio (ICER) between the intervention and control arm.

The Markov model simulates patient's clinical progression during treatment and comprises of 5 health states (Fig.1). It starts with patients in the 'stable disease' assumed to be receiving treatment with either of the therapeutic regimen. Based on the standard guidelines,(14) we assumed that standard chemotherapy or the combination with bevacizumab were repeated at 21 days interval until 'disease progression', development of 'severe complications' or attaining 'complete response'. The cycle length of the model was assumed to be one month by rounding up the 21-day interval. The treatment is halted only for a month for those who develop 'limited complications', during which, the patients are assumed to recover following management of the complications. The patients with 'complete response' or 'severe complication' may further progress to develop 'progressive disease'. Finally, disease specific death due to cervical cancer is observed after 'progressive disease'. Additionally, all-cause mortality is also assumed from all the 5 health states.(15)

The model starts with patients at 55 years of age, the median age of diagnosis for cervical cancer in India.(3) Based on the clinical evidence, we assessed 'complete response' after completion of a minimum of 6 treatment cycles.(14) Limited complication included grade 2 or higher hypertension, while grade 3 or higher thromboembolism and grade 3 fistula (both genitourinary and gastro-intestinal) represented the severe complications. In addition, nausea/vomiting and grade 4 or higher neutropenia were also modeled as acute side effects to either of the treatment regimen.(7)(8) The management of complications and acute side effects was as per standard treatment guidelines of India.(16) Patients in the 'progressive disease' received palliative care for pain management, vaginal discharge and vaginal bleeding.(16)

Fig. 1: Model Structure



Control and intervention arms

Based on the current standard of care for advanced cervical cancer cases in India,(8)(14) the control arm comprised intravenous regimen of cisplatin (50mg/m^2 on day 1) along with paclitaxel (175 mg/m^2 on day 1). In intervention arm, intravenous bevacizumab (15mg/kg on day 1) was added to the combination of cisplatin and paclitaxel.

Clinical parameters and utility values

Estimates of monthly transition probabilities (Table 1) were derived from GOG 240 trial(8)(17). Based on the method mentioned in Keller et al.,(18) the monthly probability of achieving a complete response or developing limited or severe complications was calculated by dividing the respective number of patients by the total number of patients in progression-free state (1416 for patients in intervention arm and 1148 for control arm) throughout the 30 month trial period.(8)(18)

Due to lack of stratified health-state specific data on the probability of progression from complete response or stable disease/partial response, we assumed to use a similar rate of progression from either of these health states. The monthly probability of progression

was derived from progression free survival (PFS) curves reported in GOG 240 trial.(17) We assumed a 90% probability of moving into a progressive disease after developing a severe complication.(18) The probability of disease specific mortality was derived from a study reporting stage-specific mortality rates following treatment for cervical cancer from India.(5) Lastly, we used the age-specific all-cause mortality rate as reported in the Sample Registration System (SRS) life tables for the female population of India. Utility values for different health states were obtained by analysing the data collected from 202 cervical cancer patients 6 large cancer hospitals in India, as part of the Cancer Database for Cost and Quality of Life (CaDCQoL).(19) The patients were administered the EQ-5D-5L tool to measure the health-related quality of life (HRQoL). The Indian tariff values were used to calculate the index utility score for different health states.(20) Since there were not enough sample of patients in Partial Response health state, we estimated the utility value for the same by applying the gradient of utility between the health states of 'Response' and 'Limited complications' obtained from published literature.(Table 1)(7)

Costs of treatment

The present analysis included both the health system (HSC) cost as well as the OOPE incurred during the duration of treatment. The HSC accounted for the outpatient (OPD) consultations, diagnostics, day care, inpatient stay, etc. Similarly, the OOPE included expenses incurred on travel, boarding/lodging, food, and user fee. Since the cost of drugs and diagnostics were assessed as part of HSC, we excluded them from OOPE to avoid double counting. The unit health system costs were derived from the previously undertaken costing studies from India (Table 2).(21)(22) For those diagnostics and services, where published cost data was not available, estimates from the reimbursement rates of the national social insurance scheme for central government employees of India were used.(23)(24) Price of medicines (inclusive of bevacizumab, cisplatin and paclitaxel) was assessed from the approved listed procurement prices of Rajasthan Medical Services Corporation- a large State Government purchaser organization.(25)

The quantity of various health services, diagnostics, and utilities consumed by patients in the various health states (both in the control and intervention arm), was multiplied with the unit cost of these services to estimate the cost of the cancer management at each monthly cycle till lifetime horizon. This cost included the initial baseline cost of diagnostics, delivery of therapeutic regimen, follow-up sessions, management of

complications (and adverse effects) and the cost of palliative care. The information on type and quantity of health services (including diagnostics) utilized by the patient in a particular health state was derived based on the standard guidelines and clinician's expert opinion.(14) The cost of the drugs in the intervention and control arm was calculated by multiplying the required dosage for each drug with the price of that drug, assuming an average weight and height of 55 kg and 162 cm for an Indian female.(26)

All the cost estimates in the present study pertains to the base year of 2020. The unit costs that were derived from the previous studies were inflated accordingly, based on the GDP deflator indices for India.(27) Cost estimates are presented both in Indian Rupees (₹) as well as United States Dollar (US$). Conversion rate for the year 2020 of 1 US$ = 74.13 ₹ was used.(28)

Table 1: Model Input parameters

Parameters	Value (SE)	Source
Monthly transition probabilities for the control arm		
Stable disease/partial response to complete response	0.0148 (0.0015)	(17)
Stable disease/partial response to limited complications#	0.0035 (0.0003)	(17)
Stable disease/partial response to severe complication#	0.0043 (0.0004)	(17)
Stable disease/partial response or complete response to progressive disease	0.1420 (0.0145)	(17)
Severe complications to progressive disease	0.90 (0.0918)	(7)
Progressive disease to disease specific mortality	0.1680 (0.0171)	(5)
Monthly transition probabilities for the intervention arm		
Stable disease/partial response to complete response	0.0219 (0.0022)	(17)
Stable disease/partial response to limited complications#	0.0389 (0.0039)	(17)
Stable disease/partial response to severe complication#	0.0218 (0.0022)	(17)

Stable disease/partial response or complete response to progressive disease	0.0789 (0.0080)	(17)
Severe complications to progressive disease	0.90 (0.0918)	(7)
Progressive disease to disease specific mortality	0.1680 (0.0171)	(5)
Age-specific all-cause annual mortality rates, years		
55-59	0.0103 (0.0010)	(15)
60-64	0.0163 (0.0016)	(15)
65-69	0.0251 (0.0025)	(15)
Health state utility values (Quality of life)		
Stable disease	0.406 (0.0414)	c
Partial response	0.521 (0.0531)	b
Complete response	0.694 (0.0708)	c
Limited complications	0.304 (0.0310)	c
Severe complications	0.213 (0.0217)	c
Progressive Disease	0.213 (0.0217)	c

*****Limited complications include hypertension; severe complications include thromboembolism and fistula (both genitourinary and gastro-intestinal fistula)
'a' denotes that cost was derived based on normative costing using standard treatment guidelines and expert opinion; 'b' denotes percentage gradient of response to limited complication from literature Minion et al.(7); 'c' denotes CaDCQoL study data used CBC: Complete blood count; LFT: Liver function test; RFT: Renal function test; STG: standard treatment guidelines; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; ₹: Indian rupee; US$: United States Dollar

Table 2: Cost Parameters

Parameters	Value (SE)		Source
Health system cost	₹	**US$**	
Out-patient consultation (per visit)	639 (131)	9 (2)	(21)
Day care for chemotherapy (per visit)	1038 (111)	14 (1.5)	(22)
Inpatient care (per bed day)	3207 (655)	43 (9)	(21)

PET scan	14,663 (1693)	198 (23)	(23)
Chest X-Ray	60 (7)	0.81 (0.09)	(23)
CT Chest	4500 (519)	61 (7)	(23)
CT Abdomen	4500 (519)	61 (7)	(23)
MRI Abdomen	5000 (1020)	67 (14)	(24)
CBC+RFT+LFT	585 (119)	8 (1.6)	a
CBC+RFT	360 (73)	5 (1)	a
Biopsy	1362 (145)	18 (2)	(22)
Coagulogram	553 (113)	7.5 (1.5)	(24)
Out of pocket expenditure			
User Fee (per visit)	279 (56.9)	3.7 (0.76)	c
Other direct non-medical expenditure (per visit)	1,509 (172)	20.3 (2.32)	c
Price of drugs			
Cisplatin per mg	3.36 (0.685)	0.04 (0.009)	(25)
Paclitaxel per mg	1.80 (0.367)	0.024 (0.004)	(25)
Bevacizumab per mg (Biosimilar)	35.86 (7.31)	0.48 (0.098)	(25)
Bevacizumab per mg (branded drug)	297 (60.6)	4.0 (0.817)	(50)
Cost of management of complications/side effects			
Fistula per procedure	16,000 (3265)	216 (44)	(24)
Thromboembolism per month	3075 (628)	42 (8.5)	a
Neutropenia per month	30850 (6296)	416 (85)	a
Hypertension per month	284 (58)	4 (0.8)	(51)
Nausea and vomiting per month	154 (31)	2 (0.4)	a
Grade 3 nausea and vomiting	209 (43)	3 (0.6)	a
Cost of best supportive care			
Gastro-intestinal bleeding lifetime	738 (151)	10 (2)	a
Vaginal discharge lifetime	162 (33)	2 (0.4)	a
Pain per month	607 (124)	8 (1.7)	a
2DRT	4888 (997)	66 (13)	(24)

*a' denotes that cost was derived based on normative costing using standard treatment guidelines and expert opinion, as well as published unit costs and Government procurement prices; 'b' denotes percentage gradient of stable disease to limited

complication from literature Minion et al.(7); 'c' denotes CaDCQoL study data used. CBC: Complete blood count; LFT: Liver function test; RFT: Renal function test; STG: standard treatment guidelines; CT: Computed tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; ₹: Indian rupee; US$: United States Dollar

Sensitivity analysis

A multivariable probabilistic sensitivity analysis (PSA) was undertaken to estimate the effect of joint parameter uncertainty.(29) Under PSA, all cost parameters were assigned gamma distribution, while utility values and probabilities/proportions were assigned beta distribution. Actual value of standard error (SE) was used to create a distribution around the point estimate of a parameter. In cases where SE was not reported, a variation of 40% and 20% on either side of the base value was used for cost and clinical parameters respectively. The median value of ICER along 2.5th and 97.5th percentile was calculated using 999 Monte Carlo simulations.(30) Univariate sensitivity analysis was also undertaken to assess the effect each parameter on ICER.

Univariate sensitivity analysis was done to assess the impact of uncertainty in individual parameters' on the ICER value. The results have been reported using a Tornado diagram in Fig 2, to reflect the variation in resulting ICERs with the variation in the parameters. The parameter value was decreased and increased by 20%, for parameters other than discount rates, to see its effect on deterministic ICER. The discount rates were varied to be up to 5% for the purpose of Univariate sensitivity analysis.

Ethical approval

Ethical approval was obtained from Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research, India with reference number IEC-03/20202-1565.

Results

Absolute outcomes

The absolute number of LYs and QALYs lived by a patient have been explained in table 3. Per patient LYs and QALYs lived in control arm was 1.06(0.93 - 1.20) years and 0.46 (0.36 - 0.56) years respectively (Table 3). Similarly, table 3 reports that a patient in intervention arm lived a total of 1.33(1.19 - 1.49) LYs and 0.585(0.48 - 0.70) QALYs. Further, the total lifetime cost incurred was US$ 1,478(1,308 – 1,692) and US$ 5,295(4,012 – 7,030) for a patient treated on chemotherapy alone and bevacizumab plus chemotherapy respectively, as reported in table 3.

Incremental cost, outcomes, and cost effectiveness

As reported in Table 3, over the lifetime of a patient of advanced and metastatic cervical cancer, treatment with bevacizumab results in a gain of 0.275 LYs (3.30 life months) and 0.129 QALYs (or 1.55 quality adjusted life months) at an additional cost of US$ 3,816(2,513 – 5,571) as compared to standard chemotherapy alone. This results in an incremental cost of US$ 19,080(7,230- 52,434) per LY gained and US$ 34,744(15,782-94,914) per QALY gained with the use of bevacizumab (Table 3). As per Indian guidelines, we compared the value of ICER with one-time per-capita GDP of India to conclude the cost-effectiveness of Bevacizumab.(13) We found the use of Bevacizumab incurs an incremental cost of US$ 34,744 per QALY gained which is much higher than the per capita GDP of US$ 1965 (₹ 1,45,679) during the year 2020, and hence deemed not cost-effective. Even using a 3-times per-capita GDP value of US$ 5,895 (₹ 4,37,037) as threshold, (31) Bevacizumab is not cost-effective for treating advanced and metastatic cervical cancer in India.

As shown in Fig. 3, a cost-effectiveness acceptability curve has been prepared showing the probability of the drug Bevacizumab of being cost-effective at various WTP thresholds. It explains that there is zero probability of Bevacizumab being cost-effective till the WTP threshold is US$ 13,350 which is around 6.8 time the GDP value of India.

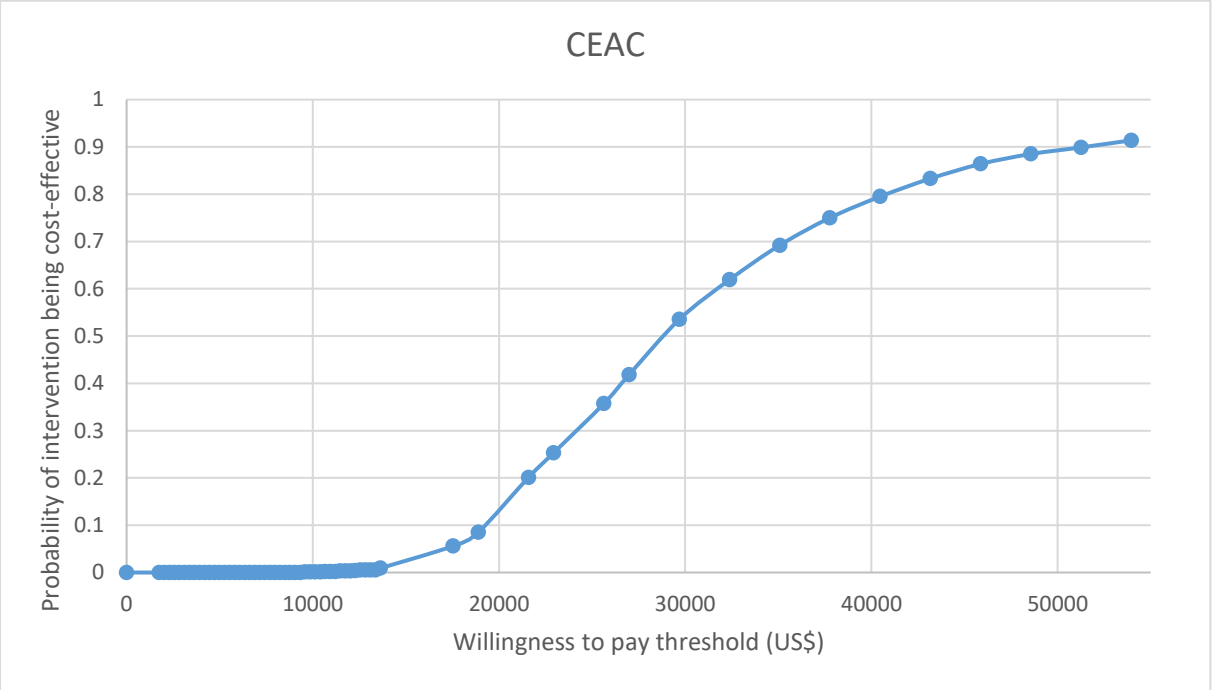
Table 3: Discounted probabilistic median costs, health outcomes and cost effectiveness of using bevacizumab along with chemotherapy as compared to chemotherapy alone for the treatment of advanced cervical cancer

Variable	Control arm	Intervention arm (Biosimilar)

Lifetime cost per patient	**₹**	1,09,617 (96,996-1,25,501)	3,92,540 (2,97,423-5,21,180)
	US$	1,478 (1,308-1,692)	5,295 (4,012-7,030)
Absolute health outcome per patient	**LY lived**	1.059 (0.925-1.21)	1.335(1.195-1.492)
	QALY lived	0.456 (0.365-0.555)	0.585 (0.475-0.695)
Incremental cost per patient	**₹**	2,82,922 (1,86,332- 4,13,041)	
	US$	3,816 (2,153- 5,571)	
Incremental health outcomes per patient	**LY gained**	0.275 (0.052- 0.469)	
	QALY gained	0.129 (0.032-0.218)	
Incremental cost per LY gained	**₹**	14,14,406 (5,36,004- 38,86,952)	
	US$	19,080 (7,230- 52,434)	
Incremental cost per QALY gained	**₹**	25,75,624 (11,69,972- 70,35,979)	
	US$	34,744 (15,782- 94,914)	

*₹: Indian rupees; US$: Unite States Dollar; LY: Life year; QALY: Quality adjusted life year; values in parenthesis indicate 2.5th and 97.5th percentile

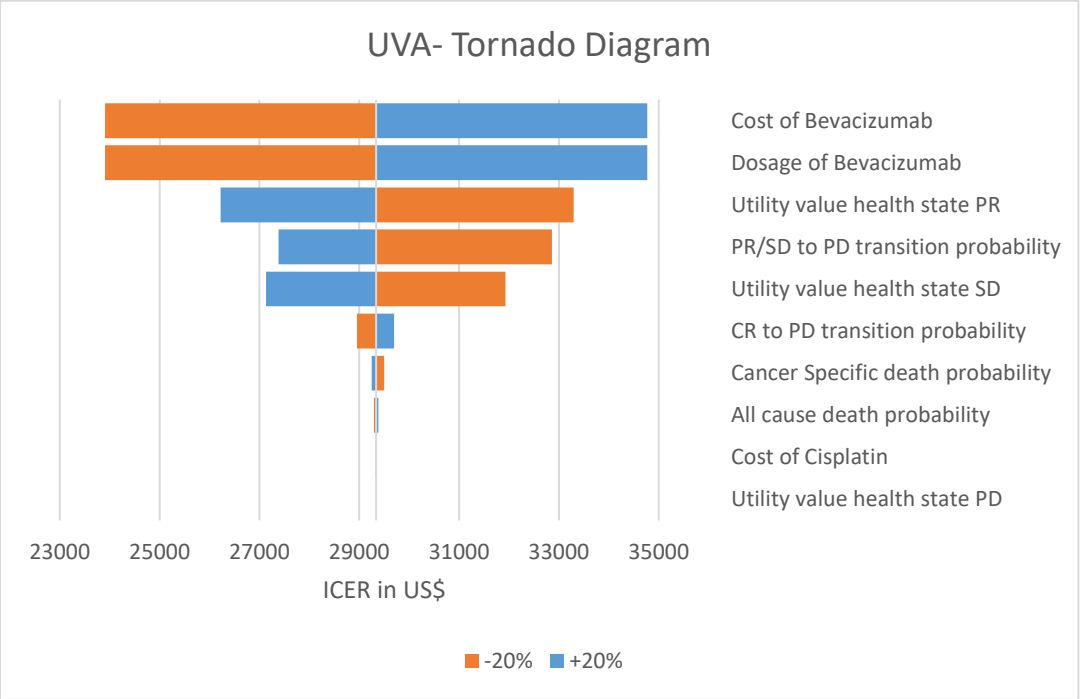
Fig 2: Cost effectiveness acceptability curve



Sensitivity analysis

Univariate analysis showed that ICER is most sensitive to price and dosage of Bevacizumab (US$ 34,771- 23,904) (Fig 2). It is also sensitive to utility values of 'Stable Disease' (US$ 27,134- 31,930) and 'Partial Disease' health states (US$ 26,222- 33,293). Further, when discount rates were varied to 5%, the ICER was US$ 29,756. Decreasing the transition probability to move from stable disease or complete response to progressive disease in case of bevacizumab by 50% and 90% resulted in an ICER of US$ 18,288 and US$ 14,691. If the price of branded drug is considered, the ICER goes up significantly higher – US$ 1,95,251 (1,12,993- 6,43,595)

Fig 3 Tornado Diagram



Model validation

The median survival time and survival rate of the control arm was compared with the local epidemiological data from India. Our study reported a median survival time of 11 months and 2-year survival rate of around 10% following treatment with routine chemotherapy. These model outcomes corroborate with the findings from an Indian prospective cohort study that reported a median survival time and 2- year survival rates of around 9 months and 12% respectively among those in the stage IV cervical cancer.(5)

We found that the lifetime months gained by a patient treated with bevacizumab plus chemotherapy as compared to chemotherapy alone is around 3.3 months. Further, 9.5%, 19.4% and 34% of patients achieved a complete response, and develop severe and limited complications respectively over the duration of treatment regimen given to a cohort of 1000 patients. All these findings are consistent with the results of GOG 240 trial.(8)(17)

Discussion

For patients with advanced and metastatic cervical cancer in India, chemotherapy is the standard of care, though outcomes remain poor. Cisplatin at a dose of 50mg/m^2 given 3 weekly was a historic standard of treatment for these patients.(32) However, with the use of cisplatin concurrent with radiation in majority of these patients, they become resistant to cisplatin for recurrent or persistent disease.(33) In view of the nature of the disease with poor gains in survival, assessment of toxicity, quality of life and cost of treatment becomes paramount.

GOG 204 trial established the doublet of paclitaxel and cisplatin as the standard of care for this subgroup of cervical cancer patients.(34)(8) Dismal outcomes after combination chemotherapy focused the attention towards molecular targeted agents. Cervical cancers are associated with increased levels of VEGF, which is associated with poor prognosis and is the target of antiangiogenesis therapy like bevacizumab.(35) GOG 240 established that addition of bevacizumab, to the standard chemotherapy increased the response rate and overall survival for these patients.(8)

Globally, 85% of the cervical cancer patients live in LMICs where access and affordability of newer drugs like bevacizumab remains limited.(36) Payer face the difficult choice of determining which interventions to include in the health benefit package of the nation.(37)(38)(39)(40) Bevacizumab, a costly anti-cancer drug has shown to improve the survival for patients with the advanced and metastatic cervical cancer.(41) The Health Technology Assessment Board of India (HTAIn) recommend the use of one times GDP per capita of India as the threshold for cost effectiveness.(13) Based on the per capita GDP of US$ 1965 (₹ 1,45,679) during the year 2020, our findings show that the treatment comprising of bevacizumab plus chemotherapy is not cost effective for the treatment of advanced and metastatic cervical cancer in India. We found that the cost of treating adverse events of this intervention is high, as a result of which the drug remains cost-ineffective even after reducing its prices similar to the prices of control arm drugs. Our study finding is in line with the results of previous economic evaluations,(7)(9) stating bevacizumab as cost in-effective in advanced cervical cancer. Economic evaluations conducted on the use of bevacizumab for other indications like metastatic renal cancer,(42) metastatic breast cancer(43) and metastatic colorectal cancer(44) have also shown it to be a cost in-effective drug.

We need to look into various measures, besides price reduction, which may help to make this treatment cost effective for India. Currently recommended dose of bevacizumab is 15mg/kg which may be reduced to lower doses 5–10mg/kg, as has been recommended for various other sites like colorectal cancer, glioblastoma, ovarian cancer, renal cell carcinoma, etc after evaluation in future trials.(45) This will reduce the cost of treatment by nearly 50%. However, as found in our sensitivity analysis, even with a reduced dosage to 7.5 mg/kg, as used in earlier ovarian cancer study, bevacizumab is not cost-effective for advanced cervical cancer.

Moore et al have identified five factors associated with poor survival in cervical cancer patients which includes poor performance status, pelvic recurrence, prior radiosensitizing chemotherapy, recurrence within 1 year and African-American race.(46) In the GOG-240 trial, using Moore's criteria, the hazard ratios for death in low-risk, medium-risk, and high-risk patients were 0.96, 0.673, and 0.536, respectively.(47) However, as shown in our sensitivity analysis, even in the best case scenario, where we reduced the probability to progress in case or bevacizumab by 90% of base value, the drug is not cost-effective. This implies that even if the drug was to be used among sub-groups where its effectiveness could be more than average, it is unlikely to offer a value for money. Doublet chemotherapy with paclitaxel and cisplatin has a tolerable toxicity profile and reasonable disease control. It is seen to be cost effective in our study and should be continued to be prescribed for resource limited countries like India.

Given the fact that novel treatments in advanced disease are not cost-effective, the focus of disease control strategies should focus on prevention. A decline of 70% in cervical cancer in the west is attributed to the effective screening and vaccination against HPV.(48) Previous cost-effectiveness analysis have shown various preventive strategies as cost-effective options for India.(10)(49)

Limitations

Based on the standard of care, we had considered chemotherapy regimen of 'cisplatin plus paclitaxel' as the control arm of the study. The effectiveness data from the GOG 240 trial for the control arm was based on the combination of 2 specific chemotherapy regimens comprising of 'cisplatin plus paclitaxel' and 'topotecan plus paclitaxel'. We have

assumed that the effectiveness parameters in terms of progression, rate of response and occurrence of complications would be same for chemotherapy regimen of 'cisplatin plus paclitaxel' as it is for the combination as assessed in the GOG 240 trial. Due to relative lack of literature, we assumed that there was a 90% probability of moving from severe complications to progressive disease.(18) A univariate sensitivity analysis to test how this assumption affects the overall findings on cost-effectiveness was done. Our univariate sensitivity analysis shows that decreasing this probability from 90% to 30%, reduces the ICER value by around 7% only. This lack of major impact on ICER is explained based on the fact that the proportion of individuals who develop severe complications is very small. As a result, we conclude that the findings of our analysis are not sensitive to the assumption of 90% probability of progression.

Conclusion

Chemotherapy along with bevacizumab is not a cost-effective alternative when compared to chemotherapy alone at a threshold of either 1-times or 3-times GDP per capita for treating advanced cervical cancer patients in India. Doublet chemotherapy with paclitaxel and cisplatin has a tolerable toxicity profile, reasonable disease control, and cost effective, hence should be continued to be prescribed in standard treatment guidelines for resource limited countries like India.

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Chapter 7: Cost-effectiveness of Ribociclib and Palbociclib in the second-line treatment of Hormone receptor-positive, HER2 negative metastatic breast cancer in post-menopausal Indian women

Introduction

Breast Cancer is the most prevalent cancer among women all over the world. It is estimated that nearly 2.4 million new cases of cancer and 623,000 deaths were attributed to breast cancer among Indian women in 2018 (1). The age-adjusted incidence and mortality rate are high as 25.8 per 100,000 women and rate of 13.3 per 100,000 women in India (2,3). Unfortunately, 20-25% of breast cancer patients in India present with upfront metastatic disease (4). Amongst the metastatic breast cancer (MBC), Hormone Receptor-positive (HR+) Human Epidermal growth factor Receptor 2-negative (HER2-) is the most common subtype (4,5). Endocrine Therapy (ET) is the mainstay of management of HR+ HER2- MBC.

HR+ HER2- MBC is considered to be an incurable disease with treatment aimed at increasing the lifespan and maintaining a good quality of life (6,7). Median overall survival is reported as 36 months (8,9). The National Cancer Grid (NCG) and Indian Council of Medical Research (ICMR), and the top-most panel of oncologists in India, recommend the use of ET with or without targeted therapies for HR+ HER2- MBC, with chemotherapy being reserved for patients with visceral crisis (10–12). First line ET among postmenopausal women predominantly consist of tamoxifen or aromatase inhibitors (AI) with or without cyclin dependent kinase-4/6 inhibitors (CDK4/6i) (10). In the second line, the treatment options vary from the use of fulvestrant as single agent, fulvestrant in combination with CDK4/6i, AI in combination with Mammalian Target of Rapamycin (mTOR) inhibitors (10). But, due to high costs associated with these agents, majority of the patients in India have to resort to chemotherapy (13).

The introduction of targeted agents like CDK 4/6i (ribociclib, palbociclib and abemaciclib) have added a new option in the management of HR+ HER2- MBC. Various trials have shown that use of CDK4/6i along with ET in this subset of MBC improves disease-free survival (DFS) and overall survival (OS) (14–17). With various available

options, the treatment for HR+ HER2- MBC is personalized in the developed world based on the prior ET received, severity of the disease (visceral crisis), and the adverse effects (AEs) profile of drug which influenced the quality of life among these patients with limited survival. However, in developing and low-income countries like India, besides the factors discussed above, cost becomes paramount for decision making with newer expensive agents like CDK 4/6i (18,19).

Ayushman Bharat-Pradhan Mantri Jan Aarogya Yojana (AB-PMJAY) (48) which is the flagship health insurance scheme aims to reduce the financial hardship and catastrophic expenditure associated with cancer treatment in India. Treatment options such as single-agent paclitaxel, single-agent capecitabine and Fulvestrant has been added as a part of its Health Benefit Package (20). Therefore, it is necessary to assess these packages designed by the experts from the lens of cost-effectiveness so as to make value-based policy decisions.

Few studies have assessed the cost-effectiveness of CDK4/6i; however, majority have evaluated the first line therapy only, and none of these studies assessed the comparison between CDK4/6i and chemotherapy (21–24). Further, majority of the studies have not included updated DFS and OS from recent updated clinical trials (21,22,24). In view of the limitation of existing evidence, we undertook this study to determine the most cost-effective treatment strategy for the second line treatment of HR+ HER2- MBC among post-menopausal women in India.

Materials and Methods

Overview of the Analysis

We undertook this cost-effectiveness analysis (CEA) using the societal perspective to determine the most cost-effective treatment strategy in the second-line setting for HR+, HER2- MBC patients in India. We took into consideration two different points of views: (I) as per the prevailing market and procurement prices (Scenario 1: Market price scenario); and (II) as per the reimbursement rates set up by the national-level health insurance scheme in India (Scenario 2: Publicly financed health insurance scenario) (20) (Table 1). The lifetime costs and consequences of the combination of CDK4/6i (both ribociclib and palbociclib) and fulvestrant, single-agent fulvestrant and chemotherapy: single-agent injection paclitaxel and single-agent oral capecitabine respectively was

calculated using standardised methods. The Incremental cost-effectiveness ratios (ICERs) were compared against the next best alternative. Our methodological principles are consistent with the Indian reference case for conducting economic evaluations used by the agency for Health Technology Assessment in India (HTAIn) (25). We used Consolidated Health Economic Evaluation Reporting Standards (CHEERS) to report the findings (26).

Table 1: Description of the scenarios

Scenario	Scenario name	Description	Cost assumptions	Effects
I	Market price scenario	As per the prevailing market prices of the drugs and treatment in the Indian context.	• Market Prices and procurement prices for all the treatment arms • OOPE: Direct non-medical expenditure (including user/procedure fees) for OPD consultation and day-care visit • Diagnostics: CGHS reimbursement rates	• LYs • QALYs
II	Publicly financed health insurance scenario	From the point of view of the publicly financed national health insurance program.	• Reimbursement rates as per ABPM-JAY HBP • Direct non-medical expenditure for OPD consultation and day-care visit	• LYs • QALYs

Model structure

A Markov model was developed in Microsoft Excel to estimate the lifetime costs and consequences among 1000 hypothetical patients (Figure 1). The model consisted of three mutually exclusive health states: Progression-free survival (PFS), Progressive disease (PD2) and death. A monthly cycle length based on the treatment schedules in the MONALEESA-3 trial was considered (14,27).

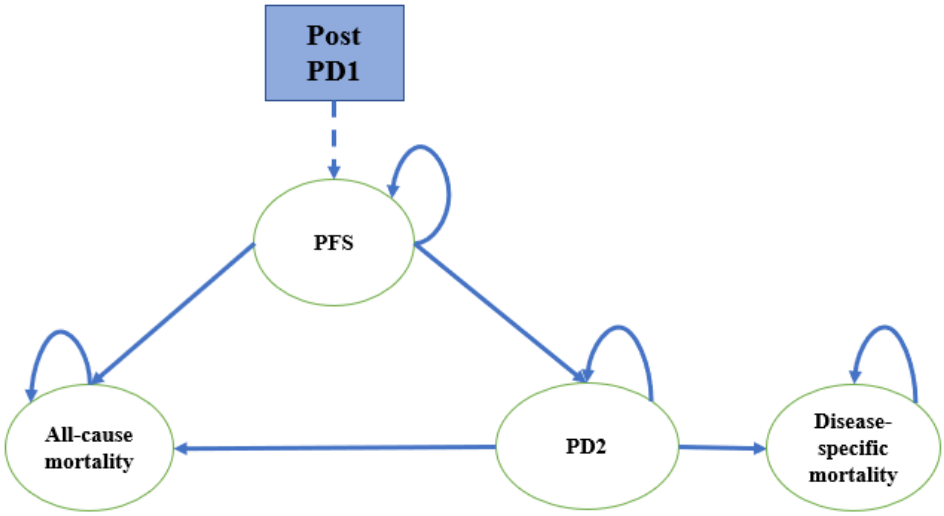

Figure 5: Schematics of the Markov state transition model. PFS: Progression-free state; PD: Progressive Disease

After the failure of first line therapy, the patient enters the model in PFS health state, where she receives the treatment. Subsequently, the patient can either stay in PFS or progress to PD2 or die. The patients in PD2 health state remain in the same health state until death. The subsequent treatment for PD2 state comprised of chemotherapy or hormone therapy or best supportive care. Disease specific mortality was assumed to occur from PD2 health state only, while all patients in both PFS and PD2 state were assumed to die due to all-cause mortality. The patient enters the model at 50 years of age which is the median age of presentation of breast cancer in India (28). All future costs and outcomes were discounted at the rate of 3% (25).

Treatment scenarios

Five treatment scenarios were modelled: (1*)* Ribociclib (600 mg/day orally on days 1–21 in a 28- day cycle) plus fulvestrant (500 mg intramuscularly (IM) on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1); (2) Palbociclib (125 mg/day orally on days 1-21 in a 28-day cycle) plus fulvestrant (500 mg IM on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle 1); (3) Fulvestrant 500 mg IM on day 1 and day 15 of cycle 1 followed by 500 mg on Day 1 of a 28-day cycle and (4) Paclitaxel 175mg/m^2 three weekly and (5) Capecitabine 1250mg/m^2 orally for 2 weeks on and 1 week off cycle. The latter two chemotherapy arms were simulated to make the analysis mimic the real-world situation as very few people are able to afford the high cost associated with CDK4/6i in India (13).

Cost of treatment of Metastatic Breast cancer

The costs were estimated from the societal perspective for all the treatment arms. However, we did not take into account the productivity losses incurred by the patients and their caregivers due to the cancer treatment in this analysis. This is in concurrence with the guidelines of reference case to undertake economic evaluation by India's HTA agency (25).

In scenario I, we took into account the prevailing market prices for the different treatment arms in the PFS and PD2 health state. The cost of treatment in the PFS state included drug acquisition costs, cost of drug administration (inpatient/day-care), direct out-of-pocket expenditure (including travel, boarding/lodging, food, user fees, informal payment and other) per OPD consultation, recurrent investigations and the management of grade 3/4 AEs (Table 2). Locally published studies and existing national health system cost database were used to elicit the unit health system cost of services provided to the patients in PFS and PD2 state including outpatient consultation, day-care visit and hospitalization (29,30). Scenario II included the reimbursement rates and direct non-medical expenditure (excluding user fees) (Table 2) in the PFS state. The reimbursement rates set up under the ambit of national publicly funded health insurance – Ayushman Bharat Pradhan Mantri Jan Aarogya Yojana (ABPM-JAY) were applied which includes the cost of the drugs, administration costs (day-care and OPD visits), supportive care as well

as the routine follow-up (31). The detailed description of the two scenarios is given in Table 1.

Separate incidence rates for grade 3-4 AEs were applied for intervention and comparator arms using the published literature (Supplementary Table 1) (27,32). MONALEESA-3 and PALOMA-3 trial data was used to determine the incidence of adverse effects in the Ribociclib and Palbociclib arms respectively (14,15). The costs were applied separately in each cycle using the treatment protocol obtained from the subject experts and standard treatment guidelines (12).

Similar methodology was applied in the PD2 health state for both the scenarios. The cost of outpatient consultation, routine laboratory and diagnostic tests, third-line therapy, best supportive care and end-of-life hospitalization were included in the Scenario I. For Scenario II, the reimbursement rates and direct non-medical expenditure for the third-line therapy was modelled. The third line treatment included chemotherapy (either Paclitaxel or Capecitabine for the other three arms), hormone therapy and palliative care (Supplementary Appendix I). It was assumed that the third line treatment (chemotherapy and hormone therapy) will be given to PD2 patients for an average of 6 months after which all the patients were given best supportive care/palliative care till death.

The OOPE component was derived from primary data collected from 843 breast cancer patients, including 105 MBC cases, across six Indian states (33). The data was analysed to compute direct non-medical expenditure (travelling, food, boarding/lodging, informal payment, others etc.) and user fees/procedure charges incurred on outpatient consultation, per bed-day hospitalization and per day-care visit. The expenditure incurred on drugs was computed using procurement rates of the medical service corporation in Rajasthan state (34) and treatment protocol based on expert opinion and standard treatment guidelines (12). For the diagnostic services in the Scenario I, we used the provider payment rates under the Central Government Health Scheme (CGHS) – a publicly financed national insurance scheme (35). All costs are reported in Indian National Rupee (₹) and converted to United States Dollar ($) using an exchange rate of 1$ = ₹ 73.4 for the year 2020-21 (36).

Table 2: Cost parameters for assessing the cost-effectiveness of CDK4/6 inhibitors combination therapy

	Scenario I	Scenario II		
Input cost parameter	**Unit cost in ₹ ($)**	**Cost per cycle in ₹ ($)**	**Source**	**Distribution**
Drug costs/Reimbursement Rates				
Tab. Ribociclib 600mg	4,357 (59)	4,357 (59)	Market Price,	γ
Tab. Palbociclib 125mg	4,286 (58)	4,286 (58)	Market Price	γ
Inj. Fulvestrant 500mg	15,840 (215)	12,000 (163)	Market Price, (20)	γ
Inj. Paclitaxel 280mg	684 (9)	11,800# (161)	Market Price, (20)	γ
Tab. Capecitabine 500mg	12.48 (0.2)	7,400# (101)	Market Price, (20)	γ
Tab. Tamoxifen 20mg	1.6 (0.02)	1,200# (16)	Market Price, (20)	γ
Tab. Letrozole 2.5mg	3.4 (0.04)	3,900# (53)	Market Price, (20)	γ
Tab. Exemestane 25mg	43 (0.6)	3,900# (53)	Market Price, (20)	γ
Tab. Anastrozole 1mg	7.6 (0.1)	3,900# (53)	Market Price, (20)	γ
Tab Loperamide	0.18 (0.002)	0.18 (0.002)	(34)	γ
ORS pouches	2.02 (0.03)	2.02 (0.03)	(34)	γ
Tab Emset 4 mg	0.145 (0.002)	0.145 (0.002)	(34)	γ
Syrup Cremaffin	83.8 (1.1)	83.8 (1.1)	(37)	γ
Tab Ibuprofen	1.0 (0.01)	1.0 (0.01)	(34)	γ
Inj. GCSF 300 mcg	89.9 (1.2)	89.9 (1.2)	(34)	γ
Tab Paracetamol 650 mg	0.73 (0.01)	0.73 (0.01)	(37)	γ
Inj. Cefipine 2g	275 (3.7)	275 (3.7)	(37)	γ
Inj. Amikacin 750 mg	26.1 (0.3)	26.1 (0.3)	(34)	γ
Tab Fluconazole 150 mg	1.12 (0.01)	1.12 (0.01)	(34)	γ
Tab Ciplox 500 mg	1.24 (0.02)	1.24 (0.02)	(34)	γ
Tab Udiliv 200 mg	6.7 (0.09)	6.7 (0.09)	(34)	γ
Tab Pyridoxine 100 mg	1.33 (0.02)	1.33 (0.02)	(34)	γ
Tab Amlodipine 5 mg	0.1 (0.01)	0.1 (0.01)	(34)	γ
Tab Augmentin 625 mg	3.89 (0.05)	3.89 (0.05)	(34)	γ
Tab Gabapentin 300 mg	0.97 (0.013)	0.97 (0.013)	(34)	γ

Betadine mouthwash	184 (2.5)	184 (2.5)	(34)	γ
Mucopain ointment	51 (0.7)	51 (0.7)	(34)	γ
Tab Metformin 500 mg	0.23 (0.003)	0.23 (0.003)	(34)	γ
Tab. Lasilactone 20mg	2.54 (0.03)	2.54 (0.03)	(34)	γ
Syrup Megastrol 800 mg	12.7 (0.17)	12.7 (0.17)	(34)	γ
Tab Omeprazole 20 mg	0.31 (0.004)	0.31 (0.004)	(34)	γ
Tab Celecoxib 200 mg	6.16 (0.08)	6.16 (0.08)	Market prices	γ
Tab Tramadol 50 mg	0.37 (0.005)	0.37 (0.005)	(34)	γ
Tab Morphine 10 mg	6 (0.08)	6 (0.08)	(34)	γ
Health system cost				
Out-patient consultation	266.2 (3.6)	Included in the Reimbursement costs	Unpublished data	γ
Day-care visit	1038 (14.1)		(30)	γ
Bed-day hospitalisation	1439 (19.6)		Unpublished data	γ
Out-of-Pocket Expenditure (OOPE)				
Per Out-patient consultation	3905* (53)	1844** (25)	Primary Data	γ
Per day-care visit	4279* (58)	1854** (25)	Primary Data	γ
Per episode of hospitalisation	9637* (131)	9637* (131)	Primary Data	γ
Cost of diagnostics (Reimbursement rates)				
Complete Blood Count	135 (1.8)	Included in Reimbursement costs	(35)	γ
Liver/Renal Function Tests	225 (3.1)		(35)	γ
Serum Electrolytes (Na, K, Ca, P, Mg)	370 (5)		(35)	γ
Electrocardiogram	50 (0.68)		(35)	γ
Echocardiography	1200 (16)		(35)	γ
CECT Chest/Abdomen	4500 (61)		(35)	γ
Chest X-Ray	60 (0.8)		(35)	γ
Urine Routine/ Microscopy	35 (0.5)		(35)	γ
Urine culture	50 (0.7)		(35)	γ
Blood culture	100 (1.4)		(35)	γ

Sputum gram staining	150 (2)		(35)	γ

Tab: Tablet; Inj.: Injection; OOPE: Out-of-Pocket Expenditure; ORS: Oral Rehydrating Solution; GCSF: Granulocyte-colony stimulating factor; CECT: Contrast-enhanced Computed Tomograph
#Total reimbursement cost (6 cycles: Paclitaxel & Capecitabine;20 cycles: Tamoxifen; 21cycles: Letrozole; 3-monthly: Exemestane & Anastrozole)
**Including the OOPE on travel, food, user fees, boarding/lodging, informal payments and others (excluding the drugs and diagnostics)*
***Including OOPE on travel, food, boarding/lodging, informal payments and others (excluding the drugs and diagnostics*

Valuation of Consequences

The outcomes were assessed in terms of life-years and QALYs. The transition rates of a patient moving from PFS to PD2 state in case of ribociclib arm was obtained from the subgroup analysis reported among the second-line HR+ HER2- MBC patients (14). For palbociclib, we assumed similar transition probability from PFS to PD2, based on evidence from a recently published network meta-analysis (32) and consultation with expert oncologists. Also, due to absence of any clear-cur subgroup analysis in the PALOMA-3 trial (15), we assumed similar efficacy for both palbociclib and ribociclib. The rates were converted to monthly transition probabilities using standard methods (38). We also accounted for time-dependent risk in the model. In case of chemotherapy arms, the transition rates were adjusted using hazard ratios obtained from a systematic review comparing the CDK4/6i with various chemotherapeutic regimens (39). Age specific all-cause mortality rates from each health state were obtained from the Sample Registration System (SRS) lifetables (40). Disease mortality rate for PD2 state for the Fulvestrant alone arm was obtained from published Indian literature (41) and then adjusted using the hazard ratios obtained from the MONALEESA-3 trial to obtain probability of dying due to breast cancer for the intervention arm (Table 2) (14).

Baseline utility values were obtained from the CaDCQoL primary data collected from 843 breast cancer patients across the country consisting of a subset of 105 MBC patients (33). The patients were administered the EQ-5D-5L tool to measure the health-related quality of life (HRQoL). The Indian tariff values were used to calculate the index utility score which was considered as a base value (25). This base value was then used to compute the utility scores for different health states (PFS and PD2) and AEs (haematological and non-haematological) using the gradient obtained from the published literature (Table 2) (42). We used the data on the proportion of patients who reported to have AEs to determine

the utility for each type of AE (Supplementary Appendix I). The comparative cost effectiveness was assessed in terms of incremental cost per QALY gained.

Table 3: Monthly input parameters used in estimating effectiveness of treatment arms

Input variables	Ribociclib + Fulvestrant	Palbociclib + Fulvestrant	Fulvestrant	Paclitaxel	Capecitabine	Distribution	Source
Clinical Parameters							
Average Proportion of patients with non-haematological AEs	0.806	0.824	0.992	0.754	0.962	β	(14,32)
Average Proportion of patients with haematological AEs	0.194	0.176	0.008	0.246	0.038	β	(14,32)
Transition Probabilities							
PFS to PD2 (0-2 months)	0.107	0.107	0.133	0.218	0.382	β	(14,39)
PFS to PD2 (2-4 months)	0.057	0.057	0.103	0.117	0.204	β	(14,39)
PFS to PD2 (4-6 months)	0.024	0.024	0.030	0.049	0.086	β	(14,39)
PFS to PD2 (6-8 months)	0.051	0.051	0.075	0.105	0.183	β	(14,39)
PFS to PD2 (8-10 months)	0.035	0.035	0.068	0.072	0.126	β	(14,39)
PFS to PD2 (10-12 months)	0.058	0.058	0.128	0.118	0.206	β	(14,39)
PFS to PD2 (12-14 months)	0.060	0.060	0.106	0.124	0.217	β	(14,39)
PFS to PD2 (14-16 months)	0.059	0.059	0.055	0.120	0.210	β	(14,39)
PFS to PD2 (16-18 months)	0.033	0.033	0.041	0.067	0.117	β	(14,39)
PFS to PD2 (18-20 months)	0.078	0.078	0.044	0.159	0.278	β	(14,39)
PFS to PD2 (20-22 months)	0.034	0.034	0.183	0.070	0.123	β	(14,39)
PFS to PD2 (22-24 months)	0.083	0.083	0.074	0.170	0.297	β	(14,39)
PFS to PD2 (24-26 months)	0.017	0.017	0.074	0.035	0.062	β	(14,39)
PFS to PD2 (26-28 months)	0.036	0.036	0.183	0.074	0.130	β	(14,39)
PFS to PD2 (28-30 months)	0.019	0.019	0.183	0.040	0.070	β	(14,39)
PFS to PD2 (30-32 months)	0.030	0.030	0.065	0.062	0.109	β	(14,39)

PFS to PD2 (32-34 months)	0.066	0.066	0.065	0.135	0.236	β	(14,39)
PFS to PD2 (34-36 months)	0.189	0.189	0.345	0.385	0.673	β	(14,39)
PFS to PD2 (36-38 months)	0.161	0.161	0.345	0.329	0.575	β	(14,39)
PFS to PD2 (38-40 months)	0.312	0.312	0.423	0.636	0.575	β	(14,39)
PFS to PD2 (40-42 months)	0.333	0.333	0.423	0.680	0.575	β	(14,39)
PFS to PD2 (42 month onwards)	0.293	0.293	0.423	0.598	0.575	β	(14,39)
PD2 to death due to the disease (50 year)	0.034	0.034	0.046	0.025	0.025	β	(14,28,41)
PD2 to death due to the disease (51 year)	0.034	0.034	0.046	0.059	0.059	β	(14,28,41)
PD2 to death due to the disease (52 year)	0.034	0.034	0.046	0.053	0.053	β	(14,28,41)
PD2 to death due to the disease (53 year)	0.034	0.034	0.046	0.071	0.071	β	(14,28,41)
PD2 to death due to the disease (54 year onwards)	0.034	0.034	0.046	0.187	0.187	β	(14,28,41)
Utility Values							
Post Progression PD1 (Base value)	0.659	0.659	0.659	0.659	0.659	β	Primary data
PFS (without AEs)	0.773	0.773	0.773	0.773	0.773	β	(42)
PFS (non-haematological AEs)	0.671	0.692	0.671	0.667	0.661	β	(32,42)
PFS (haematological AEs)	0.590	0.588	0.579	0.579	0.579	β	(32,42)
PD2	0.246	0.246	0.246	0.246	0.246	β	(42)

PFS: Progression-free state; PD: Progressive Disease; AE: Adverse Events

Sensitivity and Threshold Analyses

A probabilistic sensitivity analysis (PSA) was undertaken to test parameter uncertainty. Probability of CDK4/6i to be cost effective was assessed at a willingness to pay (WTP) threshold equal to per capita gross domestic product (GDP) as per the guidelines for health technology assessment in India (25,43). The per capita GDP of India was considered to be ₹141,493 (US$ 1,927) for the year 2020-21 (44).

For undertaking PSA, we used gamma distribution for parameters related to cost, and beta distribution for parameters related to risk of complications, overall survival and the utility scores. For rest of the parameters, we used uniform distribution to simulate random values. Upper and lower bounds were computed from the standard error estimated in the primary data, or estimates provided in the literature. Wherever the upper and lower bounds were not available, we assumed a variation of 20% on either side of base estimate for clinical parameters, and 30% variation for risk of mortality, treatment patterns, and 50% for cost parameters. Monte Carlo method was used for simulating the results, and the number of iterations were restricted to 10000 times. Median was computed along with 2.5^{th} and 97.5^{th} percentile to estimate 95% confidence interval.

A dominance analysis was undertaken in which each treatment arm was compared against the next best alternative to assess the comparative cost-effectiveness between various scenarios. Due to high cost of CDK4/6i in India, we undertook multiple PSAs at different prices of the Ribociclib and Palbociclib, in order to assess the probability of combination of CDK4/6i and ET to be cost-effective, at different levels of price reduction in the Indian context.

A univariate price threshold analysis was also undertaken at various prices for different treatment arms so as to determine the price at which a particular treatment is cost-effective at a WTP threshold of 1-time per capita GDP (₹141,493) for India.

Results

Cost & Outcomes

In scenario I, we estimated that an MBC patient incurs a lifetime cost of ₹ 2.54 million ($ 34,644) and ₹ 2.53 million ($ 34,496) when treated with the combination of ribociclib plus fulvestrant and palbociclib and fulvestrant respectively (Table 3). The lifetime cost incurred by an MBC patient was estimated to be ₹ 512,598 ($ 6,984) and ₹ 326,026 ($ 4,442) and ₹ 237,115 ($ 3,230) when treated using fulvestrant monotherapy, single-agent paclitaxel and single-agent capecitabine respectively.

In scenario II, we estimated that an MBC patient incurs a lifetime cost of ₹ 1.94 million ($ 26,459), ₹ 1.92 ($ 26,220) million, ₹ 315,387 ($ 4,296), ₹ 187,392 ($ 2,553), ₹ 153,263 ($ 2,088) when treated using ribociclib plus fulvestrant, palbociclib plus fulvestrant, fulvestrant monotherapy, single-agent paclitaxel and single-agent capecitabine arms respectively (Table 4).

An MBC patient treated with CDK 4/6i (either ribociclib or palbociclib and fulvestrant) combination therapy, fulvestrant monotherapy, paclitaxel and capecitabine has an overall mean survival of 3.6, 2.6, 2.2 and 2.0 LYs respectively. After factoring in the quality of life, this would translate into 1.4, 1.0, 0.9, 0.7 QALYs respectively.

Table 4: Per person lifetime cost and health outcomes for all the treatment arms

Outcome Variable	Ribociclib + Fulvestrant (95% CI)	Palbociclib + Fulvestrant (95% CI)	Fulvestrant alone (95% CI)	Single-agent Paclitaxel (95% CI)	Single-agent Capecitabine (95% CI)
LYs • Undiscounted	3.9 (3.2-4.7)	3.9 (3.3-4.7)	2.8 (2.3-3.4)	2.3 (2.1-2.5)	2.1 (1.9-2.3)
• Discounted	3.6 (3.0-4.2)	3.6 (3.0-4.2)	2.6 (2.2-3.1)	2.2 (2.0-2.4)	2.0 (1.8-2.2)
QALYs • Undiscounted	1.6 (1.3-1.8)	1.6 (1.3-1.9)	1.1 (0.9-1.3)	0.9 (0.8-1.0)	0.71 (0.61-0.82)
• Discounted	1.4 (1.2-1.7)	1.5 (1.3-1.7)	1.0 (0.9-1.2)	0.87 (0.7-0.99)	0.7 (0.6-0.8)
Total lifetime cost (in ₹) – Scenario I • Undiscounted	2,653,862 (1,946,873-3,612,050)	2,642,607 (1,973,980-3,508,313)	536,581 (445,950-722,315)	339,826 (281,041-411,967)	248,132 (193,236-318,061)
• Discounted	2,542,859 (1,859,251-3,461,113)	2,531,980 (1,895,996-3,364,063)	512,598 (426,125-683,620)	326,026 (270,106-394,357)	237,115 (185,296-303,147)
Total lifetime costs (in ₹) – Scenario II • Undiscounted	2,027,361 (1,394,949-2,861,491)	2,009,228 (1,387,397-2,816,556)	332,286 (248,631-440,525)	196,276 (155,886-248,035)	160,890 (120,481-214,372)
• Discounted	1,942,108 (1,332,396-2,745,553)	1,924,593 (1,319,656-2,709,734)	315,387 (236,517-414,602)	187,392 (149,308-235,997)	153,263 (115,165-203,459)

LY: Life-years; QALYs: Quality-adjusted Life-years; ₹: Indian Rupee

Cost-effectiveness

The combination of ribociclib and fulvestrant was dominated by the combination of palbociclib and fulvestrant for both the scenarios (Table 5). The combination of palbociclib and fulvestrant incurs an incremental cost of ₹ 4.85 million ($ 66,131) and ₹3.9 million ($ 52,698) per QALY gained as compared to the fulvestrant monotherapy for scenario I and II respectively which is not cost-effective at current the WTP threshold of 1-time per capita GDP (₹ 141,493) of India. Therefore, at a threshold of 1-time per capita GDP (₹ 141,493), the use of both ribociclib and palbociclib is not a cost-effective treatment modality in the Indian context.

In scenario I, single-agent paclitaxel is a non-dominated treatment strategy which incurs an incremental cost of ₹ 505,732 ($ 6,890) as compared to single-agent capecitabine which is not a cost-effective at current WTP threshold of 1-time per capita GDP (₹ 141,493) of India. Similarly, fulvestrant monotherapy offers better health outcomes at an incremental cost of ₹ 963,208 ($ 13,123) per QALY gained as compared single-agent paclitaxel. In scenario II, single-agent paclitaxel is a non-dominated strategy and offers better health outcomes than single-agent capecitabine at an incremental cost of ₹ 194,127 ($ 2,519) per QALY gained which is nearly 1.3 times the WTP threshold of India. Finally, fulvestrant monotherapy incurs an incremental cost of ₹ 660,797 ($ 9,003) per QALY gained as compared to single-agent paclitaxel.

Sensitivity and Threshold Analysis

At the current WTP threshold of one-time per capita GDP (₹ 141,493) of India, both ribociclib and palbociclib have a zero probability to be cost-effective in both the scenarios. The probability of Fulvestrant monotherapy to be cost-effective at a WTP threshold of 1-times per capita GDP is estimated to be 2% and 3% Scenario I and II respectively. Whereas the probability for single-agent paclitaxel is estimated to be 0.1% and 23% in Scenario I and II respectively.

A 95% reduction in the price of palbociclib is not enough to make the Palbociclib and Fulvestrant combination therapy to be cost-effective in the Indian context at a WTP threshold of 1-time per capita GDP.

However, when the drug price and the reimbursement rate of fulvestrant 500mg was reduced by 78% (₹ 17,520 to ₹ 3,854) and 72% (₹ 12,000 to ₹ 3,360) respectively, it becomes a cost-effective treatment option when compared with single-agent paclitaxel at a WTP threshold of 1-time per capita GDP (Figure 2)

Table 5: Cost-effectiveness of the treatment strategies for both the scenarios

Treatment arms	Scenario I (as per the current market prices)			Scenario II (as per the reimbursement rates in HBP 2.0)			Interpretation
	Costs in ₹	QALYs	Incremental cost per QALY gained	Costs in ₹	QALYs	Incremental cost per QALY gained	
Single-agent Capecitabine	237,115	0.69	-	153,264	0.69	-	ND
Single-agent Paclitaxel	326,026	0.86	505,732	187,392	0.86	194,127	ND
Fulvestrant alone	512,598	1.06	963,208	315,387	1.06	660,797	ND
Palbociclib + Fulvestrant	2,531,980	1.47	4,854,027	1,924,593	1.47	3,868,085	ND
Ribociclib + Fulvestrant	2,542,859	1.45	-	1,942,108	1.45	-	D

₹: Indian rupee; QALY: Quality-adjusted Life-years; ND: Non-dominated; D: Dominated

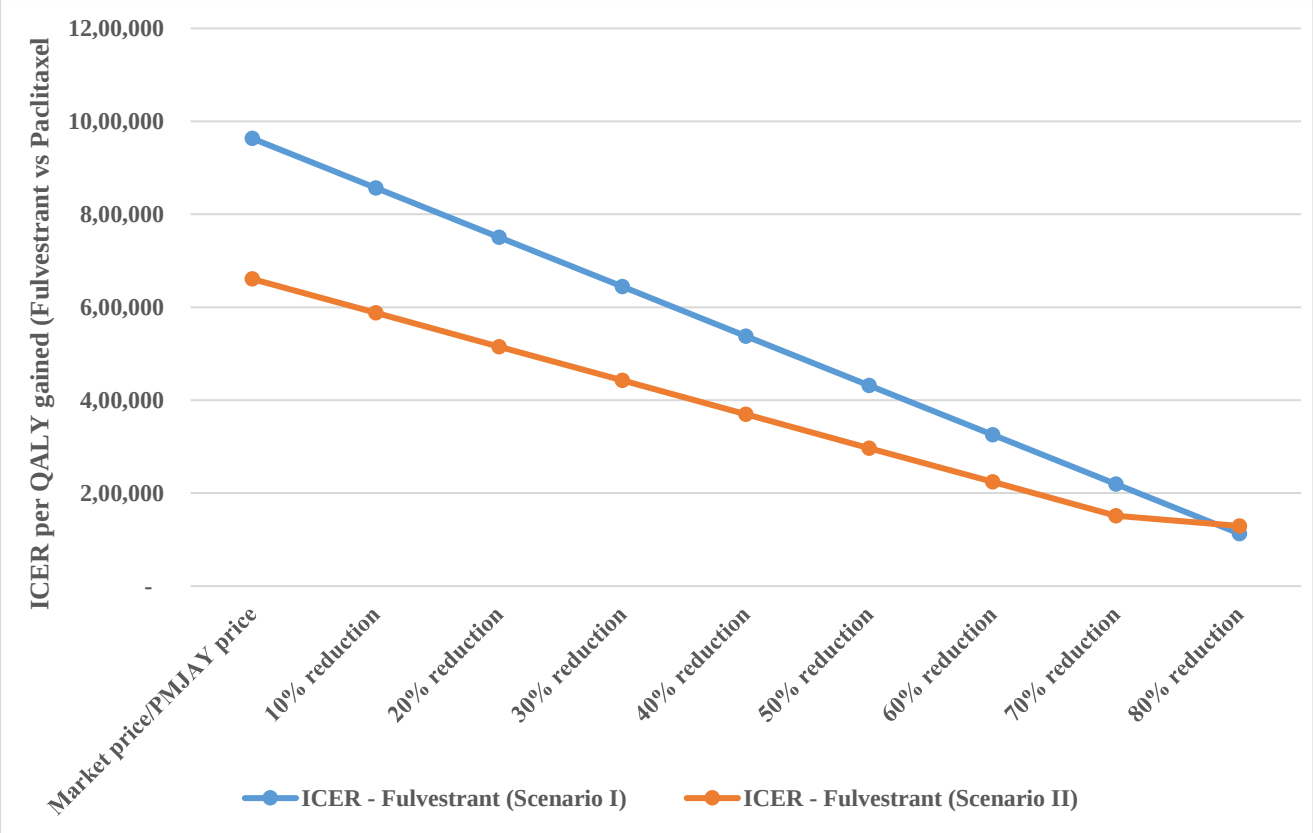

Figure 2: Price Threshold Analysis for fulvestrant monotherapy

Discussion

Breast cancer is a rising health problem in India with 1 in 22 women in urban India and 1 in 60 women in rural India being diagnosed with the disease (45). Significant number of patients in India still present with locally advanced and metastatic disease (4,46). The incidence of HR positive tumours in India varies between 20-45% (4,10,47).

Our study assessed the most cost-effective treatment option for the second-line treatment of HR+ HER2- MBC patients in India as per the prevailing market prices (Scenario I) as well as from the point of view of the national-level publicly financed health insurance schemes (Scenario II). CDK4/6i is not a cost-effective treatment modality in India even if the price is significantly reduced as compared to the current price in both the scenarios. When the market price and the reimbursement rate of Fulvestrant is reduced by 78% and 72% respectively, the fulvestrant becomes a cost-effective treatment option for HR+ HER2- MBC patients in India (Figure 2). Hence, we recommend more than 70% reduction in the existing reimbursement rates and market prices of

fulvestrant for inclusion in treatment guidelines and reimbursement under publicly funded programs.

Chemotherapy should not be the treatment of choice in HR+ HER2- MBC until endocrine resistance or visceral crisis. Our study recommends the use of fulvestrant (ET) for second-line treatment as it provides favourable health outcomes than the chemotherapeutic agents. Various meta-analyses have shown that though CDK 4/6i combined with ET have superior efficacy to ET alone, their superiority to chemotherapy has not been found to be statistically significant with respect to chemotherapy. In the meta-analysis by *Wilson et al* (2017), Palbociclib plus fulvestrant showed statistically significant improvement in PFS relative to capecitabine, mitoxantrone and pegylated liposomal doxorubicin and non-statistically significant improvement in PFS relative to paclitaxel, docetaxel, and other monotherapy or combination chemotherapy agents (39).

When chemotherapy is used for HR+ HER2- MBC, single agent chemotherapy is recommended over combination chemotherapy in view of the fewer AEs associated with single-agent chemotherapeutic regimens. Among single-agent regimens, paclitaxel and capecitabine are the most commonly used drugs. Real world evidence shows that chemotherapy is used as a first line therapy in HR + HER2- MBC irrespective of the visceral crisis and against the recommended guidelines (10). Our analysis indicates that the single-agent paclitaxel has the lowest incremental cost per QALY gained as compared to all other treatment strategies in both the scenarios but it is still not a cost-effective treatment option. Fulvestrant monotherapy is the next best treatment strategy which can be cost-effective at a price reduction of 78% and 72% from the point of view of Scenario I and Scenario II respectively.

AB-PMJAY (48) which is the flagship health insurance scheme also introduced use of Fulvestrant for MBC patients as part of their HBP 2.0 (20). Our analysis indicates that the reimbursement rates set up in the HBP 2.0 should be revised and updated so as to make them more cost-effective from the payers' as well as the societal perspective. This will not only increase the efficiency but will also be helpful in expanding the coverage for the scheme in terms of number of beneficiaries.

Model validation

The findings of our model are in concurrence with existing clinical and epidemiological evidence for both ribociclib and palbociclib (Supplementary Appendix I and II). The median OS in our model for the CDK4/6i combination arm is estimated to be 40 months which is consistent with the estimates reported in the MONALEESA-3 (median OS = 40.2 months) and PALOMA-3 (median OS = 38 months) clinical trials (14,15). Further, we have estimated a median OS of 28 months for the fulvestrant arm in our model which concurs with the findings of PALOMA-3 (median OS = 33.8 months) and MONALEESA-3 (median OS = 32.5 months) clinical trials respectively. Another study by Vaikundaraja et al. (2020) reports median OS to be 21 (95% CI: 8.9-33.1) months for fulvestrant patients (49) [50]. Therefore, our results are very much in line with the existing real-world evidence in the Indian context. A study by *Agrawal C. et al* (2020) reported the median PFS among the second-line palbociclib patients as 12 months, whereas our model estimated a median PFS of 13 months in the CDK4/6 inhibitors (both Ribociclib and Palbociclib) combination therapy arms (50). As compared to a median PFS of 10 months reported for fulvestrant monotherapy among Indian women, we estimated the median PFS in the fulvestrant arm as 9 months (49).

Our study findings report lower QALYs as compared to LYs for cancer treatment which is in line with the findings published by other model-based evaluations of cancer treatment in the Indian context (30,51,52) . We estimated an incremental gain of 0.44 and 0.45 QALYs for the ribociclib and palbociclib combination therapy respectively, as compared to fulvestrant monotherapy, which is in line with findings by *Yang et al.* (2020) (0.47 incremental QALYs) (21). The incremental gain of 1.1 LYs concurs with a recently published Canadian study which reported a gain of 1.19 incremental LYs for the ribociclib combination arm (53). *Yang et al.* (2020) and *Mamiya et al.* (2017) also reported that CDK4/6i (ribociclib and palbociclib) are unlikely to be cost-effective at current prices of these drugs (21,54). Studies such as *Mistry et al.* (2018) (22), *Suri et al.* (2019) (23) from the US and UK Payer perspective, as well as *Stellato et al* (2021) from Canadian perspective (53) also report cost-effectiveness ratios which show that CDK4/6i in combination with letrozole is not a cost-effective treatment modality, at their respective country-specific WTP thresholds.

Strengths and Limitations

We would like to highlight a few strengths of our study. Firstly, our study is the first one to report the cost-effectiveness of treatment modalities for HR+/HER2- MBC patients in the Indian context from two distinct point of views (market prices and reimbursement rates). Secondly, we took into account all possible treatment options to make the analysis as robust as possible. Thirdly, we have also incorporated the costs as well as the QoL associated with AEs due to cancer treatment. Fourthly, we used the survival data from the published Indian literature to make the results as generalisable as possible. Lastly, we have obtained the OOPE estimates from the primary data collected as a part of an ongoing multicentric study for assessing the economic burden and HRQoL among cancer patients in India (33). The OOPE estimated in our primary data analysis is in-line with the average medical expenditure reported in the National Sample Survey Organisation's (NSSO) 75th round (55). Similarly, the share of OOPE is consistent with other studies reporting costs incurred due to cancer treatment in India (56–58). We also took into account two most common CDK4/6i currently being used in India i.e., Ribociclib and Palbociclib. Abemaciclib was not included in the study as it was unavailable in the Indian market at the time of the conceptualisation of the study.

However, there are certain limitations of this analysis. Firstly, this study does not look into specific subgroups within the HR+ HER2- MBC like patients with endocrine resistance, prior disease-free interval, visceral metastases, bone only metastases, etc which might help to guide us to a more favourable patient population in whom these drugs maybe more effective. However, we do not currently have robust data for such subgroup analysis. Secondly, we did not take into account the cost of grade 1-2 AEs which might have slightly underestimated the costs. However, given the fact that the CDK4/6i is not cost-effective, inclusion of such costs would have further strengthened the conclusion. Lastly, we also did not take into account the indirect costs due to loss of productivity incurred by the patients as well as the caregivers. This was in agreement with Indian HTA guidelines, (25) and to avoid duplication (59).

Conclusion & Policy Implications

From the point of view of prevailing market prices (Scenario I) and the reimbursement rates set up under HBP 2.0 (Scenario II), none of the treatment scenarios for the second-line postmenopausal HR+ HER2- MBC patients are cost-effective in the Indian context. We recommend a reduction in the market prices and reimbursement rates for fulvestrant monotherapy to make its use represent value for money. Future research should focus to identify clinical markers like endocrine resistance, prior disease-free interval, visceral metastases, bone only metastases, brain metastases, tumour grade, progesterone receptor status, performance status, age, etc and molecular markers which point towards the inherent sensitivity for the CDK4/6i, which should be further evaluated for cost-effectiveness.

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Chapter 8: Cost Effectiveness of Temozolamide for Treatment of Glioblastoma Multiforme in India

Introduction

Glioblastoma Multiforme (GBM) is the most common and the most aggressive brain tumor in adults [1]. The prognosis for this aggressive tumor is grim, and even with the best available treatment, the survival at 2 years and 5 years is 25% and less than 10% respectively [2, 3]. The standard of care for newly diagnosed GBM patients includes maximum possible safe resection followed by adjuvant radiotherapy [4]. However, the outcomes continued to be poor and this led to the trial of various chemotherapeutic agents for GBM patients in an attempt to improve survival [5]. Among the various agents used, temozolamide has emerged superior due to the survival advantage offered [6, 7].

Temozolamide is an oral alkylating agent that crosses the blood brain barrier and induces DNA methylation and tumor cytotoxicity through cell cycle arrest [8]. The addition of concomitant temozolamide to radiation followed by 6 months of maintenance temozolamide in newly diagnosed GBM patients has been reported to improve the median overall survival by 2.5 months and the progression free survival by 1.9 months [5].

The incidence of central nervous system (CNS) tumors in India ranges from 5 to 10 per 100,000 population. Among them, GBM is the most common malignant CNS tumor [9, 10]. Incorporating temozolamide as the standard treatment in the concomitant and maintenance setting as per the standard guidelines becomes expensive in a resource limited country like India. As a result, assessment of its value for money becomes important. The majority of cost effectiveness analysis for temozolamide has been carried out for use in recurrent disease where temozolamide offers no conclusive survival advantage [11-14]. Other cost effectiveness studies have compared temozolamide with lomustine [15, 16], PCV regimen (procarbazine, lomustine and vincristine) [17] or other nitrosoureas [18]. All these are not the current standard of care, and hence not relevant in global context.

The limited number of cost effectiveness analyses which have evaluated the use of temozolamide in newly diagnosed GBM patients have reported variable results. While the drug has been shown to be cost effective in developed countries like United States [19], United Kingdom [20], Mexico [21] and Canada [20] but at the same time the drug has been shown to be cost ineffective in China [18]. There have been several methodological limitations in the above cost effectiveness studies. For example, Lamers et al [20] and Groot et al [22] reported outcomes in terms of life years and not quality adjusted life years (QALY) gained. In the study by Wu et al [18], discounted rates were not applied in view of short survival associated with GBM patients. Several cost effectiveness analyses [18, 19] have estimated outcomes up to what has been reported in trials – either till 2 years, or 5 years of onset of disease. Life term consequences have not been assessed robustly.

Finally, in view of differences in cost structure, and health care delivery, the findings of studies done elsewhere have limited generalizability in Indian context, and there is no evidence of cost effectiveness of temozolamide from India so far. In view of this, we undertook this study to estimate the incremental cost per QALY gained in the newly diagnosed GBM patients in India, who received temozolamide in addition to adjuvant radiotherapy as compared to radiotherapy alone.

Materials and Methods

A Markov model with three health states was developed in MS Excel 2013 for newly diagnosed GBM patients. The three transition health states were Progression Free Survival (PFS), Progressive Disease (PD) and death. The patients entered the model at the age of 50 years which is the most common age of presentation of GBM in India [23, 24]. Cycle length of 1 month was considered appropriate based on the maintenance treatment cycles.

One thousand patients enter the model in the PFS state. At the end of every month, each patient has a probability to move to PD, death or to stay in the PFS state. Death due to disease can occur only from the PD state and death from PFS occurs due to all-cause mortality only. This was based on the evidence from various clinical trials [6, 7]. Transition from one state to another is unidirectional and no patient can go back. A societal perspective that incorporates both the health system costs and out-of-pocket (OOP) expenditures was used, as majority of treatment costs in India are borne out-of-

pocket [25, 26]. Health outcomes were calculated as life years (LYs) and QALYs gained. The results are reported in terms of incremental cost per LY and QALY gained with the use of temozolamide. India's per capita GDP in year 2019 was US$ 2169 which was used as a cost-effectiveness threshold for the present analysis which translates to ₹ 150,000 approximately. The use of per capita GDP as cost-effectiveness threshold is recommended by Indian Government's health technology assessment agency (HTAIn); and used by many recent HTA studies conducted in Indian context. All future costs and consequences were discounted at 3% [27].

Intervention and Control arm

In the intervention arm, the newly diagnosed GBM patient after surgery were considered to have received daily temozolamide 75mg/m^2 concomitant with radiation for a period of 6 weeks, followed by 4-weekly six cycles of maintenance temozolamide. During maintenance, Temozolamide was given at a dose of 150mg/m^2 for 5 days in the first cycle and subsequently dose was escalated to 200mg/m^2 for 5 days from second to sixth cycle. The effective dose of temozolamide was calculated as per the body surface area (BSA). The BSA was derived using the weighted average height and weight [28] for the average Indian patient considering the gender distribution of GBM patients in India [23]. Patients continued the prescribed dose and schedule unless they developed grade 3 or 4 haematological toxicity or other drug related adverse reactions.

In the control arm the patients were considered to have received only adjuvant radiation without concomitant or maintenance temozolamide. During treatment, patients in both the arms underwent outpatient visits and laboratory investigations. One month after completion of radiation, midway, during maintenance therapy, on completion of maintenance treatment, and during follow up, patients underwent radiological examination to assess for the response to treatment and disease progression. Once in the PD state patients were offered best supportive care and no second line chemotherapy was accounted.

Valuation of Consequences

The data for overall survival and progression free survival as reported in the NCIC trial at 5 year follow up was used for our analysis [7]. The extent of toxicity, dose modification and drug discontinuation rates were also obtained from the same trial results obtained

at 2 years follow up [6]. The findings from the EORTC trial on effectiveness are representative of the Indian population as these are similar to what has been reported in the various real world single arm Indian studies [29-31]. However, in view of the longer follow up reported in the EORTC NCIC trial, findings from the latter were preferred for the present analysis [6, 7].

The transition probabilities were calculated to calibrate the intervention and control arms with the median survival and PFS rather reported at 6, 12, 18, 24, 36, 48, 60 months. Beyond 5 years the transition probabilities at 60 months were applied for each cycle over the lifetime. Age specific all-cause mortality reported in the Sample Registration Survey report of India was used [32]. Utility values for the GBM health states reported by Garside et al [33] were used in our analysis. The utility values were specific to the health states and type of treatment i.e. radiotherapy, chemotherapy or both (Table 1).

Costing

In both the groups, costs for conformal adjuvant radiation with a radiation dose of 60Gy in 30 fractions delivered over 6 weeks, as reported in a recent Indian study was included [34]. In addition, the cost for daily temozolamide at 75mg/m^2 (120mg) for 6 weeks, along with costs for Pneumocystis Carinii Pneumonia (PCP) prophylaxis and adverse effect management was included in the intervention arm. Both groups accounted for the cost for a weekly physician visit during radiation therapy. The cost of laboratory investigations as per standard protocols also included in both intervention and control arms [35]. Both the groups also included costs for hospitalization for 10% of patients for management of raised intracranial tension during the course of radiation therapy [35]. One month after completion of radiotherapy, both the arms included costs of Magnetic Resonance Imaging (MRI) brain for response assessment. Subsequently patients in the intervention arm were assumed to be on regular follow up with physician visits and radiological examination at a frequency as recommended by standard guidelines [35] until disease progression when patients moved to the PD state. (Table 1)

Table 1: List of key parameters used in cost-effectiveness model

Parameters	Base Case	LL	UL	Source
Transition Probabilities: No Temozolamide				
PFS to PD				
0-6	0.15	0.12	0.18	[6, 7]
6-12 cycle	0.20	0.16	0.25	
12-18 cycle	0.13	0.11	0.16	
18-24 cycle	0.14	0.11	0.17	
24-36 cycle	0.01	0.01	0.01	
36-48 cycle	0.00	0.00	0.01	
48 and above	0.00	0.00	0.01	
PD to Death				
0-6	0.09	0.07	0.11	[6, 7]
6-12 cycle	0.12	0.10	0.14	
12-18 cycle	0.17	0.14	0.20	
18-24 cycle	0.12	0.10	0.15	
24-36 cycle	0.09	0.07	0.11	
36-48 cycle	0.03	0.02	0.03	
48-60 cycle	0.09	0.07	0.11	
60 and above	0.11	0.09	0.14	
Transition Probabilities: Temozolamide				
PFS to PD				
0-6	0.099	0.079	0.119	[6, 7]
6-12 cycle	0.108	0.086	0.129	
12-18 cycle	0.056	0.045	0.068	
18-24 cycle	0.096	0.077	0.115	
24-36 cycle	0.037	0.030	0.045	
36-48 cycle	0.009	0.007	0.010	
48 and above	0.026	0.021	0.031	
PD to Death				
0-6	0.124	0.099	0.149	[6, 7]
6-12 cycle	0.115	0.092	0.138	
12-18 cycle	0.128	0.102	0.153	
18-24 cycle	0.111	0.088	0.133	
24-36 cycle	0.065	0.052	0.078	
36-48 cycle	0.034	0.027	0.041	
48-60 cycle	0.040	0.032	0.048	
60 and above	0.093	0.074	0.111	
All-cause Mortality: 50-55 years	0.001	0.001	0.001	[32]
All-cause Mortality: 55-60 years	0.001	0.001	0.001	
Utility				
PFS	0.887	0.710	1.000	[33]
PFS RT	0.824	0.659	0.989	
PFS RT with Temozolamide	0.743	0.594	0.891	
PFS with Temozolamide	0.733	0.586	0.880	
PD	0.731	0.585	0.878	
Cost Parameters (INR)				

Drug prices				
Phenytoin 100 mg	0.45	0.36	0.9	[54]
Ondansetron 4mg	2.47	1.976	4.94	[56]
Syp. Cremaffin	47	37.6	94	[54]
Cotrimoxazole DS	0.33	0.26	0.66	[56]
Dexamethasone tablet 4 mg	3.48	2.78	6.96	
Ranitidine 150 mg	0.62	0.50	1.24	
Ciprofloxacin 500mg	1.9	1.52	3.8	
Augmentin 625 mg	4.33	3.46	8.66	
Becasoule tablet (B-Complex)	0.73	0.58	1.46	
Injection GCSF (Granulocyte Colony Stimulating Factor)	350	280	700	
Tablet Temozolamide 250 mg	600	480	1200	[39]
Tablet Temozolamide 100 mg	240	192	480	
Tablet Temozolamide 20 mg	185	148	370	
Diagnostic prices				
CBC	155	124	310	[57]
RFT	259	207	518	
LFT	259	207	518	
Contrast enhanced MRI	2257	1806	4514	[58]
Serum electrolyte	100	80	200	[57]
Chest X-ray	236	189	472	[58]
Blood culture	433	346	866	
Sputum for gram stain	149	119	298	
Services (Neurosurgery/Radiotherapy/Medical Oncology/Neurology department)				
Per outpatient visit	538	430	646	[34]
Per bed day hospitalisation	3096	2477	3715	
Radiotherapy 3D-CRT	81594	65275	97913	
Cost of per day care visit	1032	826	1238	[55]
Length of Stay (LOS) in days				
Mean LOS for hospitalization among PFS patients	3.00	2.40	3.60	[41]
Mean LOS for hospitalization among PD patients	8.75	7.00	10.50	

Note: LL= Lower limit, UL= Upper Limit, PFS= Progression Free Survival, PD= Disease Progression, RT= Radiotherapy, INR= Indian National Rupee, CBC= Complete Blood Count, RFT= Renal Function Tests, LFT= Liver Function Tests

In the intervention arm, one month after completion of radiotherapy, cost for monthly temozolamide at 150mg/m^2 (1250mg) for 5 days for first cycle and 200mg/m^2(1650mg) for the remaining 5 cycles were included along with the monthly physician visits and laboratory investigations. Costs for MRI brain were added after 3 cycles of maintenance

temozolamide, and 1 month after completion of the maintenance therapy. The extent of grade 3 and 4 haematological adverse effects, which led to drug discontinuation, was assumed to be 10% in the concomitant phase and 8% in the maintenance phase [6]. Another 9% of the patients could not be escalated from 150mg/m2 to 200 mg/m2 during the monthly cycle 2-6 of maintenance temozolamide as reported in the Stupp trial [6]. Corresponding dose modification for these patients was done in our model. Costs for management of adverse effects like opportunistic infections, nausea, emesis, constipation, neutropenia/ severe infections and PCP prophylaxis were also included. The incidence of haematological adverse effects including neutropenia and severe infections, as reported in the Stupp trial, was considered as 7% in the concomitant phase and 9% in the maintenance phase [6, 8]. All adverse effects, except high risk neutropenia/ severe infection, were assumed to be treated using drugs in outpatient setting based on standard treatment guidelines [36]. Ten percent of patients in both intervention and control arm with raised ICT during treatment were assumed to be managed in inpatient setting using steroids, osmotic diuretics, antiepileptic and antiemetic drugs. Average cost of management in inpatient setting, routine or intensive care, was obtained from the national health system cost database, and from a recently conducted nationally representative hospital costing study [37, 38]. Similarly, low risk neutropenia was also assumed to be managed in outpatient setting with antibiotics and growth factors (Table 1). Patients with high risk febrile neutropenia were assumed to be hospitalised and managed with intravenous antibiotics as per culture sensitivity, growth factors and supportive care [36]. Cost of each of these drugs and hospitalization was derived from published studies, Indian national health system cost database, and prices based on market survey [34, 39, 40]. Table 1 provides prices for the drugs used in management of adverse effects.

Once the patients in both the groups entered the PD state, costs were included for best supportive care (anti epileptics, steroids) and hospitalization for life threatening episodes in 37% patients with an average hospital stay of 8.75 days [41]. For both intervention and control group patients in the PFS state, costs for 3 monthly physician visit and brain imaging were included for the first 2 years, which extended to 6 monthly visits till 4 years, and annually thereafter. Patients in the intervention arm underwent an additional MRI midway during maintenance therapy with temozolamide. All costs are

reported in Indian National Rupee (INR) and converted to US$ using an exchange rate of 71.66 INR = 1 US$ [42].

Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was carried out to ascertain the effect of variation in parameter values on incremental cost-effectiveness ratio (ICER). A variation of 20% was assumed on upper and lower sides for transition probabilities, utility weights etc. to create the uncertainty ranges for PSA. As the cost parameters are generally positively skewed in nature and hence, we assumed 20% and 100% variation for lower and upper limit respectively. In PSA, appropriate probabilistic distributions were used for different parameters like gamma distribution for cost parameters, beta distribution for transmission, transition and utility parameters; and uniform distribution for other parameters. Probabilistic model was simulated 1000 times and 2.5th and 97.5th percentile values were used to generate the confidence limits for base results.

Results

Costs

The lifetime cost of treating a newly diagnosed patient of GBM with adjuvant radiation and temozolamide was INR 181,235 (US$ 2,529). Cost of temozolamide was 15.3% of the total lifetime cost in the intervention arm. Similarly, the lifetime cost of treating the GBM patient without temozolamide was INR 105,502 (US$ 1,472). Thus, the incremental cost of treating the GBM patient with temozolamide, both in the concomitant and maintenance setting, was INR 75,120 (US$ 1,048) per patient. More than half (51.4%) of this incremental cost was on account of introduction of temozolamide. The remaining incremental cost was on account of adverse effect management, additional laboratory and radiological workup. The predominant cost in both the arms (52% in intervention arm and 79% in control arm) was that of conformal adjuvant radiation.

Outcomes and Cost-Effectiveness

Life years lived per patient in temozolamide and control arm was 1.85 (1.67 – 2.08) years and 1.26 (1.15 – 1.42) years respectively. The number of QALYs lived per patient in the temozolamide arm was 1.45 (1.21 -1.73) years versus 1.12 (0.92 – 1.33) years in the control arm. Incremental health benefit of temozolamide was 0.59 (0.53 – 0.66) LY and

0.33 (0.29 – 0.40) QALY per person. Finally, the incremental cost per LY gained was INR 119,289 (84,743 – 195,727) [US$ 1664; 95% CI: 1183 – 2731] while the incremental cost per QALY gained was INR 212,354 (138,347 – 401,466) [US$ 2963; 95% CI: 1927 – 5602].

Table 2: Costs, Health Benefits and Cost-effectiveness of Temozolamide compared to Treatment without Temozolamide

Parameters	Per Patient					
	Temozolamide			No Temozolamide		
	Median	2.5th	97.5th	Median	2.5th	97.5th
Lifetime costs per patient, INR (US$)	181,235 (2529)	156,274 (2180)	210,458 (2937)	105,502 (1472)	88,762 (1239)	122,978 (1716)
Health outcomes per patient						
Life Years	1.85	1.67	2.08	1.26	1.15	1.42
QALYs	1.45	1.21	1.73	1.12	0.92	1.33
Incremental costs, INR (US$)	75,120 (1048)	59,337 (828)	93,960 (1311)	-	-	-
Incremental benefits per patient						
Life Years	0.59	0.53	0.66	-	-	-
QALYs	0.33	0.29	0.40	-	-	-
Incremental cost effectiveness ratio, societal perspective						
INR (US$) per life year gained	119,289 (1665)	84,743 (1183)	195,727 (2731)	-	-	-
INR (US$) per QALY gained	212,354 (2963)	138,127 (1927)	401,466 (5602)	-	-	-

Note: 2.5th= 2.5th percentile, 97.5th= 97.5th percentile, INR= Indian National Rupee, US$= United States Dollar, QALYs= Quality Adjusted Life Years

Sensitivity Analysis

The findings of sensitivity analysis show that cost effectiveness is highly sensitive to progression rates from PFS to PD, quality of life scores, cost of temozolamide, cost of diagnostics, proportion of patients completing temozolamide course despite of toxicity etc. There is a 4.7% probability for temozolamide to be cost effective at the willingness to pay threshold equal to the per capita GDP. However, decreasing the price of temozolamide by 90% increases the probability of temozolamide to be cost effective to 80%. [Figure-1]

Figure 1: Probability of temozolamide use being cost effective at varying willingness-to-pay thresholds.

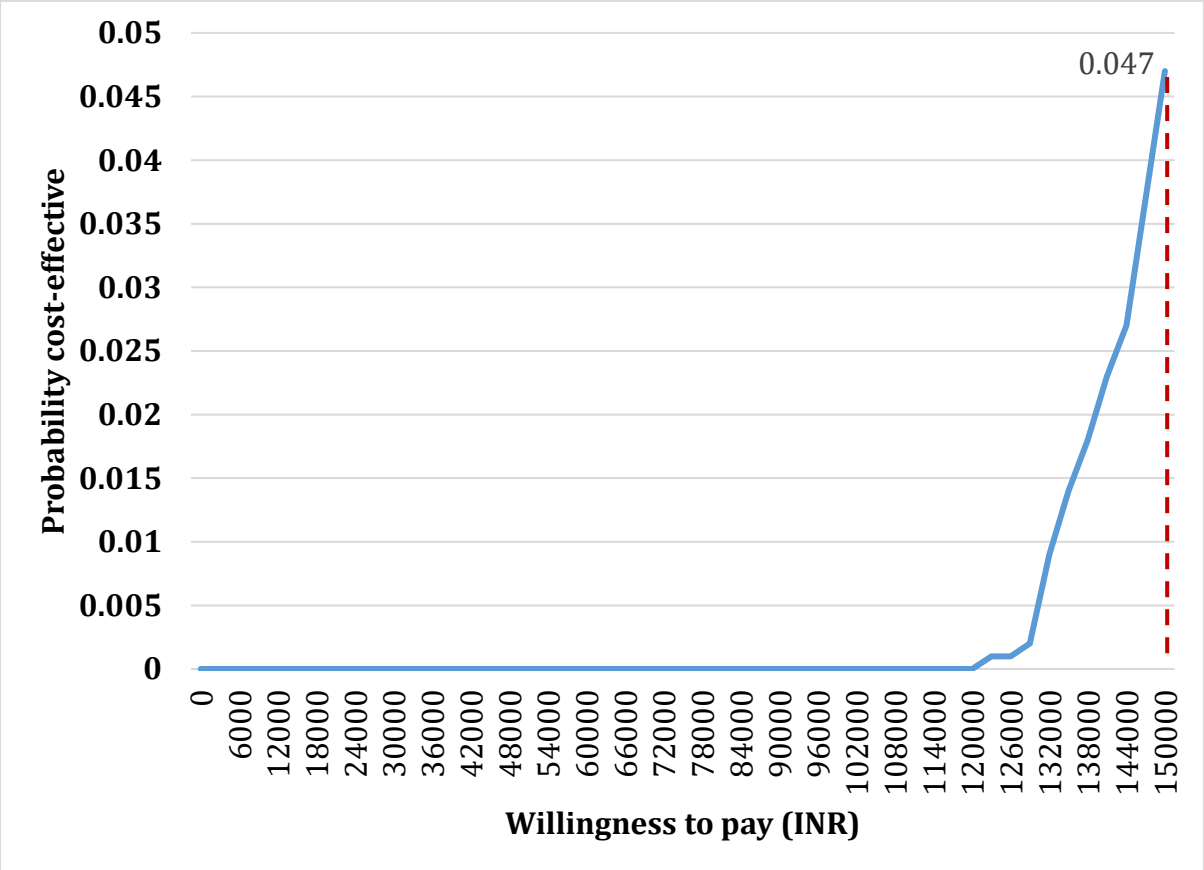
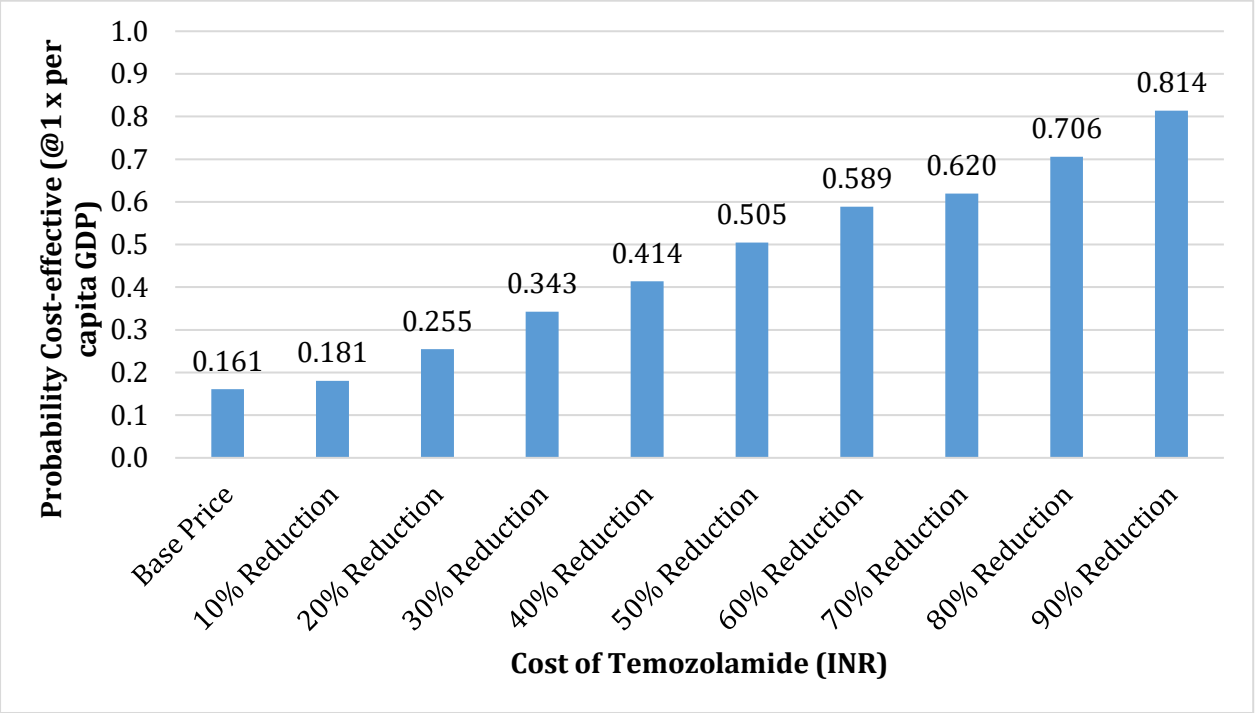


Figure 2: Price sensitivity analysis for cost-effectiveness of temozolamide



Discussion

Management of GBM continues to pose a major health challenge for oncologists in view of the dismal prognosis. Survival advantage offered with the addition of temozolamide to the standard treatment comes with its added cost and needs assessment for the value for money spent in a resource limited country like India. Our analysis found that the addition of temozolamide is not a cost-effective option in India at a willingness to pay equal to the per capita GDP.

Limited cost effectiveness studies on addition of temozolamide in newly diagnosed patients of GBM have been carried out. Majority of them have shown temozolamide to be a cost-effective option [19-22]. However, several of these studies have based their conclusion for cost-effectiveness not on the basis of any country-specific threshold, but on the basis of several other drugs being used in clinical practice with similar cost-effectiveness ratios. Secondly, most of these previous analyses [20, 22] have reported the estimate in terms of cost per LY gained, rather than cost per QALY gained. As shown in our analysis, as well as previous analyses, the gain in QALY per patient is almost half of gain in LY per patient. Hence, the estimate of ICER is likely to be sensitive to the measure of outcome valuation – LY or QALY. Given the international [43], as well as national

guidelines [44, 45], a cost per QALY estimate should be used to judge cost-effectiveness and to make decisions on resource allocation, as has been done in our analysis. Secondly, we have used India's per capita GDP as the threshold for measuring cost-effectiveness. This is again in line with the recommendations of India's health technology assessment agency [46]. The Health Technology Assessment of Board (HTAB) was set up in India in 2017, with its Secretariat (HTAIn) institutionalised in the Department of Health Research [47, 48]. The HTAIs maintains a hub-and-spoke structure for receiving topics from various policymakers and commissioning these topics for conducting research to technical agencies. The present analysis is part of one such broader study evaluating value-based pricing of anticancer drugs, for which India's National Pharmaceutical Agency has undertaken regulation of prices [49]. All the recent Indian economic evaluations which have been commissioned by the HTA agency recently [50], as well as other economic evaluations [51-53]have used the same threshold.

Another major difference between our study and previous analyses is the extent of gain in health outcomes. Majority of the previous model-based evaluations have reported a gain in LY ranging from 0.1 year to 0.25 year per person [20]. We found a gain in LY and QALY per person to be 0.58 and 0.3 year respectively. We calibrated our model based on the Stupp et al findings [6, 7]. The estimated proportion of GBM survivors on temozolamide at 12, 24, 36, 48 and 60 months as per our modelled analysis was 61.3%, 26.6%, 16.2%, 12.6% and 9.6% respectively, which is very similar to what has been reported by Stupp and colleagues (Table 3). Similarly, our estimated survivors for the non-temozolamide arm (10.8%, 4.43%, 3.6%, and 1.9% at 2, 3, 4, and 5 years respectively) closely match the previous trial (Table 3). Despite this, the differences in outcomes from other model-based cost effectiveness analyses could be due to their truncated time horizon of 5 years. On the other hand, we used a lifetime study horizon. Beyond 5 years, we used an exponential distribution to model survival benefits. In one study [20] which undertook a sensitivity analysis to report outcomes with a lifetime study horizon, a gain in 0.53 LY was reported, which is similar to our study findings. Based on the finding of the Stupp trial [6, 7], that there was right-censoring at the completion of the trial, which was disproportionately higher among the intervention arm, our approach of a lifetime study horizon seems more justified to value the full benefits. Nonetheless, it is important to highlight that even with higher health benefits, our overall conclusion is that the use of temozolamide is not cost-effective at the current price.

We have used the effectiveness data, drug discontinuation rate, drug related adverse effects from the Stupp trial [7] and the subsequent results published with a median follow up of more than 5 years of the EORTC NCIC trial [6]. Unlike some of previous analyses which use a single value of hazard ratio based upon the median OS or median PFS, we used the reported outcomes at different time intervals (6, 12, 18, 24, 36, 48, 60 months) to estimate transition probabilities for intervention and control arms. Various published Indian studies [29-31] report similar PFS and OS, as well as the corresponding drug discontinuation and adverse effects among Indian population. However, because of the long term follow up data available with the EORTC NCIC trial, this has been preferred for analysis. All costing parameters were derived from Indian studies [34, 54-58]. Price for the drug, cost of toxicity management health care facilities included as per representative Indian data.

The various strategies used in the management of recurrent GBM add to the cost without any significant survival advantage. Based on this dismal prognosis, and financial constraints, majority of patients do not receive active intervention after progressive disease. Hence as also supported by the guidelines [36], best supportive care was considered for the patients in PD and costs for subsequent chemotherapy or alternative management was not added in the analysis.

Table 3: Comparison of Model Estimates for Survival with Existing Studies

Therapy	Duration of Follow-up (Months)	Percent Patients Survived (95% C.I*)									
		Progression Free Survival					Overall Survival				
		Model Estimate	Stupp et al (2005)	Jhulka et al (2013)	Goda et al (2015)	Jalali et al (2007)	Model Estimate	Stupp et al (2005)	Jhulka et al (2013)	Goda et al (2015)	Jalali et al (2007)
Temozolamide	12	26.7	26.9	34	48.6	NR	61.3	NR	44	66	66.8
	18	18.8	18.4	NR	NR	NR	39.5	NR	NR	NR	NR
	24	10.2	11.2 (7.9-15.1)	12	NR	NR	26.6	27.2 (22.2-32.5)	NR	34	29.8
	36	6.4	6 (3.6-9.2)	NR	NR	NR	16.2	16 (12-20.6)	NR	NR	NR
	48	5.7	5.2 (3.3-8.7)	NR	NR	NR	12.6	12.1 (8.5 (16.4)	NR	NR	NR
	60	4.1	4.1 (2.1-7.1)	NR	4.1	NR	9.6	9.8 (6.4-14)	NR	7	NR
No Temozolamide	12	9.2	9.1	NR	NR	NR	50.1	NR	NR	NR	NR
	18	3.9	3.9	NR	NR	NR	20.5	NR	NR	NR	NR
	24	15.2	1.8 (0.7-3.8)	NR	NR	NR	10.8	10.9 (7.6-14.8)	NR	NR	NR
	36	1.36	1.3 (0.4-3.3)	NR	NR	NR	4.43	4.4 (2.4-7.2)	NR	NR	NR
	48	1.3	1.3 (0.4-3.3)	NR	NR	NR	3.6	3 (1.4-5.7)	NR	NR	NR
	60	1.2	1.3 (0.4-3.3)	NR	NR	NR	1.9	1.9 (0.6-4.4)	NR	NR	NR

*C. I-= Confidence Interval; NR – Not reported

Study limitations

Our study has a few limitations. Firstly, in the absence of country specific evidence on quality of life of GBM patients, we used the utility values for GBM health states reported in a published study from UK. Several of the previously conducted CEA studies have also used these utility values. Secondly, we did not incorporate the indirect costs due to lost productivity as a result of morbidity or premature mortality. However, this was in view of Indian HTA an guideline recommendation which does not support inclusion of productivity costs. Thirdly, cost for management of adverse effect prophylaxis was assumed to be constant and continuous during the treatment to facilitate the model parameters. Though this may not be representative of true life situation, but as it does not add much to the cost and was found to be insensitive in the sensitivity analysis, this assumption does not impact the results. Fourthly, we acknowledge the cost of care in the public and private sector can vary significantly [26, 59], which may alter the ICER values. We primarily used the estimates for cost of care from the studies undertaken in public sector and since the cost of care in private sector is relatively higher, using private sector costs would have increased the ICER. Our analysis using the public sector cost estimates implies temozolamide is not cost-effective and so, an analysis from private sector perspective would have made the use of temozolamide even less cost-effective. Hence, using private sector costs would not have altered the conclusion of our analysis. Lastly, we did not evaluate the cost-effectiveness of temozolamide in the patients with MGMT promoter methylated tumours vs MGMT promoter unmethylated tumours where in the former condition temozolamide results in improved survival. In India, currently MGMT promoter methylation status is not routinely checked both due to non-availability of test at all centres and additional cost associated to it. However, we find this as relevant research question and should be evaluated in future studies.

Overall, we found that use of adjuvant temozolamide along with radiation is not cost effective in India as compared to radiation alone for treatment of GBM. Reduction in price of temozolamide by 90% is likely to increase its probability to be cost effective to 80%. Indian standard treatment guidelines as well as reimbursement protocols under

the Ayushman Bharat Prime Minister Jan Arogya Yojana should consider our findings for formulation of evidence based guidelines and policies.

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Chapter 9: Cost Effectiveness of Trastuzumab for Management of Breast Cancer in India

Introduction

Breast cancer is the most common cancer among women in India and accounts for 27% of all cancers inthat country [1]. Overexpression of the oncogene human epidermal growth factor receptor 2 (*HER2/neu*) is associated with poor prognosis and high risk of recurrence [2-4]. Addition of the HER2-targeted mono- clonal antibody trastuzumab to chemotherapy in ad- juvant treatment has been shown to improve disease-free survival (DFS) by 50% and overall survival (OS) by30% [5-7]. However, trastuzumab is an expensive drug. It was reported to have been used in only 8.6% of eligiblepatients, half of whom were enrolled in a clinical trial [8].

The low rate of trastuzumab use raises the importantquestion of whether public resources should be usedto make this treatment routinely accessible in India. This question is highly relevant because of the re-cently announced ambitious Indian health insurance program, Ayushman Bharat, which includes coverageof chemotherapy for cancer treatment under the Prime Minister's Jan Aarogya Yojana (PMJAY) component [9-10]. Many cost-effectiveness analyses of trastuzumab have been reported, with variable results [11-19].The variability in findings can be attributed to differences in per-spective, modeling method, context, health care de- livery structure, price, and other input parameters.

A major limitation of the existing literature is thata majority of these model-based cost-effectiveness analyses have based their outcome valuation on the interim results of clinical trials with relatively shortfollow-up. No cost-effectiveness analysis has yet been published taking into account the long-term clinicalbenefits based on the Herceptin Adjuvant (HERA) trial (ClinicalTrials.gov identifier: NCT00045032) [7].More-over, although a majority of previous economic evaluations have used effectiveness estimates from the HERA trial, the HERA trial protocol is not commonly followed in routine clinical practice by oncologists in India [20].

We undertook this cost-effectiveness analysis of adjuvanttrastuzumab in combination with standard chemother- apy compared with chemotherapy alone in the Indian context. The base case presents the analysis for 1-yearuse of trastuzumab, which is standard practice. Detailed subgroup analyses were also undertaken, and we present cost-effectiveness findings for 6-month and 9-week trastuzumab use.

Methods

Model Overview

A Markov model was developed for HER2-positive breast cancer in Indian women (Fig 1). The 5 health states were as follows: disease-free state, locoregional recurrence (LR), metastasis, death resulting from breast cancer, and all- cause mortality. Ten percent of those who developed LR were assumed to revert back to a disease-free state in the subsequent year [21]. Thereafter, no remission from LR to back to a disease-free state was possible. Transition probability from LR to metastasis was 3 times that of disease-free state to metastasis.

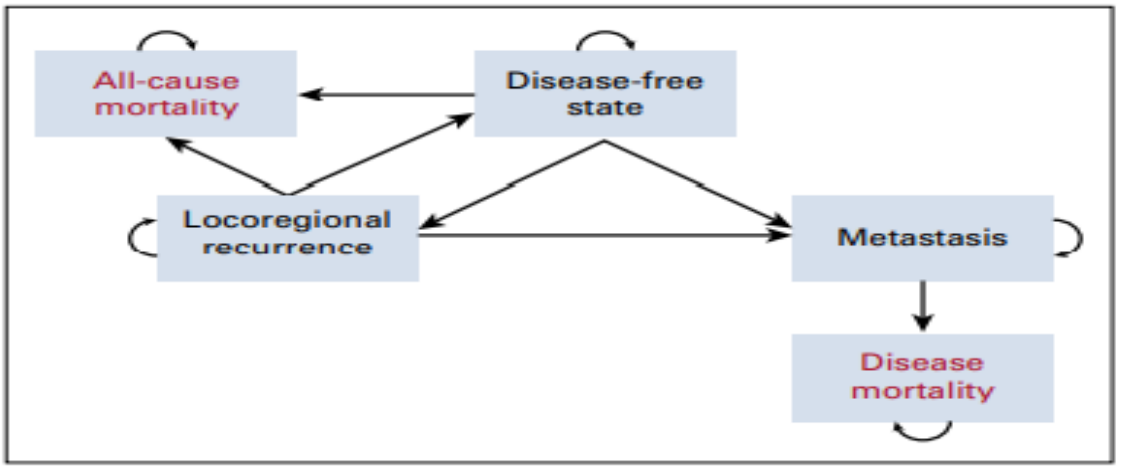

Figure 1: Model schematic

We modeled the lifetime costs and consequences of treating a cohort of patients with surgically resected HER2- positive breast cancer at age ≥ 50 years with adjuvant chemotherapy or adjuvant chemotherapy plus trastuzumab from a societal perspective. Both health system costs and out-of-pocket expenditures were estimated. Indirect costs resulting from productivity losses were not included. Out- comes were calculated on the basis of life-years (LYs) and quality-adjusted LYs (QALYs) gained. All future costs and consequences were discounted at 3% considering in- ternational best practices, as well as recently published Indian guidelines for economic evaluation [22-24]. A cycle length of 1 year was considered appropriate based on available literature [16, 18-9, 25-26]. Results are reported as in- cremental cost (Indian national rupee [INR]) per LY and QALY gained with use of trastuzumab. As per guidelines for health technology assessment in India, we used a threshold of per-capita gross domestic product (GDP) in 2019 to evaluate cost effectiveness [23].

Intervention and Control

We considered 1 year of trastuzumab along with adjuvant chemotherapy as an intervention and adjuvant chemo- therapy (comprising anthracycline and taxane-based drugs) as a counterfactual group in the base case analy- sis. The base case analysis is presented in 2 scenarios. In base case 1, we used the effectiveness evidence from the HERA trial, whereas in base case 2, the effect size of the joint analysis was used; everything else remained constant. Three alternative intervention scenarios were considered based on the duration of trastuzumab use: 1 year, 6 months, and 9 weeks, respectively. Patients in a disease- free, LR, or metastatic state were assumed to be managed as per standard international (National Comprehensive Cancer Network) and national (Indian Council of Medical Research) guidelines [27-28]. (Table-1)

Table 1: Clinical Parameters for Assessing Cost Effectiveness of Adjuvant Trastuzumab versus Chemotherapy

Parameter	Base Value	95% CI	Source
Utility			
Disease free in first year	0.749	0.579 to 0.919	16
Disease free after first year	0.847	0.703 to 0.991	16
LR	0.81	0.673 to 0.947	16
Metastatic	0.484	0.402 to 0.566	16
Transitional probability			
Standard Chemotherapy			
Disease free to LR	0.049	0.043 to 0.055	42,44
Disease free to metastatic	0.084	0.074 to 0.094	42,44
LR to metastatic	0.231	0.205 to 0.258	42,44
Metastatic to DC	0.73	0.647 to 0.813	42,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to disease free (second year only)	0.1	0.089 to 0.111	21
1-year trastuzumab			
Year 1			
Disease free to LR	0.021	0.018 to 0.023	47
Disease free to metastatic	0.035	0.031 to 0.039	47
Metastatic to DC	0.73	0.647 to 0.813	43,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.097	0.086 to 0.108	47
Year 2			
Disease free to LR	0.026	0.023 to 0.029	48
Disease free to metastatic	0.045	0.039 to 0.05	48
Metastatic to DC	0.73	0.647 to 0.813	43,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.123	0.109 to 0.137	48
LR to DFS	0.053	0.047 to 0.059	48
Years 3-15			
Disease free to LR	0.037	0.033 to 0.041	7,45,46
Disease free to metastatic	0.064	0.057 to 0.071	7,45,46
Metastatic to DC	0.73	0.647 to 0.813	43,44

Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.176	0.156 to 0.196	7,45,46
Years 16-20			
Disease free to LR	0.049	0.043 to 0.055	43,44
Disease free to metastatic	0.084	0.074 to 0.094	43,44
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LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.009	0.008 to 0.01	43,44
HR for DFS from HERA trial, year			
1	0.42		47
2	0.53		48
3-4	0.76		45
5-8	0.76		46
9-15	0.76		7
HR for DFS from joint analysis of NSABP B-31 and NCCTG N9831 trials			
Year 1-15	0.6		6
Discount rate, %	3		22-24
Proportion of patients requiring management in trastuzumab and SC arms, %			
LR			
Surgery	88.1		31
Radiotherapy	57.6		31
Chemotherapy	85		31
Hormone therapy	38.4		31
Tamoxifen	50		Expert opinion
Aromatase inhibitor	50		Expert opinion
Metastasis			
Surgery	18.8		31
Radiotherapy	36.1		31
Chemotherapy	85.7		31
Hormone therapy	42.6		31
Line of therapy			
Hormone therapy	42.6		31
First	95		Expert opinion

First and second	5		Expert opinion
Chemotherapy	85.7		31
First	75		Expert opinion
First and second	20		Expert opinion
First, second, and third	5		Expert opinion
Disease free			
Hormone therapy	50		Expert opinion
Tamoxifen	50		Expert opinion
Aromatase inhibitor	50		Expert opinion
Average trastuzumab daily dose in first year, mg/kg	8 for first cycle and 6 for next 16 cycles		47
Survival rate in SC arm, %			
At 5 years	66.1		43
At 10 years	35		44

Abbreviations: ACM, all-cause mortality; DC, death resulting from breast cancer; DFS, disease-free survival; LR, locoregional recurrence; SC, standard chemotherapy

Cost

Trastuzumab infusion at 8 mg/kg for the first cycle and 6 mg/kg for the remaining 16 cycles was considered for all patients in the first year in the intervention arm, assuming an average weight of 60 kg. The average weight of women with breast cancer in India was assumed as per findings of previous studies [29-30]. The cost for those with a disease-free health state in the intervention arm accounted for out- patient (OPD) oncology and cardiac consultation, electrocardiogram, echocardiography, mammography, and hormone therapy. For those with LR, the cost accounted for clinical examination (OPD consultation), routine diagnostic tests, and radiologic tests. Additionally, the costs of per- forming various procedures for patient management, such as local mastectomy, radiotherapy, chemotherapy, and hor- mone therapy, were included. Similarly, various diagnostic tests and management protocols

(chemotherapy, radiother- apy, hormone therapy, and surgery) as per the Indian Council of Medical Research cancer registry were taken into account (Tables 1 and 2). In addition, the cost of management of cardiac complications was included in intervention arm. The cost for patients with a disease-free health state in the control arm included oncology OPD consultation, mammography, and hormone therapy. Similarly, for those in an LR or metastatic health state, an identical set of hematologic, diagnostic, and radiologic tests and recurrent breast cancer management guidelines were followed as for the intervention arm. The treatment regimens and their use in the intervention and control arms (applicable to new or all health patients in respective health states) were followed as per standard treatment guidelines [27-28].To make the cost of treatment more in keeping with real data, we used the rates of use of various treatment options among patients in different health states, as reported in the pooled data from Indian cancer registries [31] (Table 1). Locally published studies were used to elicit the unit costs of various diagnostic and therapeutic services provided to these patients [32-33]. For those services, where published cost studies were not available, we relied on provider payment rates under the national social insurance scheme for central government employees [34]. Data on prices of medicine were obtained from procurement rates of the medical service corporation in Tamil Nadu state [35].

Valuation of Consequences

Nearly 18 cost-effectiveness studies have been undertaken to evaluate trastuzumab [11-14, 16-19, 21, 25-26,36-42]. Eight studies modeled consequences using effectiveness estimates reported in the HERA trial, whereas 6 used the joint analysis of NSABP B-31 (ClinicalTrials.gov identifier: NCT00004067) and NCCTG N9831 (ClinicalTrials.gov identifier: NCT00898898) trials. The HERA trial reported OS and DFS over a longer follow-up period and reported hazard ratios (HRs) at multiple time points, but this protocol is not commonly practiced in India or elsewhere. Moreover, crossover of patients be- tween study arms was likely to have led to an underesti- mation of the benefits of adjuvant trastuzumab. The joint analysis reported a greater benefit, with an HR of 0.60, and its protocol is commonly followed in routine practice.

Therefore, we used the efficacy data from both analyses to separately report the outcomes and cost effectiveness of 1 year of trastuzumab in 2 separate base case analyses [6].

The CONCORD study, which used data on survival out- comes from 2 Indian cancer registries, reported 5-year survival of 66.1%.43 Similarly, another Indian study that reported long-term outcomes found a 35% survival rate at 10 years [44]. We calibrated the model in the control arm (because use of trastuzumab has been reported in India among only 8.6% of eligible patients) so that the survival rates were as reported for the Indian patient population. Furthermore, using the DFS HRs from the HERA trial at each of the 5 different time points, from the first to 11th year, we applied the year-wise HRs to the control arm transition probabilities to arrive at the intervention arm transition probabilities [7, 45-48]. For the 12th to 15th years, we assumed the same HR reported in the HERA trial for 11th year; beyond year 15, we did not assume any further trastuzumab effectiveness. For computing the transition probability in the intervention arm using the effectiveness estimate of the joint analysis, we used an HR of 0.60 for each year up to 15 years.

The risk of mortality resulting from metastatic breast cancer reported in published evidence from India44 was further calibrated to match the overall breast cancer survival trends reported in the CONCORD and long-term survival analysis studies. The same risk of mortality resulting from metastasis was applied to patients in both the intervention and control arms. Age-wise risk of mortality as per Indian sample registration survey life tables was applied to women in both the intervention and control groups.49 Utility values for the disease-free state in first and subsequent years, re- spectively, were 0.749 and 0.847, whereas for LR and metastatic health states, utility values were 0.484 and 0.810, respectively (Table 2) [18].

Sensitivity Analysis

A probabilistic sensitivity analysis using second-order Monte Carlo simulation was undertaken. The values for transition probability varied by 10%, whereas values for

both utility and cost varied by 20% each around the base value. Beta distribution was used to parameterize transition probability and health state utility values. Similarly, gamma distribution was used for cost parameters. The number of iterations was restricted to 1,000.

We undertook a subgroup analysis to assess the cost effectiveness of 6-month and 9-week trastuzumab use compared with standard chemotherapy. The HRs for DFS and cardiac events with 6 versus 12 months of trastuzumab use were derived from estimates reported in 2 trials, PERSEPHONE and PHARE, respectively [50-51]. Because the estimates of each of the 2 trials were slightly different, the incremental cost-effectiveness ratios (ICERs) were com- puted separately using the HR for DFS reported in each trial. The HRs for DFS of 1.07 and 1.08 as reported in the PERSEPHONE and PHARE trials, respectively, were applied to the transition probabilities of 1-year trastuzumab use as computed earlier in the base model to derive transition probabilities for 6-month trastuzumab use. The probability of dying with metastasis was similar to that of the base case. Similarly, transition probabilities for 9-week trastuzumab use were computed using hazard rates and cardiac events from 9 weeks versus 12 months of trastu- zumab separately as reported in the Short HER (HR, 1.13) and FinHER trials [51-53].

A threshold analysis was undertaken to ascertain the price at which the ICER value was below the per capita GDP. The threshold was justified based on economic evaluations conducted in India [22]. Indian health technology assessment guidelines [23], and a recent oncologic cost-effectiveness analysis conducted in India [54-56].

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First and second	20		Expert opinion
First, second, and third	5		Expert opinion
Disease free			
Hormone therapy	50		Expert opinion
Tamoxifen	50		Expert opinion
Aromatase inhibitor	50		Expert opinion
Average trastuzumab daily dose in first year, mg/kg	8 for first cycle and 6 for next 16 cycles		47
Survival rate in SC arm, %			
At 5 years	66.1		43
At 10 years	35		44

NOTE. 1 US$ = INR 69.92.

Abbreviations: BCT, breast-conserving therapy; CBC, complete blood count; CECT, contrast-enhanced computed tomography; CRT, conformal radiation therapy; ER, estrogen receptor; INR, Indian national rupee; LFT, liver function test; OPD, outpatient department; PET, positron emission tomography; PR, progesterone receptor; SC, standard chemotherapy; USG, ultrasound sonography.

Table 2- Cost Parameters for Assessing Cost Effectiveness of 1-Year Adjuvant Trastuzumab SC

Parameter	Unit cost		95% CI		Source
Drug					
Annual (lifetime) trastuzumab cost	2,41,963	3,447	1,73,825 to 2,75,523	2,486 to 3,940	35
Daily hormone therapy (tamoxifen)	0.86	0.01	0.66 to 1.06	0.01 to 0.02	35
Daily hormone therapy (letrozole)	0.58	0.01	0.41 to 0.72	0.01 to 0.01	35
Chemotherapy (paclitaxel + docetaxel)	544	8	436 to 653	6 to 9	35

Chemotherapy (zoledronic, 1 vial)	70	1	54 to 86	0.8 to 1.2	35
Line therapy, chemotherapy (capecitabine, 1 500-mg tablet)	15	0.2	11 to 18	0.2 to 0.3	35
Line therapy, chemotherapy (carboplatin + gemcitabine + vinorelbine)	2,696	39	2,086 to 3,306	30 to 47	35
Line therapy, hormone therapy (fulvestrant)	67,920	971	52,548 to 83,292	752 to 1,191	Review of market prices
Clinical and radiologic tests					
ECG	18	0.3	14 to 22	0.2 to 0.3	33
Echocardiography	358	5	277 to 439	4 to 6	33
OPD cardiac consultation	259	4	109 to 408	2 to 6	33
OPD consultation	150	2	116 to 184	2 to 3	34
Mammography	370	5	286 to 454	4 to 6	34
Bone scan	3,934	56	3,044 to 4,824	44 to 69	34
CBC, BCT, and LFT	187	3	84 to 289	1 to 4	Review of market prices
CECT chest	4,500	64	3,482 to 5,518	50 to 79	34
CECT abdomen	4,500	64	3,482 to 5,518	50 to 79	34
Biopsy of recurrence	1,257	18	973 to 1,541	14 to 22	32
ER, PR, and HER2/neu	2,750	39	2,128 to 3,372	30 to 48	Review of market prices
PET scan	14,663	210	11,344 to 17,982	162 to 257	34
Local mastectomy, simple	12,650	181	9,787 to 15,513	140 to 222	34
3D CRT	75,000	1,073	58,026 to 91,974	830 to 1,315	58
Day care	958	14	741 to 1,175	11 to 17	32
Chest x-ray	60	1	46 to 74	1 to 1	34
USG abdomen	323	5	250 to 396	4 to 6	34

RESULTS

One-Year Trastuzumab: Base Case 1 (HERA trial effectiveness)

The lifetime discounted cost per patient for those receiving 1 year of adjuvant trastuzumab with chemotherapy was found to be INR 341,046 (US$4,878; Table 3). Similarly, patients receiving adjuvant chemotherapy alone incurred a lifetime cost of INR 110,151 (US$1,575). The in- cremental cost per patient of trastuzumab use was INR 230,895 (US$3,302; Table 3). The number of QALYs lived per patient among those re- ceiving trastuzumab and chemotherapy alone were 6.6 and 5.3 years, respectively. The incremental health benefits gained per patient after treatment with trastuzumab were 1.48 LYs and 1.29 QALYs.

Overall, our findings show that use of trastuzumab for 1 year would incur an incremental cost of INR 156,291 (US$2,235) per LY gained and INR 178,877 (US$2,558) per QALY gained (Table 3). The value of incremental cost per QALY gained would be more than the per capita GDP of India; therefore, use of trastuzumab for 1 year would not be considered cost effective in the Indian setting.

One-Year Trastuzumab: Base Case 2 (joint analysis effectiveness)

The lifetime and incremental costs per patient with trastu- zumab were INR 3,37,935 (US$4,833) and INR 2,27,784 (US$3,258), respectively. The LYs and QALYs lived per patient using trastuzumab were 8.7 and 7.0, respectively. The incremental health benefits per patient were found to be 1.93 life-years and 1.69 QALYs gained. As a result, 1-year trastuzumab use would incur an additional cost of INR 1,18,096 (US$1,689) per LY and INR 1,34,413 (US$1,922) per QALY gained (Table 3).

Table 3: Deterministic costs, effects, and cost-effectiveness of 1-Year Trastuzumab Use as compared with SC

1 Year Trastuzumab Use			
Finding (discounted)	**HERA Trial**	**Joint Analysis of NSABP B-31 and NCCTG N9831 Trials**	**SC**
Lifetime cost per patient, INR	3,41,046	3,37,935	1,10,151
Health consequences per patient			

LYs	8.3	8.7	6.8
QALYs	6.6	7	5.3
Incremental cost, INR	2,30,895	2,27,784	
Incremental benefit			
LYs	1.48	1.93	
QALYs	1.29	1.69	
ICER			
INRs per person LY gained	1,56,291	1,18,096	
INRs per person QALY gained	1,78,877	1,34,413	

Abbreviations: ICER, incremental cost-effectiveness ratio; INR, Indian national rupee; LY, life-year; QALY, quality-adjusted life-year; SC, standard chemotherapy.

Subgroup and Sensitivity Analyses

The incremental cost per QALY gained with 6-month trastuzumab use was found to be INR 110,455 (US$1,580) and INR 114,060 (US$1,631) when effectiveness estimates from the PERSEPHONE and PHARE trials, respectively, were used. The incremental cost of 9-week trastuzumab use per QALY gained was found to be INR 43,264 (US$619) and INR 34,268 (US$490) considering the effectiveness reported in the Short HER and FinHER trials, respectively. Each of these ICER estimates falls within the cost-effectiveness threshold of per capita GDP (Table 4).

The findings of cost effectiveness are highly sensitive to the price of trastuzumab, DFS utility after 1 year, and transition probability from a disease-free to metastatic state in the chemotherapy arm. The findings of the probabilistic sen- sitivity analysis suggest that there is a 4% probability for 1-year trastuzumab use to be cost effective at a willingness- to-pay threshold equal to the per capita GDP (Figs 2 and 3). However, reducing the price by 15% to 35% increases the probability of 1-year trastuzumab use being cost effective to 90% (Fig 3).

Table 4: Probabilistic Costs, Consequences, and Probability of Being Cost Effective for 1-Year, 6-Month, and 9-Weeks Adjuvant Trastuzumab Use

Incremental per person								
				Cost per QALY gained				
	Cost			Mean		95% CI		
	INR	US$	QALYs (95% CI)	INR	US$	INR	US$	Probability of Cost Effectiveness at Per Capita GDP
1-year adjuvant trastuzumab use								
HERA trial	1,33,163	1,905	1.29 (1.04 to 1.54)	1,04,503	1,495	104,470 to 104,537	1,494 to 1,495	4
Joint analysis of NSABP B-31 and NCCTG N9831 trials	2,27,915	3,260	1.69 (1.39 to 1.99)	1,35,713	1,941	135,672 to 135,754	1,940 to 1,942	57.3
6-month adjuvant trastuzumab use								
PERSEPHONE trial	1,21,331	1,735	1.09 (0.86 to 1.31)	1,12,957	1,616	112,920 to 112,994	1,615 to 1,616	88.6
PHARE trial	1,20,954	1,730	1.06 (0.85 to 1.28)	1,15,282	1,649	115,243 to 115,320	1,648 to 1,649	88.2
9-week adjuvant trastuzumab use								
Short HER trial	39,309	562	0.91 (0.71 to 1.11)	43,702	625	43,684 to 43,719	625 to 625	100
FinHER trial	64,369	921	1.88 (1.54 to 2.22)	34,600	495	34,588 to 34,612	495 to 495	100

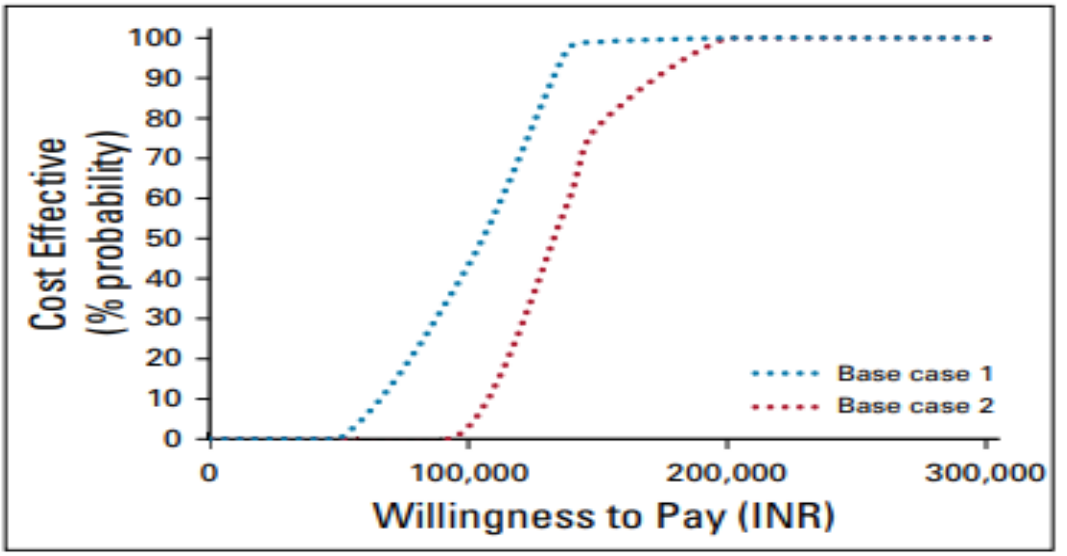

Figure 2: Probability of 1-year trastuzumab use being cost effective at varying willingness-to-pay thresholds. INR, Indian national rupees

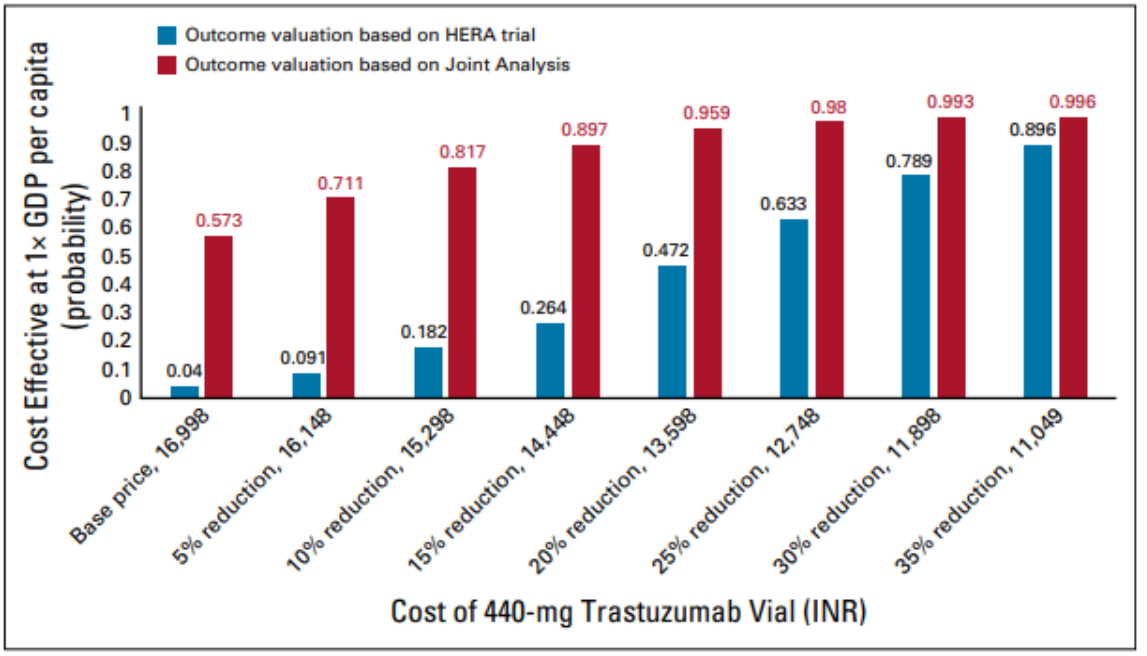

Figure 3 Price sensitivity analyses for cost-effectiveness of 1-year trastuzumab use. GDP, gross domestic product; INR, Indian National Rupee

Discussion

Overall, our findings indicate that trastuzumab use for 1 year is not cost effective at its current price. However, with a 15% to 35% reduction of price, 1-year trastuzumab use would be cost effective. Use of trastuzumab for both 6 months and 9 weeks is cost effective. However, with a statistically similar number of QALYs gained, 9 weeks of trastuzumab use has a lower incremental cost and hence is the most efficient option.

We have presented our results using effectiveness data from a variety of different trials. Second, we used estimates of HRs as reported at different time points (as in the HERA trial) rather than a constant HR, which has been assumed in most of the previous economic evaluations. Third, we calibrated our model for the counterfactual scenario to predict survival based on breast cancer survival from much more pragmatic and representative of the Indian population.

With regard to cost, our parameter values for the cost of management of breast cancer and its complications were obtained from locally published cost studies [32-33] or re-imbursement rates under 1 of India's largest social insurance programs for provider payments [34,58]. Similarly, the patterns of treatment use specific to each stage of disease were based on analysis of hospital-based cancer registries.31 Hence, our cost analysis seems realistic from the national viewpoint. The incremental gain in LYs has ranged from 0.6 to 2.87 in various studies, whereas QALYs gained have varied from 0.49 to 2.83 [11-14, 16-19, 21, 25, 26, 36-42, 59]. We found the incremental health benefit after treatment with trastuzumab to be 1.48 LYs and 1.29 QALYs, both of which are well within the range of values in published evidence.

The incremental cost per QALY gained in terms of pur- chasing power parity ranges from 4,819 international dollars (Int$) to Int$110,283, with a median value of Int$40,998. Our study finding for an ICER (Int$8,954) fell within this range. The relatively lower ICER for trastuzumab use found in India could be attributable to India's relatively lower drug prices and differences in health care delivery structure.

Considering the huge disease and economic burden that cancer imposes, several publicly financed health insurance schemes have been implemented in India [60]. The PMJAY, which is the largest tax-funded health insurance scheme for the poor in India, also includes cancer treatment in its benefit package [9-10]. Given the evidence from our study, it is recommended that insurance schemes provide for 9-week 2 Indian cancer registries. Therefore, our findings are trastuzumab treatment for patients with HER2/neu-positive breast cancer. Furthermore, the National Pharmaceutical Pricing Authority should consider reducing the price of trastuzumab by at least 35%, such that 1-year trastuzumab use would also become cost effective. The network of cancer hospitals as part of the National Cancer Grid could develop a mechanism for common procurement of chemotherapy drugs, which would likely bring down prices [20].

There has been significant emphasis on the development of standard treatment guidelines based on evidence from health technology assessments [23,61]. It is recommended that in addition to clinical evidence on effectiveness, evidence on cost effectiveness be considered while framing clinical guidelines. Empirically derived evidence on transition probabilities and long-term survival to parameterize such cost-effectiveness models is currently lacking. More research is needed using longitudinal studies. Second, there is a lack of clinical data on quality of life at different stages of cancer survival. In the absence of such a study from India, we had to use a valuation study conducted elsewhere. Finally, we recommend generation of a cost database or reference cost menu that could be used by researchers to populate such economic models. This would help reduce the uncertainty.

Conclusion

In conclusion, our study findings show that 1-year use of trastuzumab is not cost effective, or there is significant uncertainty around its cost effectiveness. Reducing the price of the drug by 35% would make 1-year trastuzumab use cost effective. In the current scenario, use of trastu- zumab for 9 weeks is the most efficient option. The clinical guidelines and provider payments for cancer treatment under health

insurance schemes should be accordingly revised.

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SECTION-B: Assessment of economic burden and health-related quality of life among cancer patients in India

Chapter 10: Assessment of economic burden and health-related quality of life among cancer patients in India

Introduction

Traditionally, the burden of cancer is measured in terms of the health outcomes like mortality and morbidity. However, economic measures are equally important for cancer outcome research [1]. These include the cost of services or lost wages incurred as a result of the disease and its treatment [2]. The cost of cancer has gained considerable importance internationally, given the rising health-care costs and its financial consequences. High out-of-pocket payments and the indirect costs associated with cancer treatment, often result in financial toxicity [3] [4] [5]. Therefore, characterization and prediction of these costs, alongside other health outcomes such as both quantity and quality of life, is important for planning strategies to mitigate the financial hardship.

Secondly, considering the increasing costs of diagnostics and therapeutic interventions for cancer, their formal assessment is imperative to inform value-based standard treatment guidelines [6]. Economic evaluations are increasingly used to inform the allocation of health care funds to ensure best value for money being spent. In order to facilitate such analyses in providing the evidence for priority setting, strong information systems will need to be put in place [7]. India has established a health technology assessment agency (HTAIn), which commissions economic evaluation of new interventions, drugs, diagnostics and treatment strategies. The draft Indian reference case for undertaking economic evaluation as part of health technology assessment (HTA), recommends the use of quality adjusted life years (QALYs) as an index to measure the health consequences [8][9]. Computing QALYs requires valuation of health related quality-of-life (HRQOL) or utility scores for different health states. Estimating the utility scores by collecting primary data in each study is time consuming and resource intensive. A database of HRQOL scores for different health states of cancer patients would go a long way to facilitate quick HTA analyses.

The second important evidence need for HTA analyses is cost data. In the context of health financing in India, cost of a service comprises of two parts – health system cost and out-of-pocket expenditure (OOPE). A national health system cost database has been

recently created [10]. Another nationally representative study to measure health system cost of tertiary care hospitals, which includes oncology services, is being carried out in more than 100 hospitals in 11 states [11]. For OOPE, while National Sample Surveys assess the expenditure for all types of morbidities, the sample of cancer patients in this data is a mere 500 at all-India level. Several types of specific cancers do not even have a single case [12] [13]. Hence the main gap in evidence for conducting HTA is robust data for OOPE among cancer patients, which can be stratified by type of cancer, its health states, levels of severity and type of treatment.

The HTAIn in India has commissioned the present study to evaluate the value-based prices for 42 anticancer drugs, which have come under price regulation [14]. Several cancer treatments have been evaluated on grounds of cost-effectiveness. As part of this study, primary data was also collected from cancer patients on costs and HRQOL, which will help to develop a national database of patient costs and quality of life among cancer patients in India – '*National Cancer database for Costs and Quality of Life* – CaDCQoL'. This database would serve to build an open-access data repository to derive estimates of cancer-related medical care costs borne by the patients, indirect costs due to loss of productivity and HRQOL by type of cancer, stage or severity, as well as by treatment approach. This chapter provides the detailed description of data collection plan followed for assessment of out-of-pocket expenditure (OOPE) and HRQOL for each specific type of cancer by stage, site and treatment approach

Methods and Analysis

The health-care costs were estimated using the patient's perspective. A cross-sectional study was conducted to recruit cancer patients at purposively selected seven public health care facilities providing cancer care in India.

Selection of healthcare facilities

A multi-stage stratified sampling technique was followed to recruit cancer patients. In the first stage, the states/regions were selected on the basis of epidemiological transition level (ETL) of top 10 cancers in India. The ETL state groups were defined on the basis of the trends of top 10 cancer types responsible for the highest proportion of cancer disability adjusted life years (DALYs) in India [15]. The states with a relatively lower ratio of DALYs from communicable, maternal, neonatal and nutritional diseases to those from

non-communicable diseases including cancer and injuries combined in 2016 indicate higher ETL. Therefore, the ETL state groups were classified as low level ETL state group (ratio 0·56–0·75), middle ETL state group (0·31–0·55) and high ETL state group (less than 0·31). Among high ETL states, Chandigarh (Punjab) and Tamil Nadu were randomly selected. Similarly among middle and low ETL states, Delhi & Maharashtra and Assam were selected respectively. The selection of these states also ensures geographical representation of the country as shown in Figure 1. Inclusion of Assam ensures presence of northern-east region, which has been reported to have differences in patterns of cancer, owing to significant difference in risk factors [16]. At the second stage, seven health-care facilities were purposively selected in order to choose hospitals in these states which cater to largest volume of oncology patients. Two of the selected hospitals in our sample, are among the top 10 hospitals in terms of cancer treatment claims as part of the largest insurance scheme in India – the *Ayushman Bharat Pradhan Mantri Jan Arogya Yojana* (ABPM-JAY) [17]. At the third stage, probability proportional to size (PPS) method will be used to select patients from each of the disease management groups in these selected health care facilities.

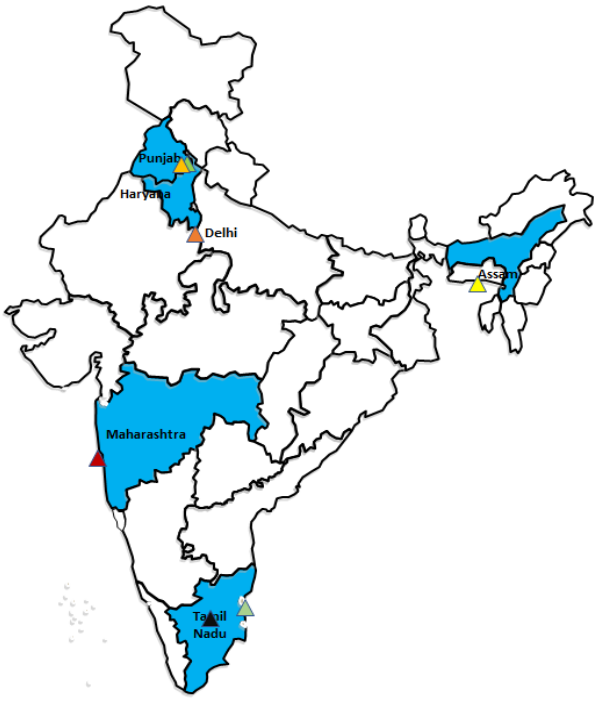

Figure 1: Selected states for proposed study

Table 1: Summary of data collection at selected sites

Duration of data collection	Name of the Centre	Sample size	
		OPD	IPD
05 /10 /2020 to 24/03/2022	GMCH-32, Chandigarh	2395	478
06/10/2020 to 24/03/2022	BBCI, Assam	2073	516
8/10/2020 to 27/08/2021	PGIMER, Chandigarh	931	149
07/10/2020 to 15/11/2021	AIIMS, New Delhi	1243	102
02/12/2020 to 24/03/2022	Adyar Cancer Centre, Chennai	1330	365
05/01/2021 to 31/12/2021	CMC, Vellore	935	435
07/10/2021 to 24/03/2022	Tata Memorial Hospital, Mumbai	880	316
Total	All sites	9787	2361
Grand Total	All sites	12,148	

Patient recruitment

- *Sampling technique*

The patients were recruited prospectively at outpatient and inpatient departments of the selected public health care facilities. The period of data collection at each centre ranged between 14-16 months. However, since the start of data collection was not same across all centres, the data collection had spread out over October 2020 to March 2022. A systematic random sampling technique was used to recruit the patients using sampling interval chosen on the basis of an average daily number of patients in each health facility, and to achieve the desired sample size. This was applicable to health care facilities having common clinics for treating all types of cancers. However, in case of stand-alone cancer centres with different clinics representing different disease management groups (DMGs), a sample of patients were recruited from each of the DMGs using the PPS method. An illustration of the detailed sampling strategy is shown in Figure 2.

- *Inclusion criteria*

The patients diagnosed with any type of cancer irrespective of age and gender seeking hospitalised and non-hospitalised treatment for any stage at selected health care facilities were included in the study. The study recruited three types of cancer patients in outpatient setting viz. newly diagnosed (who have been recently diagnosed with cancer), on-treatment (patients who are on some form of active cancer treatment like chemotherapy/radiotherapy etc.) and follow-up cases (patients whose treatment has been completed and are on maintenance therapy). The inpatient department includes cancer wards, high-dependency unit (HDU), intensive care unit (ICU) etc. Newly admitted cancer patients who were hospitalised overnight (last 24 hours) due to cancer were recruited. Each patient was followed up on a daily basis till discharge for capturing information on expenses incurred during last 24 hours. The HRQOL was assessed on the day of the recruitment. The case definitions used for patient recruitment at outpatient and inpatient settings are described in supplementary appendix S1.

- *Data collection instruments*

  The outpatients and hospitalised patients were interviewed using pretested structured interview schedule to collect information on socio-demographic characteristics, household consumption expenditure, clinical data, out-of-pocket expenditure and quality of life (See supplementary appendix, S2 and S3). Data on indirect costs was also elicited by interviewing both patients and their caregivers. Indirect costs refer to the value of time lost because the patient and the caregivers are unable to carry out normal productive activities because of cancer. Therefore, patients and all their caregivers (one or multiple) accompanying the patient while seeking non-hospitalised treatment as well as during the period of hospitalisation, were interviewed to estimate indirect costs using a pretested structured interview schedule given in supplementary appendix S4. The detailed decription on estimation of indirect costs is given in chapter 11. During patient interviews at outpatient setting, the newly diagnosed, on-treatment patients and follow-up cases who sought care within the last 30 days were interviewed for the direct medical expenditure incurred since the last visit for non-hospitalised treatment such as outpatient consultation, diagnostic tests, day-care sessions (chemotherapy or radiotherapy), drugs purchased from pharmacy stores etc. along with the indirect costs due to loss of productivity. Thus, the mean OOPE since the last hospital visit or during the past 30 days since the

present visit, whichever is less (if the last visit was less than 30 days ago) was estimated.

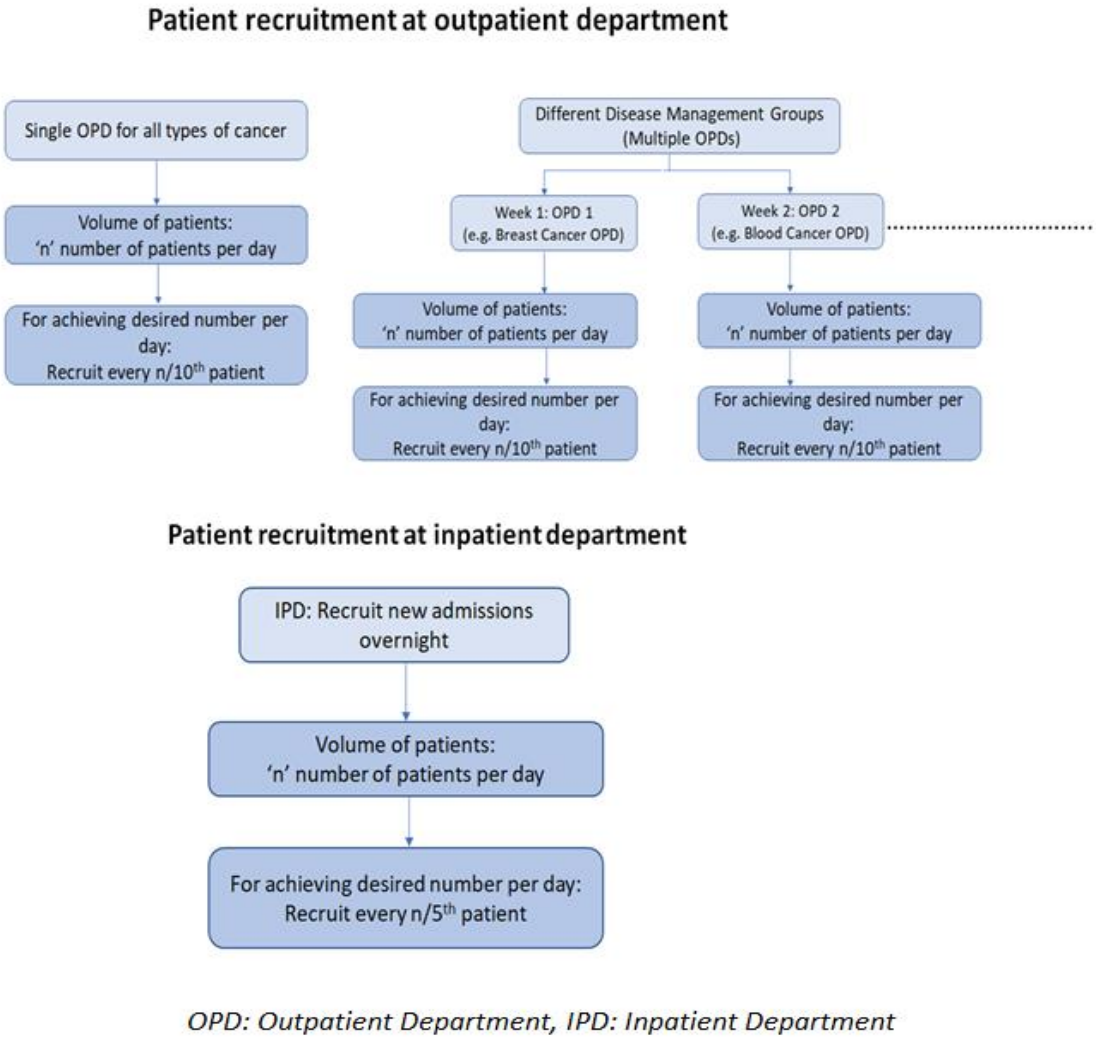

Figure 2: Sampling strategy for patient recruitment

Additionally, patients recruited in outpatient setting were also interviewed for any episode of hospitalization, type of hospital (whether public/private), expenditure incurred on hospitalization during last one year, and the source of financing health care expenditure. However, follow-up cases who sought care more than 30 days ago were interviewed telephonically at 15th day following recruitment to elicit data on expenditure incurred on treatment since their last visit to estimate per visit OOPE on cancer. Other information such as socio-demographic characteristics, morbidity profile, consumption expenditure, OOPE and HRQOL will be captured on the day of recruitment. This is because such follow-up cases with last visit more than 30 days

ago are less likely to recall the expenditure incurred since the last visit [22]. At the time of recruitment, the investigators were trained to develop a good rapport with patients, and a minimum of 2-3 contact numbers were elicited to ensure high response rate on day 15th over telephone. Further, cancer patients require repetitive contact with health-care providers owing to the nature of the disease and hence it was likely that cancer patients would be more responsive during follow-up. Such a methodology of collecting information on OOPE using telephonic interviews has been reported to be valid in several previous studies reporting the follow-up rate of more than 80% using telephonic interviews [23] [24].

The generic health related quality of life data was collected using EuroQol 5-dimensional 5- level (EQ5D5L) for estimation of utility scores among patients of different cancers [25] [26]. EQ-5D-5L is a generic questionnaire intending to cover five attributes of well-being: mobility, self-care, usual activity, pain/discomfort and anxiety/depression [27] [28]. Each attribute of EQ-5D-5L has five levels: (1) no problems, (2) slight problems, (3) moderate problems, (4) severe problems and (5) extreme problem. The summary of data collection plan for outpatients is shown is Figure 3.

Similarly, patients who have been hospitalized overnight were interviewed daily till discharge to collect information on direct medical expenses incurred during last 24 hours on hospitalisation including inpatient stay in cancer ward/HDU/ICU/surgical procedure in inpatient setting etc., indirect costs due to loss of wages as well as HRQOL. However, rest of the information such as socio-demographic characteristics, clinical information, consumption expenditure was recorded on the day of recruitment. The bills of expenditure incurred on medicines, hospital charges, procedure, diagnostics etc. will be obtained to improve the accuracy of data.

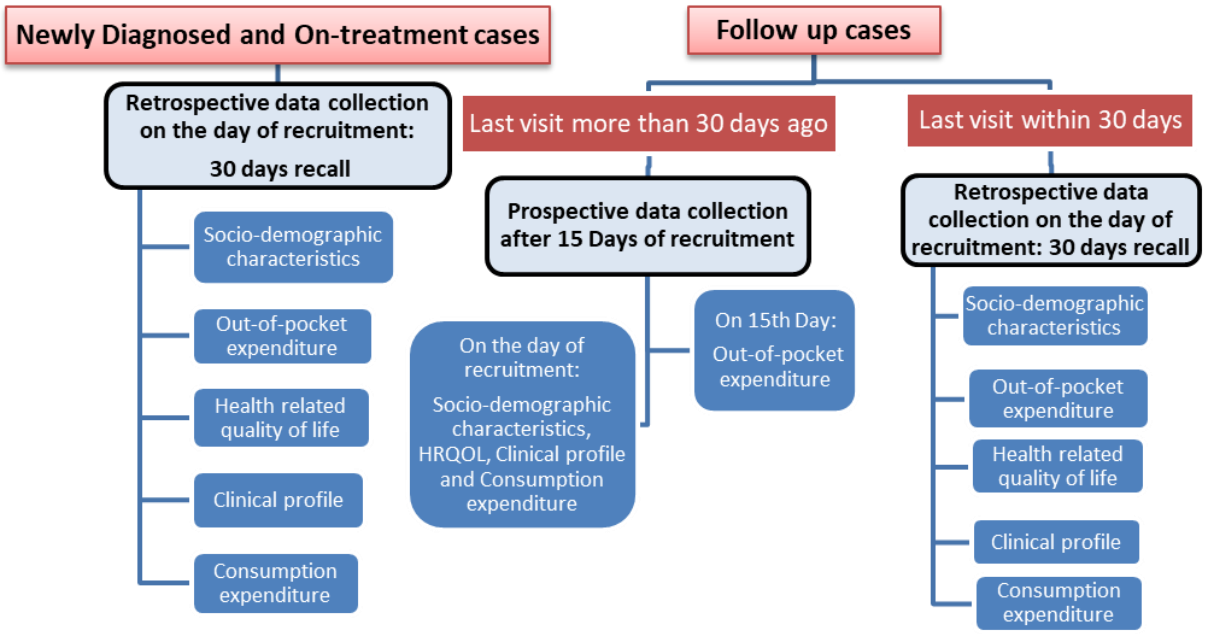

Figure 3: Data collection plan for different types of cancer patients

Data analysis

The data on quality of life was analysed to compute utility scores using Indian tariff value set [29]. This is the first study in India on valuation of health outcomes to use the Indian tariff values to determine utility weights for cancer patients. The mean out-of-pocket expenditure along with standard error was computed with respect to type of cancer, health state, type of treatment (chemotherapy, radiotherapy, surgery etc.) and setting (outpatient, hospitalisation, intensive care) using clinical information obtained. For calculating indirect costs, human capital approach was used [30]. Loss of working days was recorded, that is the days that a person (patient as well as the caregiver) missed or remained absent from his/her work due to hospital stay. For those actively employed in the labor workforce, per day income as reported by the individual was used for calculations. For individuals not part of the workforce, an average minimum daily wage rate for India specific to gender and area of residence (rural/urban) was imputed as detailed in chapter 10 [31]. The extent of financial risk protection was assessed in terms of catastrophic health expenditure, impoverishment and distress financing. Expenditure on cancer treatment which exceeds the threshold of 40% of non-food household consumption expenditure was considered as catastrophic health care expenditure (CHE) [32] [33]. Households which have either borrowed money (with or without interest) or

have sold their assets (like land, home, cattle, etc.) to cope with the expenditure were classified to have faced distress financing [34] [35].

Multiple logistic regression analysis was performed to examine the association of CHE and the distress financing with factors including age, sex, income status, treatment modality, insurance status, locality and stage at the time of diagnosis. Impoverishment was also calculated in terms of relative increase in poverty headcount. We also compared poverty head counts before and after OOP payments for hospitalization. The pre hospitalization poverty headcount (Pre Hp) was calculated using mean per-capita consumption expenditure (MPCE; xi) using the Tendulkar committee's poverty line (PL) cut off of INR 961 per person per month [36].

$$\text{Pre Hp} = 1/n \sum (xi \leq PL)$$

Where n = number of individual

The post hospitalization poverty headcount was also computed in a similar manner by netting out OOP payments for hospitalization from consumption expenditure and then comparing with poverty line

$$\text{Post Hp} = 1/n \sum (xi - OOP \leq PL)$$

Where n = number of individuals

Study outcomes

- Mean per visit OOPE incurred on non-hospitalized treatment of cancer
- Mean OOPE incurred per episode of hospitalisation
- Mean OOPE incurred for outpatients and inpatients, according to cancer site, stage of cancer, type of treatment, presence/absence of adverse events, line of treatment and response to treatment
- Catastrophic health expenditures (CHE), impoverishment and distress financing due to cancer treatment
- HRQOL of cancer patients, by type of cancer, treatment, disease stage, presence/absence of adverse events, line of treatment and response to treatment.

Patient and public involvement

Patients were involved in the present study to capture information on direct medical expenditure incurred on cancer treatment, indirect costs due to loss of productivity and health-related quality of life. A written informed consent was obtained from all study participants who are more than 18 years of age. In case of severely ill or critical patients, we did wait for the patient's condition to improve and then interviewed the patient to collect the required information. This was important since the evidence suggests a need to preferably interview the person affected to elicit data on HRQOL [37]. Accordingly, we obtained informed consent also from the severely ill patient However, in case of minors, the informed consent was obtained from parents/guardians. Further, in case of minors information on OOPE and HRQOL was gathered from parents/guardians and proxy respondents (care providers) respectively. This has also been done in several previous studies [38] [39].

Results

Sociodemographic and clinical profile of cancer patients

A total of 9,897 patients were recruited in the study and data was collected on out-of-pocket expenditure (OOPE) incurred by patients on cancer treatment in India. Out of these, 2,736 patients reported at least one episode of hospitalisation in last one year. The expenditure incurred on different episodes of hospitalisation was also elicited from these patients. The sociodemographic profile of cancer patients recruited in the study has been presented in Table 1.

Socio-demographic profile of patients seeking non-hospitalized treatment and hospitalization

Among patients who received non-hospitalised treatment, 58.3% were females and 41.7% were males. Similarly, among hospitalized cases, 58.8% were females and 41.2% were males. Majority of the patients belonged to the age group of 45-60 years (40.5%) followed by 31-45 years (26.1%) and above 60 years (22.2%). Similar trends were found among hospitalized cancer cases with 41.5% patients in age group of 45-60 years followed by 27.3% in 31-45 years and 20.1% were in age group of 60 years and above. Majority of cancer patients were found to be from rural areas (65% outpatients and 62.7% inpatients) followed by urban areas (34.5% outpatients and 35.5% inpatients) and meagre proportion in slums (1.4% outpatients and 1.8% inpatients).

Approximately 60% of the patients seeking non-hospitalized treatment were covered under different publically financed insurance schemes, private health insurance and patient-aided programmes. Nearly, 10.3% patients were enrolled in national flagship insurance scheme i.e. '*Ayushman Bharat Pradhan Mantri Jan Arogya Yojana*' (AB-PMJAY); 33% under state-sponsored publically financed health insurance schemes, 5.8% availed social insurance schemes including central government health scheme (CGHS), Ex-servicemen contributory health scheme (ECHS) etc.; 3.8% availed private health insurance (voluntary private health insurance-1.6%, employer supported other than government or PSU 1.2% and others-1%) and 6.3% were insured through patient support programmes (philanthropists/NGOs/charitable trusts).

Among hospitalized cases, majority (62.8%) were found to be covered under different health insurance schemes- 13.3% patients were enrolled in AB-PMJAY, 33.1% availed state-sponsored publically financed insurance schemes, 7% were covered under social insurance schemes, 3.3% had private health insurance (voluntary health insurance-1.2%, employer supported than government and PSU-1.1% and others-1%) and 6.1% were insured through patient aided schemes by philanthropists/NGOs/charitable trusts.

Table-1: Sociodemographic profile of cancer patients

Sociodemographic characteristics	Non-hospitalised treatment		Hospitalisation	
	N	%	N	%
Age groups (in years)				
0-15	311	3.20%	74	2.70%
16-30	778	7.90%	229	8.40%
31-45	2559	26.10%	747	27.30%
45-60	3965	40.50%	1135	41.50%
Above 60	2174	22.20%	551	20.10%
Gender				
Male	4078	41.70%	1127	41.20%
Female	5709	58.30%	1609	58.80%
Area of Residence				
Urban	3381	34.50%	972	35.50%
Rural	6269	64.10%	1715	62.70%
Slum	137	1.40%	49	1.80%
Education				
No education	2124	21.70%	594	21.70%
Primary & Middle	3435	35.10%	949	34.70%
Up to Senior Secondary	2942	30.10%	804	29.40%
Graduation & above	1286	13.10%	389	14.20%
Wealth Quintile				
Poorest	1958	20%	499	18.20%
Poor	1960	20%	492	180.00%
Middle	1956	20%	550	20.10%
Rich	1956	20%	584	21.30%
Richest	1957	20%	611	22.30%
Marital Status				
Unmarried	895	9.10%	233	8.50%
Married	7823	79.90%	2173	79.40%
Separated/Divorced	66	0.70%	22	0.80%
Widow/Widower	1003	10.20%	308	11.30%
Health insurance				
AB-PMJAY	1009	10.30%	365	13.30%

State Government Sponsored#	3230	33%	905	33.10%
Social Insurance Scheme	568	5.80%	191	70.00%
Private Health Insurance	369	3.80%	90	3.30%
Philanthropist/NGO	618	6.30%	167	6.10%
Not covered	3993	40.80%	1018	37.20%
Total	**9787**		**2736**	

#State government sponsored category includes patients enrolled in AB-PMJAY and other state health insurance schemes

Direct out-of-pocket expenditure on cancer treatment

The mean OOPE of INR 3,33,408 (S.E 5947.41) was found to be incurred on non-hospitalized cancer treatment and an expenditure of INR 57,553 on hospitalisation. The total mean annual direct OOPE on cancer treatment was found to be INR INR 3,49,497 (S.E. 6047.95) as shown in Figure 1.

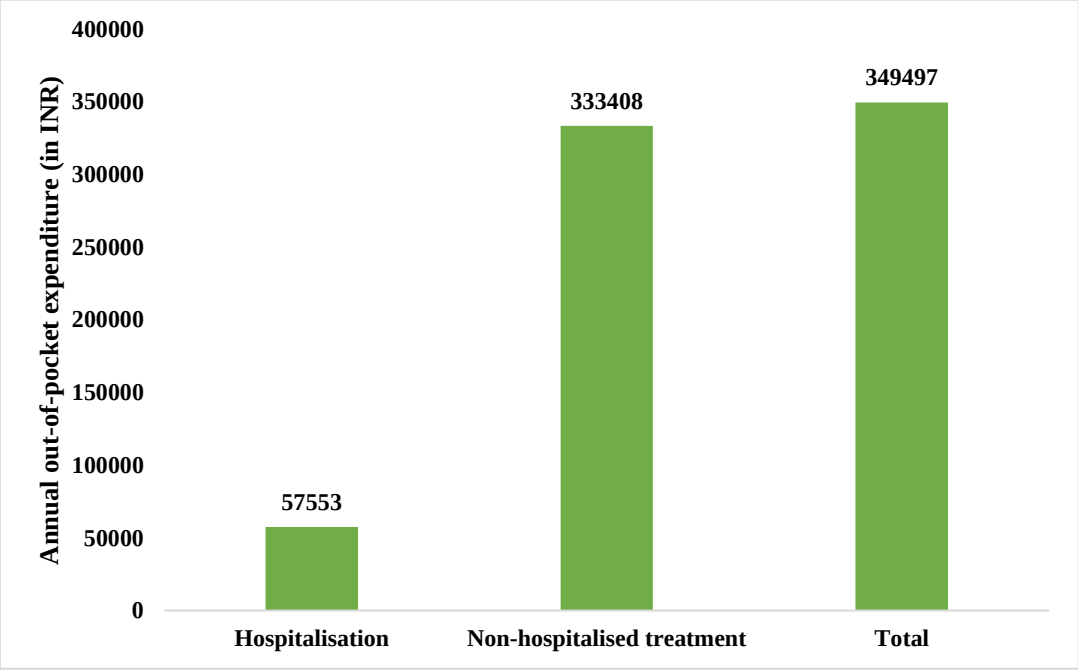

Figure 1: Annual out-of-pocket expenditure on cancer treatment

Out-of-pocket expenditure (OOPE) on non-hospitalised cancer treatment

Per visit mean OOPE on non-hospitalized cancer treatment including chemotherapy, radiotherapy, maintenance therapy, diagnosis and follow-up was found to be INR 8,053 [standard error (SE) 143.7]. A stratified analysis was done to determine the association between mean OOPE and socio-demographic characteristics of cancer patients (Table 2). The difference in OOPE estimates for non-hospitalised treatment was found to be

statistically significant ($p<0.05$) for various parameters, such as age, gender, level of education, wealth quintile and health insurance status. However, area of residence and marital status showed no significant association ($p>0.05$) with OOPE.

Mean direct OOPE on non-hospitalised treatment and its association with socio-demographic characteristics of cancer patients

Mean OOPE incurred was found to be the highest among patients above 60 years of age [INR 8,900 (293.6)] followed by those in the age group of 0-15 years [INR 8,334 (648.3)], 45-60 years [INR 7,977 (237.0)], 16-30 years [INR 7,663 (411.3)], and 31-45 years [INR 7,537 (287.6)]. OOPE was also found to be higher among males [INR 8,907 (227.5)] as compared to females [INR 7,444 (184.7). The OOPE was found to be increasing with increase in level of education [INR 8,585 (293.2) for up to senior secondary education and INR 10,545 (542.8) for graduation and above]. However, OOPE incurred by patients with primary and middle level education [INR 7,137 (205)] or no education [INR 7,292 (229.5)] was comparable. Highest OOPE was incurred by patients belonging to richest income quintiles [INR 12,260 (394.5)] followed by rich [INR 9,307 (323.4)], middle [INR 7,565 (319.3)], poor [INR 6,301 (313.1)], and the poorest [INR 4839 (198.2)] wealth quintiles. Patients who were not covered under any health insurance schemes incurred the highest OOPE [INR 10,092 (278.5)]. Patients insured through philanthropists/NGOs incurred the lowest expenditure [INR 4,164 (315)] followed by those who were enrolled in state government sponsored publically financed health insurance schemes [INR 5840 (174.3)], AB-PMJAY [INR 7,989 (326.7)], private health insurance [INR 9567 (869.3)] and social insurance schemes [INR 9,669 (636)]. It is to be noted that state sponsored schemes also comprise of patients insured through AB-PMJAY as well as state-specific schemes.

Table 2: Association between socio-demographic characteristics and out-of-pocket expenditure (OOPE) for non-hospitalised cancer treatment

Sociodemographic characteristics	Number of patients, N (%)	Mean OOPE in INR (SE)	Median OOPE in INR (IQR)	p-value
Age groups (in years)				
0-15	311 (3.2%)	8334 (648.3)	5000 (8220)	0.018
16-30	778 (7.9%)	7663 (411.3)	4000 (7150)	
31-45	2559 (26.1%)	7537 (287.6)	3350 (6900)	
45-60	3965 (40.5%)	7977 (237.0)	3700 (7600)	
Above 60	2174 (22.2%)	8900 (293.6)	4115 (8900)	
Gender				
Male	4078 (41.7%)	8907 (227.5)	4400 (8890)	0.001
Female	5709 (58.3%)	7444 (184.7)	3400 (6900)	
Area of Residence				
Urban	3381 (34.5%)	8056 (293.2)	3100 (7500)	0.591
Rural	6269 (64.1%)	8079 (158.2)	4050 (7700)	
Slum	137 (1.4%)	6821 (776.7)	3200 (7600)	
Education				
No education	2124 (21.7%)	7292 (229.5)	3700 (6900)	<0.01
Primary & Middle	3435 (35.1%)	7137 (205.0)	3350 (6900)	
Up to Senior Secondary	2942 (30.1%)	8585 (293.2)	3969 (8410)	
Graduation & above	1286 (13.1%)	10545 (542.8)	4685 (10123)	
Wealth Quintile				
Poorest	1958 (20%)	4839 (198.2)	2000 (4335)	<0.01
Poor	1960 (20%)	6301 (313.1)	3077 (5800)	
Middle	1956 (20%)	7565 (319.3)	4000 (7400)	
Rich	1956 (20%)	9307 (323.4)	4500 (8650)	
Richest	1957 (20%)	12260 (394.5)	6420 (12580)	
Marital Status				
Unmarried	895 (9.1%)	7623 (386.4)	4000 (7160)	0.254
Married	7823 (79.9%)	8153 (162.9)	3800 (7900)	
Separated/Divorced	66 (0.7%)	5204 (831.4)	2490 (6970)	

Widow/Widower	1003 (10.2%)	7845 (478.4)	3200 (6520)	
Health insurance				
AB-PMJAY	1009 (10.3%)	7989 (326.7)	4200 (7700)	<0.01
State Government Sponsored#	3230 (33%)	5840 (174.3)	2900 (5100)	
Social Insurance Scheme	568 (5.8%)	9669 (636.0)	4199 (10090)	
Private Health Insurance	369 (3.8%)	9567 (869.3)	2941 (8611)	
Philanthropist/NGO	618 (6.3%)	4164 (315.0)	1500 (3375)	
Not covered	3993 (40.8%)	10092 (278.5)	5200 (9800)	
Total	**9787**	**8053 (143.7)**	**3730 (7600)**	

#State government sponsored category includes patients enrolled in AB-PMJAY and other state health insurance schemes

Mean direct OOPE on non-hospitalised treatment and its association with clinical characteristics of cancer patients

Majority (78%) of the patients were diagnosed with solid cancers and 21.5% with haematological cancers (Table 3). For the rest of the patients (0.4%), the primary site of cancer was not known. The highest proportion (22.1%) of cancer patients were in stage III, followed by stage IV (16%), stage II (12.1%), and stage I (4.2%). A small proportion (0.04%) of cancer patients were diagnosed with carcinoma in situ. At the time of recruitment, 44% of the cancer patients had received chemotherapy since their last visit to the hospital, 3.5% had received radiotherapy, 5.3% had undergone surgery, 2.4% received hormone therapy, 2.4% were on palliative care, and 9.3% received a combination of the therapies mentioned above. The rest of the patients had visited the hospital for diagnostic purpose (1%), maintenance therapy (1.8%), and for receiving other treatments (17%; blood transfusion, follow up, under observation, supportive care, etc.).

Per-visit mean OOPE incurred on non-hospitalised treatment was found to be INR 8,053 (143.7). The results of the stratified analysis showed that clinical characteristics, such as type of cancer, type of treatment, stage of cancer, response to treatment, and adverse effect of treatment were significantly associated ($p<0.05$) with OOPE incurred on non-hospitalised treatment. No significant association was found between OOPE incurred and the line of treatment received ($p>0.05$).

Among different cancer types, OOPE was found to be the highest for haematological cancers [INR 8,728 (282.9)] followed by solid cancer [INR 7,882 (167)], and lowest for cancers of unknown primary site [INR 6,385 (866.4)]. Among different types of treatments received since last visit, OOPE on diagnostics was found to be highest [INR 14,653 (1455.8)] followed by surgery [INR 9,420 (282.9)], maintenance therapy [INR 9,048 (904.3)], radiotherapy [INR 9,016 (772.1)], chemotherapy [8,491 (235.6)], palliative care [INR 8,387 (751)], and combination therapy [INR 6,637 (332.8)]. Among patients with progressive disease, mean OOPE was found to be higher [INR 7,737 (521.8)] than patients in progression-free survival health state [INR 5,731 (315.9)].

Table 3: Association between clinical characteristics and out-of-pocket expenditure (OOPE) for non-hospitalised cancer treatment

Clinical characteristics	Number of patients, N (%)	Mean OOPE in INR (SE)	Median OOPE in INR (IQR)	p-value
Type of cancer				
Solid	7618 (78%)	7882 (167.0)	3500 (7500)	0.041
Haematological	2101 (21.5%)	8728 (282.9)	4400 (8400)	
Cancer of Unknown Primary Site	42 (0.4%)	6385 (866.4)	5235 (6700)	
Type of treatment				
Chemotherapy	4304 (44%)	8491 (235.6)	4200 (7521)	<0.01
Radiotherapy	347 (3.5%)	9016 (772.1)	4000 (8100)	
Palliative care	236 (2.4%)	8387 (751)	4000 (7335)	
Surgery	519 (5.3%)	9420 (687.6)	3850 (9080)	
Combination therapy*	913 (9.3%)	6637 (332.8)	3280 (6698)	
Hormone Therapy	238 (2.4%)	4244 (851.8)	1300 (2600)	
Maintenance Therapy	179 (1.8%)	9048 (904.3)	5500 (7310)	
Diagnostics	97 (1.0%)	14653 (1455.8)	9700 (15407)	
Others	1666 (17%)	5412 (236.6)	2178 (4900)	
No Information	1288 (13.2%)	10210 (462.8)	5220 (11305)	
Cancer Stage				
Carcinoma in Situ	4 (0.41%)	4896 (1849.0)	4012 (5691)	<0.01
Stage I	413 (4.2%)	5538 (602.2)	2400 (5020)	
Stage II	1181 (12.1%)	7229 (369.7)	3350 (6080)	
Stage III	2165 (22.1%)	7639 (375.9)	3200 (7060)	

Stage IV	1564 (16%)	9565 (384.1)	5000 (9400)	
No Information	4460 (45.6%)	8178 (186.8)	4000 (8005)	
Response to Treatment				
Progression Free Survival	2402 (24.5%)	5731 (315.9)	2197 (4600)	<0.01
Progressive Diseases	450 (4.6%)	7737 (521.8)	3775 (8100)	
Ongoing	5394 (55.1%)	8514 (179.2)	4215 (7800)	
Treatment not started	1334 (13.6%)	11232 (459.4)	6250 (12500)	
No Information	207 (2.1%)	3209 (313.3)	1762 (3685)	
Line of Treatment				
First Line	6817 (69.7%)	7558 (151.1)	3500 (6950)	0.181
Second Line	1146 (11.7%)	8234 (595.6)	3655 (7570)	
Third Line	163 (1.7%)	9657 (1229.8)	4880 (9080)	
Fourth Line	20 (0.2%)	9145 (2909.6)	4925 (9880)	
Others*	5 (0.1%)	3786 (1747.3)	2030 (1400)	
Treatment not started	1334 (13.6%)	11232 (459.4)	6250 (12500)	
No Information	302 (3.1%)	3638 (339.8)	1668 (3657)	
Adverse Effects				
Without Adverse Effects	564 (5.8%)	3354 (273.2)	1300 (2348)	<0.01
With Adverse Effects	5145 (52.6%)	8379 (184.4)	4000 (7820)	
No Information	4078 (41.7%)	8293 (250.1)	3800 (8020)	
Total	**9787**	**8053 (143.7)**	**3730 (7600)**	

**Combination therapy: Chemotherapy + Radiotherapy, Surgery + Radiotherapy, Surgery + Chemotherapy, Surgery + Chemotherapy + Radiotherapy, Others-Fifth/sixth line of treatment*

Out-of-pocket expenditure on hospitalisation

The estimated annual mean direct OOPE on hospitalisation (all episodes in last one year) was INR 57,553 (2953.4). The results of the stratified analysis to determine the association between OOPE on hospitalisation and socio-demographic and clinical characteristics of cancer patients are given in Table 4. Among the hospitalised cancer patients, 55.1% were hospitalised in public and 44.9% in private hospitals. Majority (57.6%) were hospitalised for more than five days. Overall, it was found that the area of residence, level of education, wealth quintile, health insurance coverage, type of hospital,

and duration of hospital stay were significantly ($p<0.05$) associated with OOPE incurred by patients on hospitalisation. However, the difference in the OOPE incurred was statistically insignificant ($p>0.05$) for variables like age, gender, and marital status.

Highest OOPE was concentrated among patients belonging to urban areas [INR 75,034 (6406.6)], followed by rural areas [INR 48,257 (2925.8)] and slums [INR 36,127 (6763.0)]. OOPE showed a declining trend with decreasing level of education among cancer patients. Patients with graduation or higher level of education were found to have incurred the highest OOPE [INR 1,11,723 (14673.5)] followed by those with up-to senior secondary education [INR 61,058 (4266.5)], primary and middle school education [INR 41,614 (3644.4)], and no education [INR 42, 800 (4379.5)]. Patients belonging to the richest wealth quintile incurred the highest OOPE [INR 84,400 (6446.8)] on hospitalisation followed by the rich [INR 63,216 (7916.3)], middle [INR 56,946 (8102.9)], poor [INR 43,832 (4043.2)], and the poorest income quintiles [32.250 (3476.7)]. Health insurance coverage also showed a significant impact on OOPE wherein the patients covered under various insurance schemes like state-sponsored health insurance schemes [INR 40,462 (3406.3)], AB-PMJAY [INR 32,824 (3872.5)], social insurance schemes [INR 71,258 (17246.8)] and private health insurance [INR 96,871 (15203.3)] were found to incur lesser expenditure on cancer treatment as compared to those who were not covered [INR 81,596 (6090.6)]. Considering the type of hospital, cancer patients incurred a significantly higher OOPE in private hospitals [INR 79, 342 (5382.8)] than in public hospitals [INR 39,784 (2945.4)]. It was observed that OOPE increased with increasing duration of hospital stay; the highest OOPE [INR 76,273 (4796.3)] was incurred by patients whose duration of hospitalisation exceeded five days.

Mean direct OOPE due to hospitalization and its association with socio-demographic and clinical characteristics of cancer patients

OOPE was also found to be highest among patients above 60 years of age [INR 60,986 (SE-9110.6)]. It was found to be comparable for age groups 16-30 years [INR 60,156 (8524.8)] and 45-60 years [INR 59,934 (3884.6)], but lesser for age groups 31-45 years [INR 52,148 (5311.8)] and 0-15 years [INR 41,979.5 (7790.5)]. Male patients incurred higher OOPE [INR 63,340 (5595.5)] than female patients [INR 53,500 (3088.5)]. For married and widowed patients, OOPE incurred was found to be comparable [INR 57,033

(3314.2) and INR 56,479 (9217), respectively], but lower among separated/divorced individuals [INR 17,607 (11,310.4).

Table-4: Association between direct out-of-pocket expenditure (OOPE) on hospitalisation and sociodemographic and clinical characteristics of patients

Category	Number of patients, N (%)	Mean OOPE in INR (SE)	Median OOPE in INR (IQR)	p-value
Age groups (in years)				
0-15	74 (2.7%)	41979 (7790.5)	16150 (35000)	0.681
16-30	229 (8.4%)	60156 (8524.8)	15000 (67000)	
31-45	747 (27.3%)	52148 (5311.8)	15000 (46000)	
45-60	1135 (41.5%)	59934 (3884.6)	15000 (58000)	
Above 60	551 (20.1%)	60986 (9110.6)	15000 (47000)	
Gender				
Male	1127 (41.2%)	63340 (5595.5)	15000 (55000)	0.124
Female	1609 (58.8%)	53500 (3088.5)	15000 (48000)	
Area of Residence				
Urban	972 (35.5%)	75034 (6406.6)	20000 (75500)	<0.01
Rural	1715 (62.7%)	48257 (2925.8)	15000 (42000)	
Slum	49 (1.8%)	36127 (6763.0)	15000 (47500)	
Education				
No education	594 (21.7%)	42800 (4379.5)	10000 (34000)	<0.01
Primary & Middle	949 (34.7%)	41614 (3644.4)	10000 (39000)	
Up to Senior Secondary	804 (29.4%)	61058 (4266.5)	20000 (55000)	
Graduation & above	389 (14.2%)	111723 (14673.5)	35000 (101000)	
Wealth Quintile				
Poorest	499 (18.2%)	32250 (3476.7)	0 (30000)	<0.01
Poor	492 (18%)	43832 (4043.2)	11750 (44775)	
Middle	550 (20.1%)	56946 (8102.9)	15000 (45500)	
Rich	584 (21.3%)	63216 (7916.3)	18000 (44250)	
Richest	611 (22.3%)	84400 (6446.8)	26000 (70000)	
Marital Status				
Unmarried	233 (8.5%)	67592 (9105.6)	17300 (63100)	0.471
Married	2173 (79.4%)	57033 (3314.2)	15000 (47000)	
Separated/Divorced	22 (0.8%)	17607 (11310.4)	1000 (10000)	
Widow/Widower	308 (11.3%)	56479 (9217)	15000 (57500)	
Health insurance				<0.01
AB-PMJAY	365 (13.3%)	32824 (3872.5)	10000 (25000)	
State Government Sponsored[#]	905 (33.1%)	40462 (3406.3)	8000 (40000)	
Social Insurance Scheme	191 (7%)	71258 (17246.8)	15000 (55000)	
Private Health Insurance	90 (3.3%)	96871 (15203.3)	52335 (110000)	

Philanthropist	167 (6.1%)	20801 (4088.5)	0 (20000)	
Not covered	1018 (37.2%)	81596 (6090.6)	25000 (70000)	
Type of hospital				<0.01
Public	1507 (55.1%)	39784 (2945.4)	15000 (30000)	
Private	1229 (44.9%)	79342 (5382.8)	20000 (90000)	
Duration of hospitalization (days)				
1	107 (3.9%)	17131 (2532.3)	6000 (23000)	<0.01
2	207 (7.6%)	24908 (3465.1)	8000 (23000)	
3	292 (10.7%)	30720 (2780.5)	12000 (37000)	
4	294 (10.7%)	28251 (2737.9)	10000 (28736)	
5	260 (9.5%)	49695 (7826.1)	15000 (44000)	
>5	1576 (57.6%)	76273 (4796.3)	20000 (77000)	
Total	2736	**57553 (2935.4)**	15000 (50000)	

#State government sponsored category includes patients enrolled in AB-PMJAY and other state-specific health insurance schemes

Source of financing for cancer treatment

Non-hospitalised treatment

Most patients (74.3%) used salary or savings to finance cancer-related non-hospitalised treatment. Besides salary or savings, 16.2% patients borrowed money without interest from relatives/friends, 4.4% borrowed money with interest, 2.2% of the patients had to sell assets, 1.8% paid though health insurance, and 1.4% patients resorted to other means of financing.

Hospitalisation

As observed for non-hospitalised treatment, most cancer patients (67%) finance their hospitalization cost from salary or savings. Health insurance was the second most common (14.3%) source of financing for hospitalisation followed by borrowing from

relatives/friends without interest (12.7%), borrowing with interest (3.1%), selling of assets (1.6%), and others (1.4%).

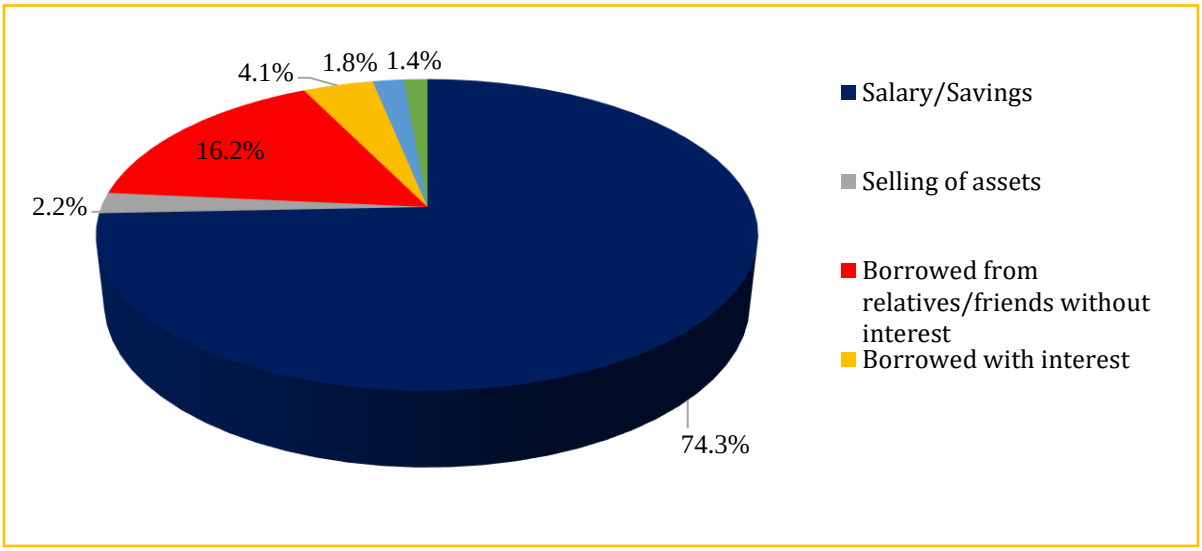

Figure 2: Source of financing for cancer-related non-hospitalised treatment

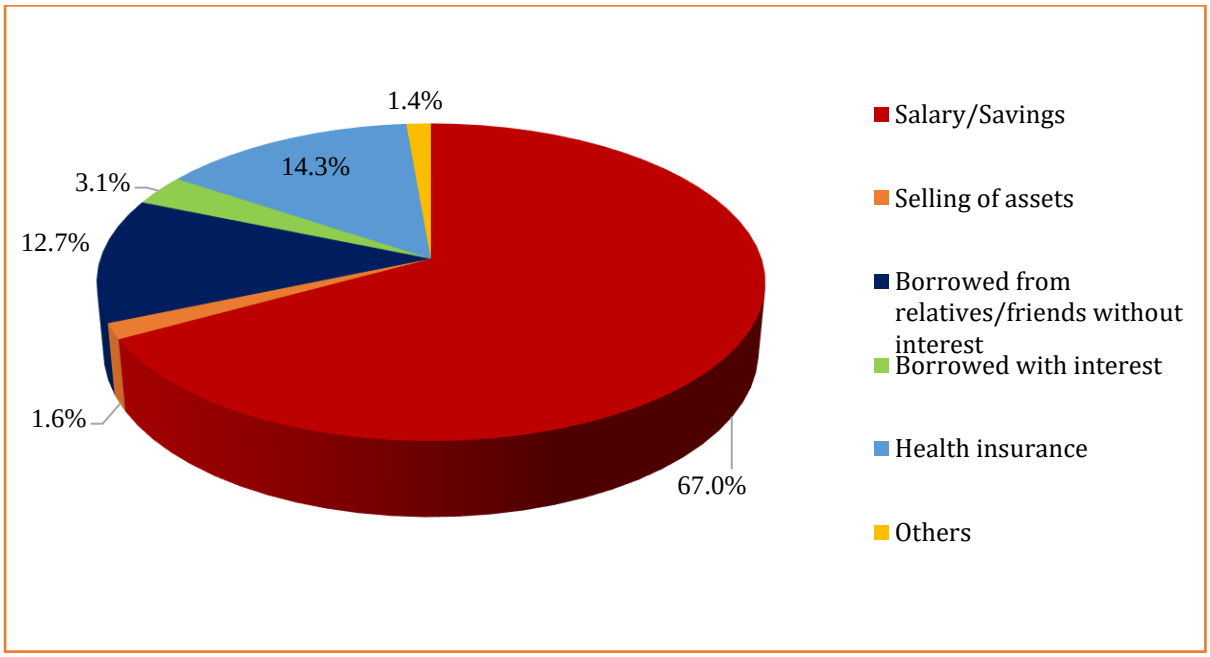

Figure 3: Source of financing for cancer-related hospitalisation

Determinants of out-of-pocket expenditure due to non-hospitalized and hospitalized treatment

The study also determined the factors affecting OOPE due to cancer-related hospitalization (Table 5) and non-hospitalised treatment (Table 6).

Non-hospitalised treatment

The results of the regression analysis showed that OOPE incurred by female patients (B= -609.49, p<0.05) was significantly lower as compared to male patients. In addition, the OOPE incurred by patients with up to senior secondary (B = 1573.3) or graduation and above (B = 1912.82) level of education were found to be significantly higher (p<0.05) as compared to those with no education. Patients from the rich and richest wealth quintiles incurred significantly higher OOPE (B = 2531.89 and B = 5297.59; p<0.05) as compared to poorest income groups. Further, patients insured under different health insurance schemes (except private health insurance) were found to have incurred lower OOPE as compared to those who were not insured (B= -2010.76 for AB-PMJAY; B = -3004.54; B = -1440.55; B = -4165.63; p<0.05). Significantly higher OOPE was incurred by patients on diagnostics [B = 5810.12, p<0.05]. [Table 5]

Table 5: Factors affecting out-of-pocket expenditure on non-hospitalised treatment

Parameter		B	Std. Error	95% Confidence Interval		Sig.
				Lower	Upper	
(Intercept)		6870.01	802.68	5296.79	8443.23	0.000
Age		16.57	10.06	-3.15	36.28	0.100
Gender Ref Male	Female	-609.49	308.80	-1214.74	-4.25	0.048
Education Ref No Education	Primary & Middle	547.75	404.30	-244.67	1340.17	0.176
	Up to Senior Secondary	1573.31	420.41	749.32	2397.29	<0.01
	Graduation & above	1912.82	524.81	884.21	2941.43	<0.01
Wealth Quintile (Reference-Poorest)	Poor	556.71	459.08	-343.06	1456.49	0.226
	Middle	1088.85	480.42	147.25	2030.45	0.024
	Rich	2531.89	488.94	1573.60	3490.19	<0.01
	Richest	5297.59	487.55	4342.00	6253.17	<0.01
Health Insurance (Reference -Not Covered)	AB-PMJAY	-2010.76	547.03	-3082.91	-938.60	<0.01
	State Sponsored	-3004.54	355.34	-3701.00	-2308.08	<0.01
	Social Insurance Scheme	-1440.55	667.73	-2749.28	-131.83	0.031
	Private Health Insurance	110.61	799.79	-1456.95	1678.16s	0.890
	Philanthropist	-4165.63	616.50	-5373.94	-2957.31	<0.01
Type of Cancer (Reference-Solid)	Hematological	91.79	392.22	-676.94	860.53	0.815
	CUPS	-1483.27	2336.62	-6062.96	3096.42	0.526
Type of Treatment (Reference-Chemotherapy)	Radiotherapy	467.38	756.20	-1014.74	1949.51	0.537
	Palliative care	-58.63	898.86	-1820.37	1703.10	0.948
	Surgery	860.37	630.40	-375.18	2095.92	0.172
	Combination Therapy	-1941.23	497.05	-2915.44	-967.02	<0.01

	Maintenance Therapy	-1475.90	1052.71	-3539.18	587.38	0.162
	Diagnostic	5810.12	1377.12	3111.01	8509.22	<0.01
	Hormone Therapy	-3134.94	902.25	-4903.31	-1366.56	0.001
	Others	-2993.18	393.06	-3763.56	-2222.80	<0.01

Hospitalisation

Mean OOPE incurred by patients having an education of graduation and above was found to be significantly higher (B = 46593.70) as compared to those with no education. Further, OOPE incurred by patients belonging to middle (B = 34572.02), rich (B = 36344.15), and richest (B = 43654.91) wealth quintiles were significantly higher ($p<0.05$) as compared to those from the poorest income groups. In addition, patients insured under different health insurance schemes (except private health insurance) were found to have incurred lower OOPE as compared to those who were not insured (B= -33008.28 for AB-PMJAY; B = -45858.64 for state government sponsored schemes; B = -23258.06 for social insurance schemes; B = -4165.63 for philanthropists/NGOs; $p<0.05$). For patients covered under private health insurance schemes, the OOPE incurred was higher (B = 8634.69) than those who are not covered. However, the results were not statistically significant ($p>0.05$). Significantly higher OOPE was incurred by patients who sought hospitalization in private hospitals [B = 50549.82, $p<0.05$] as compared to public hospitals. Significant increase in OOPE was found with increase in duration of hospitalisation (B = 2569.45). [Table 6]

Table 6: Factors affecting out-of-pocket expenditure due to cancer-related hospitalization

Parameter	B	Std. Error	95% Confidence Interval		Sig.
			Lower	Upper	
(Intercept)	-9102.86	16518.72	-41478.96	23273.24	0.582
Age	154.18	200.98	-239.73	548.09	0.443

Area of Residence (Ref- Urban)	Rural	-4308.35	6239.64	-16537.81	7921.12	0.490
	Slum	-24898.64	21476.60	-66992.01	17194.72	0.246
Education (Ref- No Education)	Primary & Middle	-3153.33	7692.62	-18230.57	11923.92	0.682
	Up to Senior Secondary	9466.83	8093.85	-6396.82	25330.48	0.242
	Graduation & above	46593.70	10091.52	26814.68	66372.73	0.000
Wealth Quintile (Ref- Poorest)	Poor	15692.82	9450.94	-2830.68	34216.32	0.097
	Middle	34572.02	9722.62	15516.03	53628.01	0.000
	Rich	36344.15	9831.22	17075.31	55612.99	0.000
	Richest	43654.91	9888.88	24273.07	63036.75	0.000
Health Insurance (Ref-Not Covered)	ABPMJAY	-33008.28	9050.98	-50747.87	-15268.68	0.000
	State Sponsored	-45858.64	7254.09	-60076.40	-31640.88	0.000
	Social Insurance Scheme	-23258.06	11452.12	-45703.80	-812.31	0.042
	Private Health Insurance	8634.69	15981.69	-22688.85	39958.23	0.589
	Philanthropist	-70747.81	12812.55	-95859.96	-45635.67	0.000
Type of Hospital (Ref- Public)	Private	50549.82	6187.38	38422.78	62676.86	0.000
Duration of stay during hospitalization (total number of days)		2569.45	198.84	2179.74	2959.16	0.000

Health care burden due to cancer, stratified according to primary cancer site

A stratified analysis was also done to ascertain the OOPE incurred based on the primary site of cancer for both hospitalisation and non-hospitalised treatment. For hospitalisation, the highest OOPE was found to be incurred on kidney and ureter cancer [INR 70,429], followed by colorectal cancer [INR 54,520], leukaemia [INR 46,245], lymphoma [38,552] & breast cancer [INR 37,692], and the lowest OOPE was incurred on penile cancer [INR 9394]. For non-hospitalised treatment, highest OOPE was incurred on kidney and ureter cancer [INR 13,017], followed by prostate cancer [INR 12,060], lung cancer [INR 11,968], multiple myeloma [INR 11,550], lymphoma [10,627] and the lowest OOPE was found to be incurred on testicular cancer [INR 5,793].

In addition, the health care burden (defined as OOPE as a proportion of consumption expenditure) was computed for different categories of cancers based on primary site as shown in Table 7. The overall health care burden due to hospitalisation was found to be 12% and 43.5% for non-hospitalised treatment. For hospitalisation, the highest health

care burden was for kidney and ureter cancer (29.5%). Other cancer categories with high health care burden include colorectal cancer (19.9%), leukaemia (18.8%), bladder cancer (15.6%), lymphoma (15.3%), breast cancer (15%), and other haematological cancers (15%). However, for non-hospitalised treatment, health care burden was found to be the highest for prostate cancer (67.3%) followed by lung cancer (58.2%), kidney & ureter cancer (56.3%), bone cancer (52.6%), skin cancer (52.5%), colorectal cancer (51.7%), and lymphoma (50.6%).

Table 7: Average OOPE on cancer treatment and health care burden by cancer type

Category of Cancer	Hospitalisation			Non-hospitalised treatment		
	OOPE (INR)	Annual Consumption Expenditure (INR)	Health care burden* (%)	OOPE (INR)	Monthly Consumption Expenditure (INR)	Health care burden*(%)
Bladder cancer	34720	222942	15.6%	7885	17670	44.6
Bone cancer	11039	242571	4.6%	9207	17507	52.6
Brain and other nervous system cancer	20014	253429	7.9%	7126	19065	37.4
Breast cancer	37692	250784	15.0%	6797	16961	40.1
Cancer of unknown primary site (CUPS)	14204	235100	6.0%	6228	16254	38.3
Cervical and Uterine cancer	19593	247193	7.9%	6346	18023	35.2
Colorectal cancer	54520	274361	19.9%	9049	17505	51.7
Head and Neck cancer	19150	236969	8.1%	8163	17910	45.6
Oral cancer	22503	237534	9.5%	7139	18718	38.1
Kidney and Ureter Cancer	70429	238461	29.5%	13017	23123	56.3
Leukaemia	46245	245331	18.8%	6919	18786	36.8
Lung cancer	26649	247803	10.8%	11968	20579	58.2
Lymphoma	38552	252143	15.3%	10627	21003	50.6
Multiple Myeloma	23093	277242	8.3%	11550	23438	49.3
Ovarian cancer	17106	226384	7.6%	6394	18475	34.6
Pancreatic and Biliary cancer	22494	248233	9.1%	8857	18607	47.6
Prostate cancer	22935	229352	10.0%	12060	17932	67.3
Penile cancer	9394	197278	4.8%	7732	17251	44.8
Skin cancer	16470	211310	7.8%	9429	17959	52.5
Soft tissue tumours	11706	222316	5.3%	6062	17007	35.6
Testicular cancer	9940	234309	4.2%	5793	19009	30.5

Upper GI tract cancer	24031	230288	10.4%	8622	17110	50.4
Other haematological cancers	32867	219408	15.0%	10548	21694	48.6
Other cancers*	36408	212806	17.1%	7854	18068	43.5
Total	**30535**	**245752**	**12.4%**	**8053**	**18499**	**43.5%**

Financial toxicity due to cancer treatment

Catastrophic health expenditure

The overall prevalence of catastrophic health expenditure among cancer patients was found to be 84% for non-hospitalised treatment and 28.5% for hospitalisation. The prevalence of impoverishment was also found to be 67% due to non-hospitalised cancer treatment and 17% due to hospitalisation.

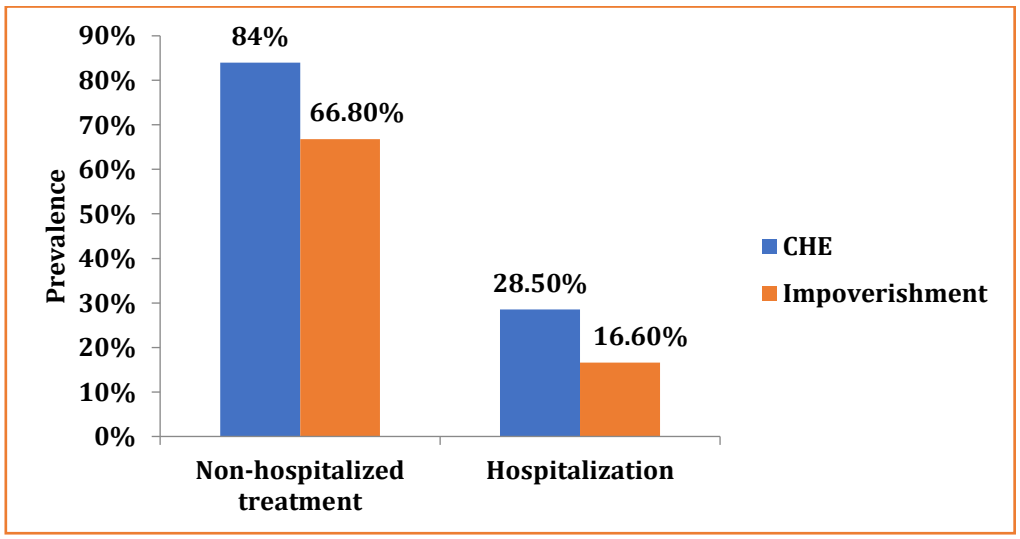

Figure 4: Prevalence of CHE and impoverishment due to cancer treatment

Prevalence of catastrophic health expenditure (CHE) due to cancer treatment

The prevalence of CHE was found to lie in the range of 82.6% to 88.4% and 25.3% to 31.1% among different age groups due to non-hospitalized and hospitalized cancer treatment respectively. CHE was found be more among males (86.4% for non-hospitalised treatment and 29.4% for hospitalisation) than females (82.3% for non-hospitalised treatment and 27.9% for hospitalisation). Based on the level of education, opposite trends in the prevalence of CHE were seen for hospitalisation and non-hospitalised treatment. For non-hospitalised treatment, the prevalence of CHE decreased with increasing level of education (range: 79.9% to 86.5%). However, for hospitalisation,

the prevalence of CHE increased as the level of education increased (range: 24.6% to 36.6%). Furthermore, the prevalence of CHE was highest among outpatients belonging to rural areas (89%) followed by urban areas (75.2%) and slums (75.2%). However, for hospitalisation, it was found to be more concentrated among patients from slums (34.7%) than in urban (28.6%) and rural areas (28.3%).

For both non-hospitalised treatment and hospitalisation, the prevalence of CHE showed a declining trend from poorest to the richest income quintiles. The prevalence of CHE due to non-hospitalised treatment was highest (91.7%) among poorest income group (versus 75.7% among richest quintile). Similar trends were found for CHE due to hospitalisation (33.7% among poorest versus 19.6% among richest).

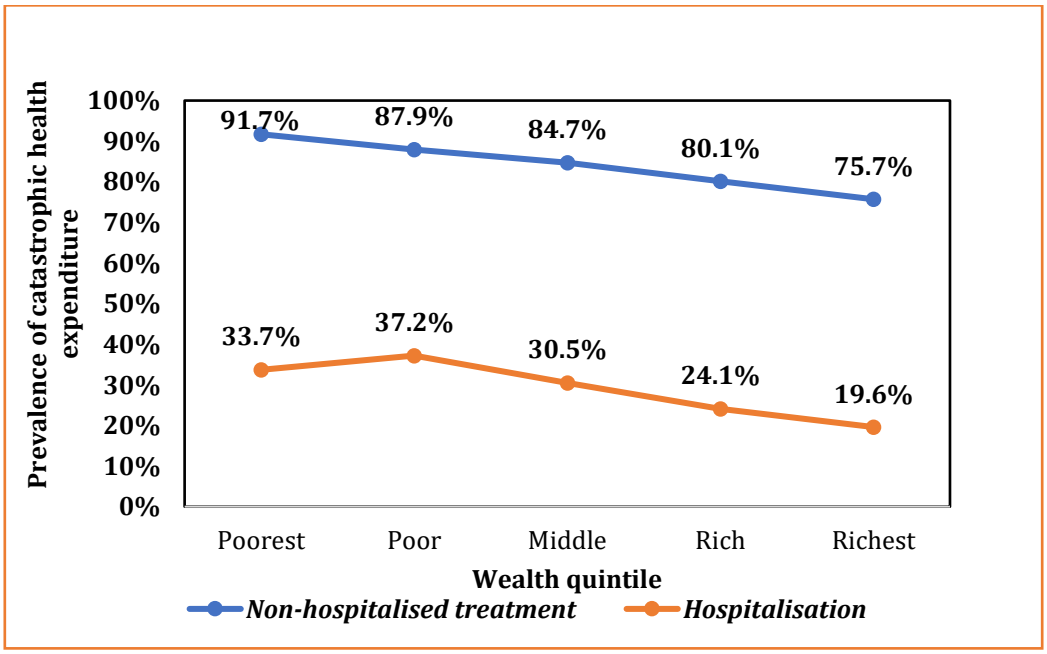

Figure 5: Prevalence of CHE based on wealth quintiles

The prevalence of CHE was highest among patients with no insurance coverage for non-hospitalised treatment (85.7%). Among hospitalized cases, prevalence of CHE was highest among patients insured under private health insurance (46.1%) followed by patients with no insurance (34.1%). Further, among the hospitalized cancer cases, the prevalence of CHE was the lowest among patients who were insured through philanthropists/NGOs (18.6%) and AB-PMJAY (19.7%).

Among different cancer types, the prevalence of CHE was found to be highest for non-hospitalized treatment of cancers of unknown primary site (92.7%) followed by

haematological cancers (87.2%) and solid cancers (83.1%). For non-hospitalised treatment, CHE was highest for diagnostics (91.5%) and lowest for hormone therapy (68.4%). The prevalence of CHE was comparable among patients who received chemotherapy (86.6%), radiotherapy (87%), palliative care (85.2%), surgery (82.8%), and combination therapy (80.3%).

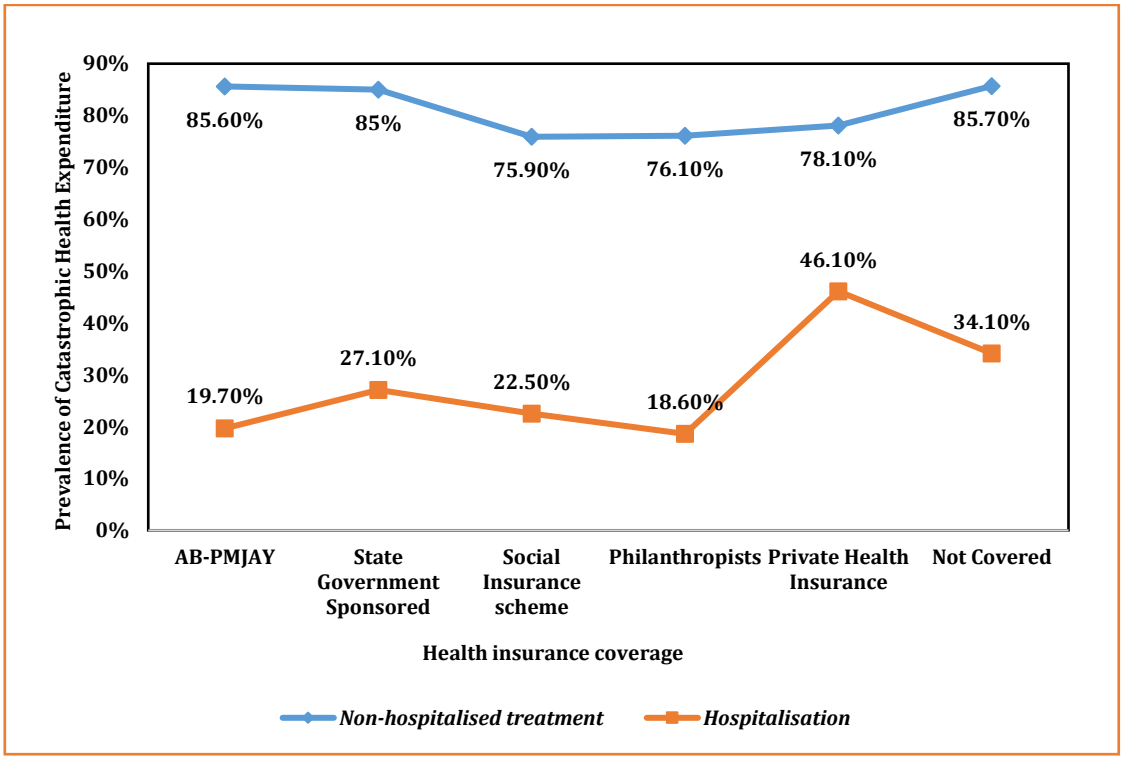

Figure 6: Prevalence of CHE based on health insurance coverage

The prevalence of CHE was higher among patients who sought hospitalization in private hospitals (36.8%) than public hospitals (21.8%). The prevalence of CHE also increased with increase in the duration of hospitalisation; 13.1% for one-day hospitalisation and 34.6% for those hospitalised for more than five days.

Determinants of catastrophic health expenditure (CHE) due to cancer treatment

Logistic regression analysis was run to determine the factors influencing catastrophic health expenditure on cancer-related hospitalisation and non-hospitalised treatment.

Non-hospitalised treatment

The results of the analysis showed that the likelihood of CHE was about four times higher for patients from rural areas (β = 3.839, p<0.05) as compared to those from urban areas. Patients from slum areas had a 5.7% higher likelihood of experiencing CHE than those from urban areas. However, the relationship was found to be statistically insignificant (β = 1.057, p=0.880). The likelihood of CHE was the highest among patients in the poorest wealth quintile as compared to richest income groups. The odds of CHE were 53.3%, 73.3%, 86.1%, and 88.4% for poor, middle, rich and richest income quintles respectively) and were found to be statistically significant (p<0.05).

As compared to patients with no health insurance coverage, the likelihood of CHE due to non-hospitalised treatment was 40.4%, 53.1%, 53.8%, 21.5%, and 72.1% lower among those covered under AB-PMJAY, state government sponsored, social insurance scheme, private health insurance, and philanthropists/NGOs, respectively. These odds were found to be statistically significant (p<0.05) for all categories of health insurance except for private health insurance (p=0.441). When compared to patients who received chemotherapy, it was found that the likelihood of CHE was significantly lower among patients who received hormone therapy (β=0.319, p<0.05) and other treatments (β=0.592, p<0.05). The odds of CHE were also lower among patients who received radiotherapy, palliative care, surgery, maintenance therapy, and diagnostics as compared to those who received chemotherapy. However, the results were found to be statistically insignificant (p>0.05). Among the type of cancers, patients with haematological cancers were four times more likely to experience CHE than those diagnosed with solid cancer. However, this relationship was found to be statistically insignificant (p>0.05). As the stage of cancer increased, the likelihood of CHE also increased among cancer patients. However, a statistically significant relationship was found for stage IV cancer only with 1.8 times (β=1.820. p<0.05) higher odds of CHE as compared to stage 1 cancer patients. Patients with ongoing response to treatment had a 54.7% (β = 1.547, p<0.05) higher likelihood of experiencing CHE than those in the progression-free survival stage. For patients in the progressive disease state, the odds were 44.3% higher in comparison to progression-free survival stage patients, however, no statistically significant association was noted (β = 1.443, p>0.05). Variables such as age, gender, marital status, level of

education, type of cancer, line of treatment, and adverse effects of treatment did not significantly affect the odds of experiencing CHE.

Hospitalisation

The results of the logistic regression analysis showed that the likelihood of CHE was about 29.3% higher for patients from rural areas (β=1.293, p<0.05) and 83% higher for slum areas when compared to those belonging to urban areas. Patients with higher level of education showed higher odds of CHE as compared to those with no education. However, the odds were statistically significant for educational level of up to senior secondary (β=1.437, p<0.05) and graduation and above (β=1.947, p<0.05). The likelihood of CHE was found to be decreasing from poor to richest wealth quintiles as compared to poorest income groups. However, the odds were found to be statistically significant only for the rich (β = 0.619, p<0.05) and richest (β = 0.376, p<0.05) quintiles. A statistically significant (p<0.05) trend of decreasing odds of CHE was observed for patients covered under health insurance schemes, wherein the likelihood of CHE was 54.7%, 62.1%, 49.9%, and 81.9% lower among patients covered under AB-PMJAY, state government sponsored schemes, and philathropists/NGOs, respectively. However, the odds of CHE were found to be approximately 40% higher for patients with private health insurance. Hospitalisation in private hospitals and a longer duration of hospital stay were significantly associated with higher odds of CHE (β=2.235 for private hospitals and β=1.025 for duration of stay; p<0.05).

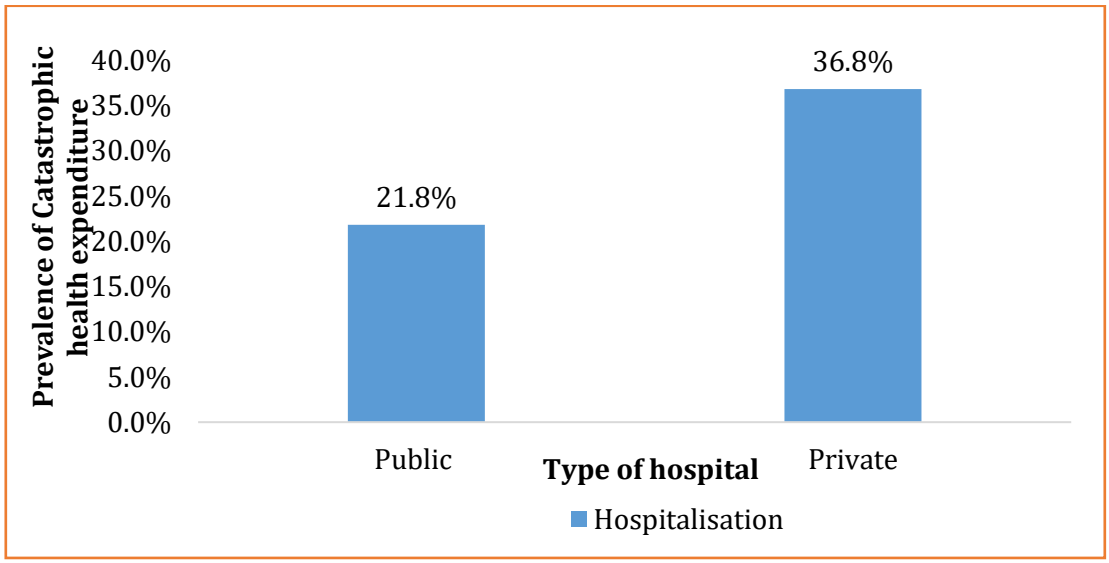

Figure 9: Prevalence of catastrophic health expenditure based on type of hospital

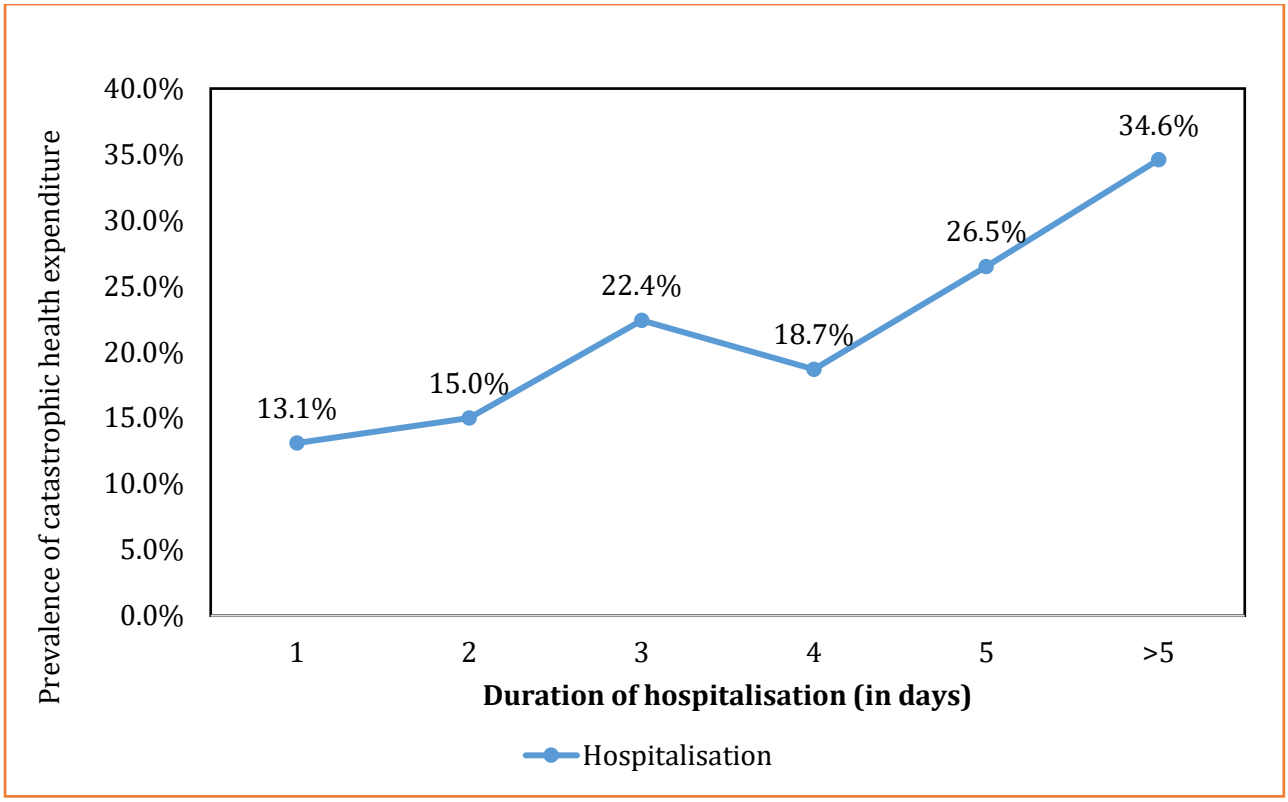

Figure 10: Prevalence of catastrophic health expenditure based on duration of hospitalisation

Table 8: Determinants of catastrophic health expenditure (CHE) for cancer-related non-hospitalized treatment and hospitalisation

	Non-hospitalised treatment				Hospitalisation			
Patient characteristics	**No. of patients (N)**	**Prevalence of CHE (%)**	**CHE**	**p-value**	**No. of patients (N)**	**Prevalence of CHE (%)**	**CHE**	**p-value**
			Adjusted Odds Ratio (95% CI)				**Adjusted Odds Ratio (95% CI)**	
Age groups								
0-15	311 (3.2%)	88.4%	1.009 (1.000,1.018)	0.047	74 (2.7%)	31.1%	0.999 (0.992 ,1.007)	0.878
16-30	778 (7.9%)	87.9%			229 (8.4%)	30.6%		
31-45	2559 (26.1%)	82.6%			747 (27.3%)	26.9%		
45-60	3965 (40.5%)	82.9%			1135 (41.5%)	30.5%		
Above 60	2174 (22.2%)	85.7%			551 (20.1%)	25.3%		
Gender								
Male	4078 (41.7%)	86.4%	Reference		1127 (41.2%)	29.4%	Reference	
Female	5709 (58.3%)	82.3%	0.967 (0.766 ,1.221)	0.779	1609 (58.8%)	27.9%	1.026 (0.847,1.243)	0.790
Area of Residence								
Urban	3381 (34.5%)	75.2%	Reference		972 (35.5%)	28.6%	Reference	
Rural	6269 (64.1%)	89.0%	3.881 (3.106,4.849)	<0.01	1715 (62.7%)	28.3%	1.293 (1.056,1.582)	0.013
Slum	137 (1.4%)	75.2%	1.057 (0.517,2.16)	0.880	49 (1.8%)	34.7%	1.83 (0.952,3.517)	0.070
Education								
No education	2124 (21.7%)	86.5%	Reference		594 (21.7%)	24.6%	Reference	
Primary & Middle	3435 (35.1%)	84.4%	0.929 (0.698,1.238)	0.617	949 (34.7%)	25.7%	1.037 (0.803,1.338)	0.782
Up to Senior Secondary	2942 (30.1%)	83.5%	0.934 (0.689,1.268)	0.663	804 (29.4%)	30.8%	1.437 (1.1,1.879)	0.008
Graduation & above	1286 (13.1%)	79.9%	1.233 (0.836,1.817)	0.290	389 (14.2%)	36%	1.947 (1.41,2.69)	0.000
Wealth Quintile								
Poorest	1958 (20%)	91.7%	Reference		499 (18.2%)	34%	Reference	
Poor	1960 (20%)	87.9%	0.451 (0.309,0.659)	<0.01	492 (18%)	37%	1.149 (0.863,1.531)	0.342
Middle	1956 (20%)	84.7%	0.25 (0.168,0.371)	<0.01	550 (20.1%)	31%	0.837 (0.62,1.131)	0.247
Rich	1956 (20%)	80.1%	0.13 (0.088,0.191)	<0.01	584 (21.3%)	24%	0.527 (0.385,0.723)	0.000
Richest	1957 (20%)	75.7%	0.108 (0.073,0.159)	<0.01	611 (22.3%)	20%	0.329 (0.237,0.458)	0.000
Marital Status								
Unmarried	895 (9.1%)	85.8%	Reference		233 (8.5%)	31%	Reference	
Married	7823 (79.9%)	84.1%	1.255 (0.781,2.016)	0.348	2173 (79.4%)	29%	0.997 (0.684,1.453)	0.987
Separated/Divorced	66 (0.7%)	78.8%	1.052 (0.351,3.152)	0.928	22 (0.8%)	5%	0.106 (0.013,0.845)	0.034
Widow/Widower	1003 (10.2%)	82.2%	1.071 (0.594,1.93)	0.819	308 (11.3%)	28%	0.983 (0.602,1.605)	0.944

Health insurance								
Not covered	3993 (40.8%)	85.7%	Reference		1018 (37.2%)	34.1%	Reference	
AB-PMJAY	1009 (10.3%)	85.6%	0.596 (0.389,0.913)	0.018	365 (13.3%)	19.7%	0.453 (0.332,0.617)	<0.01
State Sponsored	3230 (33%)	85.0%	0.469 (0.36,0.611)	0.000	905 (33.1%)	27.1%	0.379 (0.299,0.481)	<0.01
Social Insurance Scheme	568 (5.8%)	75.9%	0.462 (0.283,0.753)	0.002	191 (7%)	22.5%	0.501 (0.338,0.741)	0.001
Private Health Insurance	369 (3.8%)	78.1%	0.785 (0.424,1.453)	0.441	90 (3.3%)	46.1%	1.394 (0.877,2.216)	0.16
Philanthropist	618 (6.3%)	76.1%	0.279 (0.178,0.436)	0.000	167 (6.1%)	18.6%	0.181 (0.114,0.288)	<0.01
Type of cancer								
Solid	7618 (78%)	83.1%	Reference		-	-	-	-
Haematological	2101 (21.5%)	87.2%	4.264 (0.531,34.23)	0.172	-	-	-	-
CUPS	42 (0.4%)	92.7%	1		-	-	-	-
Type of treatment								
Chemotherapy	4304 (50.6%)	86.6%	Reference		-	-	-	-
Radiotherapy	347 (4.1%)	87.0%	0.906 (0.57,1.441)	0.676	-	-	-	-
Palliative care	236 (2.8%)	85.2%	0.653 (0.343,1.243)	0.195	-	-	-	-
Surgery	519 (6.1%)	82.8%	0.791 (0.542,1.156)	0.226	-	-	-	-
Combination therapy*	913 (10.7%)	80.3%	0.867 (0.64,1.173)	0.354	-	-	-	-
Maintenance Therapy	179 (2.1%)	90.4%	0.394 (0.052,2.966)	0.366	-	-	-	-
Diagnostic	97 (1.1%)	91.5%	0.908 (0.082,10.032)	0.937	-	-	-	-
Hormone Therapy	238 (2.8%)	68.4%	0.319 (0.193,0.525)	<0.01	-	-	-	-
Others	1666 (19.6%)	79.0%	0.592 (0.364,0.962)	0.034	-	-	-	-
No Information	1288 (13.2%)	85.2%			-	-	-	-
Cancer Stage								
Carcinoma in Situ	4 (0%)	100.0%	1		-	-	-	-
Stage I	413 (4.2%)	78.6%	Reference		-	-	-	-
Stage II	1181 (12.1%)	82.3%	1.156 (0.773,1.729)	0.479	-	-	-	-
Stage III	2165 (22.1%)	82.2.%	1.234 (0.856,1.779)	0.260	-	-	-	-
Stage IV	1564 (16%)	88.5%	1.82 (1.206,2.746)	0.004	-	-	-	-
No Information	4460 (45.6%)	84.2%			-	-	-	-
Response to Treatment								
Progression/ Disease Free Survival	2402 (24.5%)	75.0%	Reference		-	-	-	-
Progressive Diseases	450 (4.6%)	83.5%	1.443 (0.839,2.479)	0.185	-	-	-	-
Ongoing	5394 (55.1%)	86.5%	1.547 (1.153,2.077)	0.004	-	-	-	-
Not Applicable	1334 (13.6%)	90.3%			-	-	-	-
No Information	207 (2.1%)	83.0%			-	-	-	-

Line to Treatment								
First Line	6817 (69.7%)	82.9%	Reference		-	-	-	-
Second Line	1146 (11.7%)	83.2%	0.84 (0.588,1.201)	0.336	-	-	-	-
Third Line	163 (1.7%)	88.3%	1.917 (0.632,5.813)	0.25	-	-	-	-
Fourth Line	20 (0.2%)	75.0%	0.199 (0.036,1.107)	0.065	-	-	-	-
Other	5 (0.1%)	80.0%	1		-	-	-	-
Not Applicable	1334 (13.6%)	90.3%			-	-	-	-
No Information	302 (3.1%)	81.7%			-	-	-	-
Adverse Effect								
Without Adverse Effect	564 (5.8%)	75.0%	Reference		-	-	-	-
With Adverse Effect	5145 (52.6%)	86.3%	1.128 (0.741,1.716)	0.574	-	-	-	-
No Information	4078 (41.7%)	82.4%			-	-	-	-
Type of hospital	**-**	**-**	**-**					
Public	-	-	-	-	1507 (55.1%)	21.8%	Reference	
Private	-	-	-		1229 (44.9%)	36.8%	2.235 (1.833,2.724)	<0.01
Duration of hospitalisation (days)								
1	-	-	-	-	107 (3.9%)	13.1%	1.025 (1.019,1.032)	<0.01
2	-	-	-		207 (7.6%)	15.0%		
3	-	-	-		292 (10.7%)	22.4%		
4	-	-	-		294 (10.7%)	18.7%		
5	-	-	-		260 (9.5%)	26.5%		
>5	**-**	**-**	**-**		1576 (57.6%)	34.6%		
Total	**9787**	84.0%			**2736**	28.5%		

Prevalence of impoverishment due to cancer treatment

The prevalence of impoverishment ranged from 13.2% to 22.2% across different age groups among cancer patients for hospitalisation and from 64.9% to 72.3% for non-hospitalised treatment. Impoverishment was found to be concentrated more among males (17.7% due to hospitalization and 71% due to non-hospitalized treatment) than females (15.8% due to hospitalization and 63.6% due to non-hospitalized treatment).

Patients belonging to rural areas faced the greatest impact of impoverishment (71.6%) due to non-hospitalised treatment. However, for hospitalisation, impoverishment was found to be more concentrated among cancer patients belonging to urban areas (17.2%). For non-hospitalised treatment, among different levels of education, the prevalence of impoverishment was the highest among cancer patients with no education (68.3%) and for hospitalization, it was more prevalent among patients with educational level of graduation or above (24.1%). The prevalence of impoverishment declined with increase in the level of income, from poorest to richest income groups for both hospitalisation and non-hospitalised treatment (Figure 7).

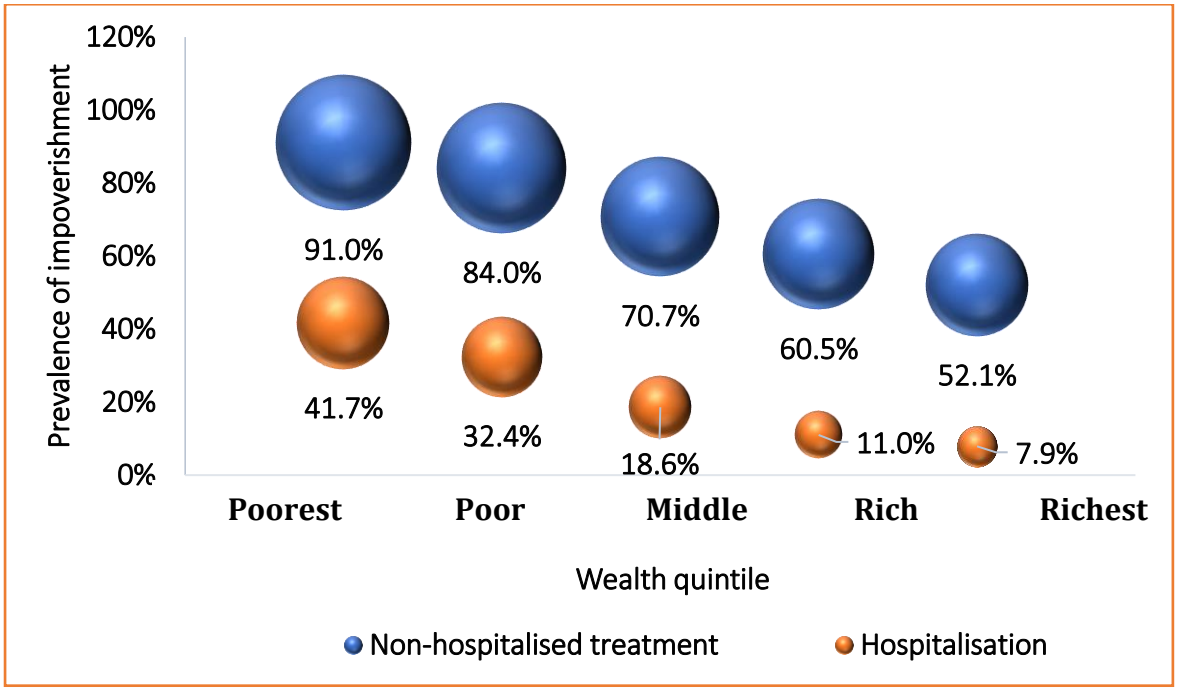

Figure 7: Prevalence of impoverishment based on wealth quintile

As observed for CHE, the prevalence of impoverishment was found to be the highest among cancer patients who were not covered under any insurance schemes for non-

hospitalised treatment (70.4%) and among patients with private health insurance for hospitalization (24%). The prevalence of impoverishment was the lowest for patients insured through philanthropists/NGOS (55.3% for non-hospitalised treatment and 11.4% for hospitalisation).

The prevalence of impoverishment was found to be the highest among patients seeking non-hospitalised treatment for cancer of unknown primary site (74.1%), followed by haematological (72.7%) and solid cancers (65%). Among different types of cancer treatments, highest impoverishment was observed for diagnostics (81.7%) during non-hospitalised treatment.

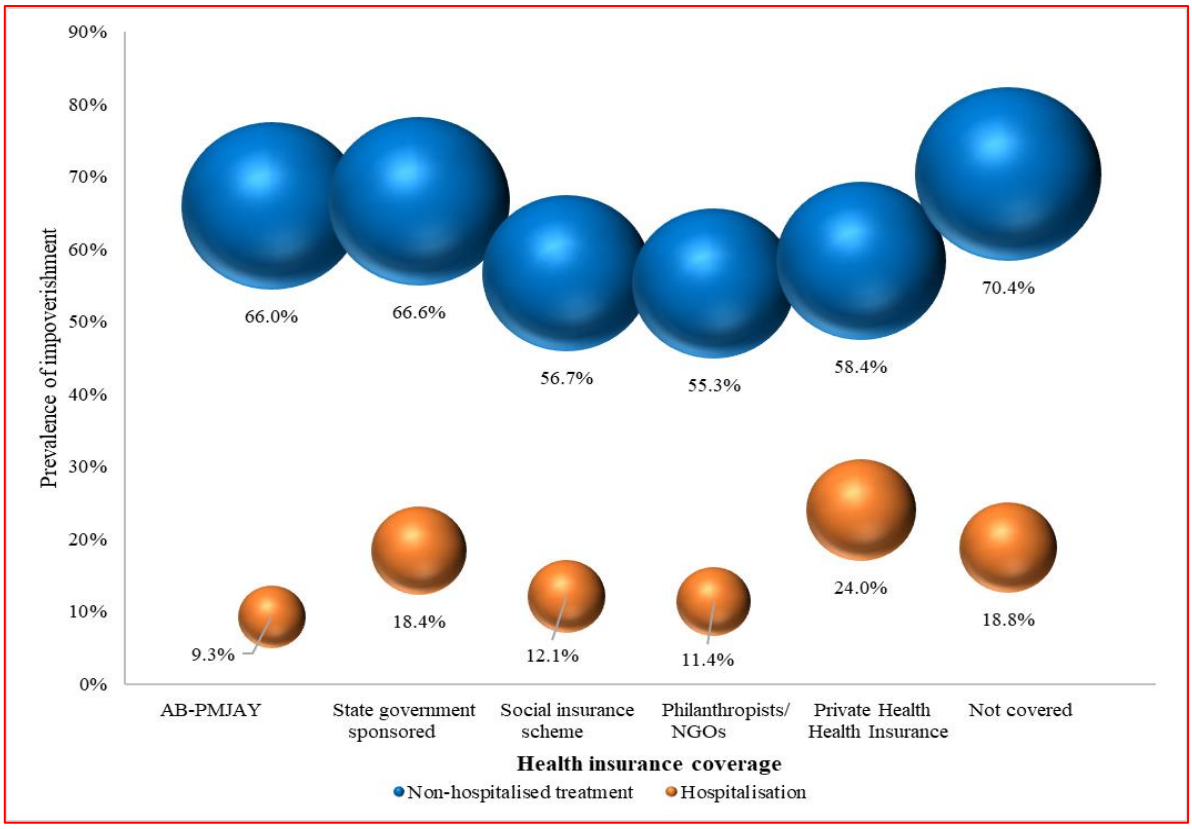

Figure 8: Prevalence of impoverishment based on health insurance coverage

Determinants of impoverishment due to cancer treatment

The results of the logistic regression analysis to determine the factors influencing impoverishment due to cancer-related hospitalisation and non-hospitalised treatment are shown in Table 6.

Non-hospitalised treatment

The results of the analysis showed that the likelihood of impoverishment was about 2.5 times higher for patients from rural areas ($\beta=2.431$, $p<0.05$) as compared to those from urban areas. The odds of impoverishment increased with increasing level of education. However, the odds were found to be statistically insignificant ($p>0.05$). The likelihood of impoverishment was found to be lesser for richer wealth quintiles as compared to the poorest wealth quintile. The odds of impoverishment were found to be 80%, 94%, 93% and 98% lower for the poor, middle, rich and the richest wealth quintile as compared to the poorest wealth quintile, respectively ($p<0.05$). The odds of impoverishment were also found to be significantly higher ($\beta=1.534$, $p<0.05$) for married patients than that of unmarried patients. As compared to patients with no health insurance coverage, the likelihood of impoverishment due to non-hospitalised cancer treatment was 45.5%, 47.8%, 52.5%, 30.4%, and 61.4% lower among those covered under AB-PMJAY, state government sponsored, social insurance scheme, private health insurance, and philanthropists/NGOs, respectively. These odds were found to be statistically significant ($p<0.05$) for all categories of health insurance except for private health insurance ($p=0.196$). In comparison to the patients who received chemotherapy, it was found that the likelihood of impoverishment was higher for diagnostics ($\beta=2.775$, $p>0.05$), palliative care ($\beta=1.484$, $p>0.05$), and surgery ($\beta=1.048$, $p>0.05$), however, the results were statistically insignificant. The likelihood of getting impoverished was significantly lower among patients who received hormone therapy ($\beta=0.319$, $p<0.05$) as compared to those on chemotherapy. The odds of impoverishment were also lower among patients who received radiotherapy ($\beta=0.897$), combination therapy ($\beta=0.921$), maintenance therapy ($\beta=0.702$), and others ($\beta=0.685$) as compared to those who received chemotherapy. However, the results were found to be statistically insignificant ($p>0.05$). As the stage of cancer increased, the likelihood of impoverishment also increased among cancer patients. However, a statistically significant relationship was found only for stage IV

cancer with 54.5% (β=1.545. p<0.05) higher odds of impoverishment. Patients with ongoing response to treatment had a 58.1% (β = 1.581, p<0.05) higher likelihood of experiencing impoverishment than those in the progression-free survival stage. For patients in the progressive disease state, the odds were 27% higher as compared to progression-free survival state patients, however, no statistically significant association was noted (β=1.270, p>0.05). Variables such as age, gender, marital status (other than married patients), level of education, type of cancer, type of treatment (other than hormone therapy), line of treatment, and adverse effects of treatment did not significantly affect the odds of experiencing impoverishment.

Hospitalisation

The results of the analysis showed that the likelihood of impoverishment was about 34.4% higher for patients from rural areas (β=1.344, p<0.05) as compared to those from urban areas. The odds of impoverishment increased with increasing level of education. However, the odds were found to be statistically significant only for graduation and above level of education (β=2.311, p<0.05). The likelihood of impoverishment decreased for higher wealth quintiles as compared to the poorest wealth quintile. The odds of impoverishment were found to be 30%, 65.5%, 84% and 91.4% lower for the poor, middle, rich and the richest wealth quintile as compared to the poorest wealth quintile, respectively. However, the results were found to be statistically significant for the middle, rich and the richest wealth quintile only (p<0.05). A statistically significant (p<0.05) trend of lesser odds of impoverishment was observed for patients covered under health insurance schemes, wherein the likelihood of impoverishment was 62.1%, 58.6%, 51.5%, and 85.6% lower among patients covered under AB-PMJAY, state government sponsored schemes, and philathropists/NGOs, respectively. However, the odds of impoverishment were found to be approximately 15.2% (β=1.152, p=0.653) higher for patients with private health insurance. Hospitalisation in private hospitals and a longer duration of hospital stay were significantly associated with higher odds of impoverishment (β=2.927 for private hospitals and β=1.032 for duration of stay; p<0.05).

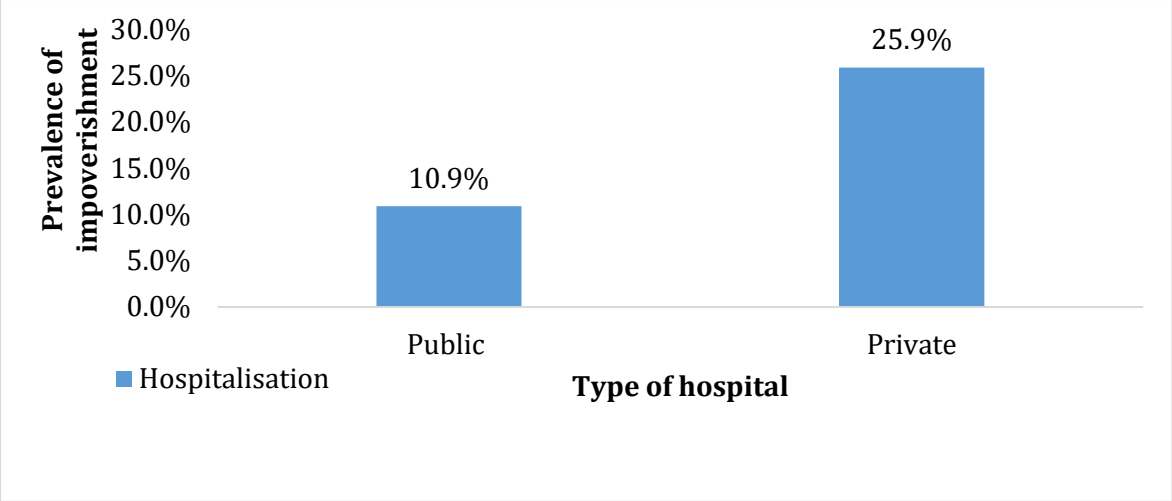

Figure 8: Prevalence of impoverishment based on type of hospital

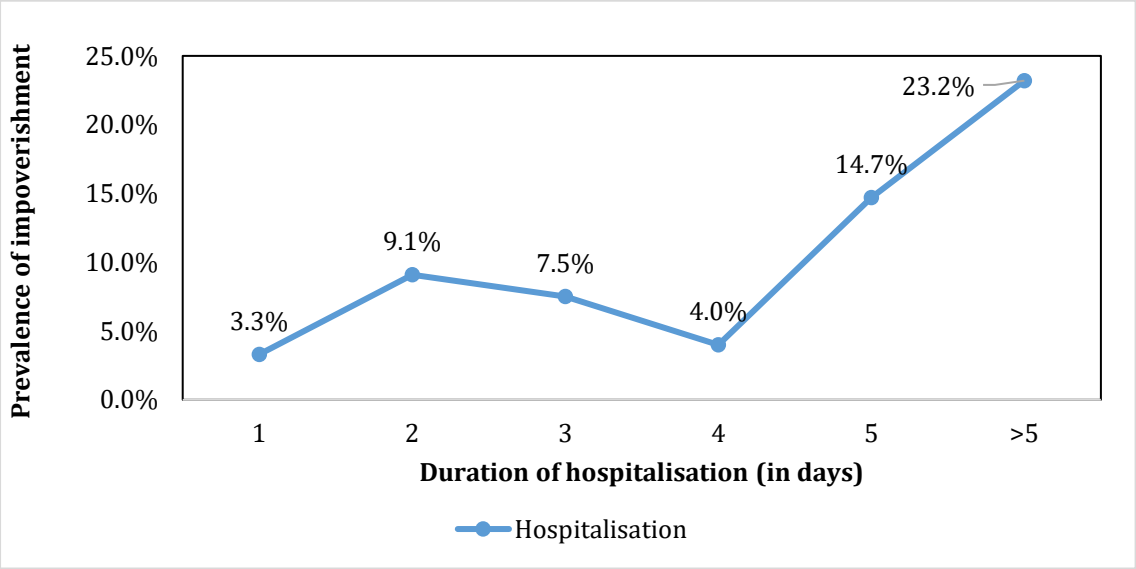

Figure 9: Prevalence of impoverishment based on duration of hospitalization

Table 9: Determinants of impoverishment for cancer-related non-hospitalized treatment and hospitalisation

	Non-hospitalised treatment				Hospitalisation			
Category	**Number of patients (N)**	**Prevalence of impoverishment (%)**	**Impoverishment Adjusted Odds Ratio (95% CI)**	**p-value**	**Number of patients (N)**	**Prevalence of impoverishment (%)**	**Impoverishment Adjusted Odds Ratio (95% CI)**	**p-value**
Age groups								
0-15	311 (3.2%)	71.9%	1.006 (0.998,1.014)	0.143	74 (2.7%)	18.0%	0.997 (0.986,1.008)	0.618
16-30	778 (7.9%)	72.3%			229 (8.4%)	22.2%		
31-45	2559 (26.1%)	65.5%			747 (27.3%)	16.2%		
45-60	3965 (40.5%)	64.9%			1135 (41.5%)	17.4%		
Above 60	2174 (22.2%)	68.9%			551 (20.1%)	13.2%		
Gender								
Male	4078 (41.7%)	71.0%	Reference		1127 (41.2%)	17.7%	Reference	
Female	5709 (58.3%)	63.6%	0.857 (0.703,1.045)	0.127	1609 (58.8%)	15.8%	0.902 (0.693,1.176)	0.446
Area of Residence								
Urban	3381 (34.5%)	58.9%	Reference		972 (35.5%)	17.2%	Reference	
Rural	6269 (64.1%)	71.6%	2.431 (1.975,2.991)	<0.01	1715 (62.7%)	16.4%	1.344 (1.016,1.778)	0.038
Slum	137 (1.4%)	54.4%	1.061 (0.525,2.147)	0.869	49 (1.8%)	9.5%	0.856 (0.282,2.599)	0.783
Education								
No education	2124 (21.7%)	68.3%	Reference		594 (21.7%)	12.7%	Reference	
Primary & Middle	3435 (35.1%)	67.9%	1.081 (0.848,1.378)	0.528	949 (34.7%)	17.5%	1.317 (0.909,1.909)	0.145
Up to Senior Secondary	2942 (30.1%)	67.3%	1.21 (0.935,1.566)	0.148	804 (29.4%)	14.4%	1.116 (0.753,1.655)	0.585
Graduation & above	1286 (13.1%)	60.8%	1.376 (0.989,1.916)	0.058	389 (14.2%)	24.1%	2.311 (1.494,3.576)	<0.01
Wealth Quintile								
Poorest	1958 (20%)	91.0%	Reference		499 (18.2%)	41.7%	Reference	
Poor	1960 (20%)	84.0%	0.201 (0.077,0.521)	0.001	492 (18%)	32.4%	0.701 (0.376,1.304)	0.262
Middle	1956 (20%)	70.7%	0.061 (0.023,0.157)	<0.01	550 (20.1%)	18.6%	0.345 (0.184,0.645)	0.001
Rich	1956 (20%)	60.5%	0.028 (0.011,0.072)	<0.01	584 (21.3%)	11.0%	0.159 (0.083,0.305)	<0.01
Richest	1957 (20%)	52.1%	0.018 (0.007,0.047)	<0.01	611 (22.3%)	7.9%	0.086 (0.044,0.169)	0.001
Marital Status								
Unmarried	895 (9.1%)	69.3%	Reference		233 (8.5%)	22.3%	Reference	
Married	7823 (79.9%)	67.0%	1.534 (1.005,2.343)	0.047	2173 (79.4%)	16.0%	0.796 (0.481,1.319)	0.377
Separated/Divorced	66 (0.7%)	65.4%	0.735 (0.255,2.121)	0.569	22 (0.8%)	7.1%	0.246 (0.028,2.136)	0.203
Widow/Widower	1003 (10.2%)	62.5%	1.18 (0.697,1.997)	0.538	308 (11.3%)	16.7%	0.799 (0.411,1.553)	0.508
Health insurance								
Not covered	3993 (40.8%)	70.4%	Reference		1018 (37.2%)	18.8%	Reference	
AB-PMJAY	1009 (10.3%)	66.0%	0.545 (0.392,0.757)	<0.01	365 (13.3%)	9.3%	0.379 (0.243,0.591)	<0.01
State Sponsored	3230 (33%)	66.6%	0.522 (0.421,0.648)	<0.01	905 (33.1%)	18.4%	0.414 (0.3,0.573)	<0.01

Social Insurance Scheme	568 (5.8%)	56.7%	0.475 (0.31,0.728)	0.001	191 (7%)	12.1%	0.485 (0.283,0.831)	0.008
Private Health Insurance	369 (3.8%)	58.4%	0.696 (0.402,1.205)	0.196	90 (3.3%)	24%	1.152 (0.623,2.131)	0.653
Philanthropist	618 (6.3%)	55.3%	0.386 (0.232,0.644)	<0.01	167 (6.1%)	11.4%	0.144 (0.064,0.326)	<0.01
Type of cancer								
Solid	7618 (78%)	65.0%	Reference		-	-	-	-
Haematological	2101 (21.5%)	72.7%	1.122 (0.332,3.791)	0.853	-	-	-	-
CUPS	42 (0.4%)	74.1%	0.615 (0.095,3.974)	0.610	-	-	-	-
Type of treatment								
Chemotherapy	4304 (50.6%)	69.0%	Reference		-	-	-	-
Radiotherapy	347 (4.1%)	68.0%	0.897 (0.611,1.316)	0.577	-	-	-	-
Palliative care	236 (2.8%)	69.0%	1.484 (0.803,2.744)	0.208	-	-	-	-
Surgery	519 (6.1%)	64.7%	1.048 (0.742,1.481)	0.789	-	-	-	-
Combination therapy*	913 (10.7%)	57.6%	0.921 (0.717,1.182)	0.517	-	-	-	-
Maintenance Therapy	179 (2.1%)	75.2%	0.702 (0.076,6.456)	0.754	-	-	-	-
Diagnostic	97 (1.1%)	81.7%	2.775 (0.235,32.832)	0.418	-	-	-	-
Hormone Therapy	238 (2.8%)	50.0%	0.398 (0.23,0.69)	0.001	-	-	-	-
Others	1666 (19.6%)	60.5%	0.685 (0.4,1.172)	0.167	-	-	-	-
No Information	1288 (13.2%)	73.6%			-	-	-	-
Cancer Stage					-	-	-	-
Carcinoma in Situ	4 (0%)	0.0%			-	-	-	-
Stage I	413 (4.2%)	58.9%	Reference		-	-	-	-
Stage II	1181 (12.1%)	60.8%	1.143 (0.778,1.68)	0.497	-	-	-	-
Stage III	2165 (22.1%)	63.9%	1.27 (0.886,1.823)	0.194	-	-	-	-
Stage IV	1564 (16%)	70.5%	1.545 (1.054,2.263)	0.026	-	-	-	-
No Information	4460 (45.6%)	68.9%			-	-	-	-
Response to Treatment					-	-	-	-
Progression/ Disease Free Survival	2402 (24.5%)	55.3%	Reference		-	-	-	-
Progressive Diseases	450 (4.6%)	66.9%	1.27 (0.787,2.049)	0.328	-	-	-	-
Ongoing	5394 (55.1%)	68.3%	1.581 (1.189,2.1)	0.002	-	-	-	-
Not Applicable	1334 (13.6%)	79.8%			-	-	-	-
No Information	207 (2.1%)	73.8%			-	-	-	-
Line to Treatment					-	-	-	-
First Line	6817 (69.7%)	64.4%	Reference		-	-	-	-
Second Line	1146 (11.7%)	65.4%	0.956 (0.686,1.334)	0.793	-	-	-	-
Third Line	163 (1.7%)	69.7%	1.356 (0.577,3.187)	0.485	-	-	-	-
Fourth Line	20 (0.2%)	55.0%	0.611 (0.111,3.373)	0.572	-	-	-	-
Other	5 (0.1%)	66.7%			-	-	-	-
Not Applicable	1334 (13.6%)	79.8%			-	-	-	-
No Information	302 (3.1%)	66.7%			-	-	-	-

Adverse Effect					-	-	-	-
Without Adverse Effect	564 (5.8%)	56.3%	Reference		-	-	-	-
With Adverse Effect	5145 (52.6%)	68.2%	1.359 (0.852,2.169)	0.198	-	-	-	-
No Information	4078 (41.7%)	66.1%			-	-	-	-
Type of hospital	**-**	**-**	**-**					
Public	-	-	-	-	1507 (55.1%)	10.9%	Reference	
Private	-	-	-		1229 (44.9%)	25.9%	2.927 (2.236,3.831)	<0.01
Duration of hospitalisation (days)	-	-	-					
1	-	-	-	-	107 (3.9%)	3.3%	1.032 (1.023,1.041)	<0.01
2	-	-	-		207 (7.6%)	9.1%		
3	-	-	-		292 (10.7%)	7.5%		
4	-	-	-		294 (10.7%)	4.0%		
5	-	-	-		260 (9.5%)	14.7%		
>5	**-**	**-**	**-**		1576 (57.6%)	23.2%		
Total	**9787**	**66.8%**			2736	16.6%		

Assessment of health-related quality of life among cancer patients in India

The HRQOL of 9787 cancer patients seeking non-hospitalized treatment and 2359 hospitalized cases was assessed using EQ-5D-5L and EQ-VAS methods. Among non-hospitalized cancer cases, majority of patients were in the 45-60 years age group (40.5%) followed by 31-45 years (26.1%) and above 60 years (22.2%). The disease was found to be more prevalent among females (58.3%). More than half of the participants were residing in rural areas (64.1%) followed by urban areas (34.5%) with only 1.4% in slums. Nearly 80% were married and others were unmarried (9.1%) and widow/widower (10.2%), with 0.7% being widowed/separated from their spouses. Detailed sample characteristics are summarised in Table 1.

Socioeconomic variations of the EQ-5D-5L index among cancer patients seeking non-hospitalized treatment

The mean EQ-5D5L utility score among cancer patients seeking non-hospitalized treatment was estimated as 0.655 (95% CI: 0.648, 0.662). The mean EQ-VAS score was computed as 64.33 (95% CI: 63.97, 64.68). The mean EQ-5D-5L indices by socioeconomic groups of cancer patients are presented in Table 1. Females were found to have a higher HRQOL (EQ-5D-5L) index (0.675 [95% CI: 0.667-0.684]) compared to males (0.627 [95% CI: 0.615-0.638]). The highest mean EQ-5D-5L score among patients aged 31-45 years was 0.707 [95% CI: 0.694-0.719]. All scores were lower in the older age groups, including 0.653 [95% CI: 0.641-0.664] and 0.590 [95% CI: 0.574-0.605] among patients aged 45-60 years and 60 years and above respectively.

Higher HRQOL was observed among cancer patients of urban and rural areas (0.709 and 0.631 respectively) as compared to those of slum area (0.451). Furthermore, HRQOL among cancer patients were found to be lowest among richest income groups (0.619) as compared to poor (0.707), middle (0.628) and poorest income groups (0.744). (Table 1)

The mean EQ-5D-5L utility scores observed for solid, haematological and cancers of unknown primary site were 0.639 [95% CI: 0.631-0.647], 0.719 [95% CI: 0.705-0.733] and 0.502 [95% CI: 0.355-0.649] respectively. The HRQOL decreased with the increase in clinical severity (p value < 0.001). The stage-4 cancer patients had poorest HRQOL

(0.569) followed by stage 3 (0.693), stage 2 (0.710) and stage 1 (0.750). Further, cancer patients with adverse effects were found to have lower quality of life (0.642) as compared to patients with no adverse effects (0.840). Significant differences were observed for mean utility scores for variables namely age, gender, education, residential status, income quintile, marital status, health insurance coverage status, type of cancer, treatment response and presence of adverse effects. However, there was no signficant difference observed between EQ-5D-5L scores due to line of treatment. (Table 1)

Table 1: Mean health-related quality of life (HRQoL) score for cancer-related non-hospitalised treatment

Sociodemographic Category	Sample size N (%)	Mean HRQoL score		Vas Score	
		Mean (95%CIs)	p-value	Mean (95%CIs)	p-value
Age groups					
0-15	311 (3.2%)	0.607(0.562,0.653)	<0.01	58.63 (56.76,60.51)	<0.01
16-30	778 (8.0%)	0.699 (0.674, 0.725)		66.34 (64.92,67.76)	
31-45	2559 (26.1%)	0.707 (0.694, 0.719)		65.89 (65.17, 66.61)	
45-60	3965 (40.5%)	0.653 (0.641, 0.664)		64.24 (63.69,64.78)	
Above 60	2174 (22.2%)	0.590 (0.574, 0.605)		62.74 (62.02,63.46)	
Gender					
Male	4078 (41.7%)	0.627 (0.615,0.638)	<0.01	62.98 (62.42,63.53)	<0.01
Female	5709 (58.3%)	0.675 (0.667,0.684)		65.29 (64.83, 65.75)	
Area of Residence					
Urban	3381 (34.5%)	0.709 (0.697, 0.720)	<0.01	67.37 (66.72, 68.03)	<0.01
Rural	6269 (64.1%)	0.631 (0.622, 0.640)		62.70 (62.28, 63.12)	
Slum	137 (1.4%)	0.451 (0.374, 0.527)		63.65 (60.82, 66.47)	
Education					
No education	2124 (21.7%)	0.563 (0.546, 0.580)	<0.01	61.37 (60.65, 62.10)	<0.01
Primary & Middle	3435 (35.1%)	0.650 (0.638, 0.662)		63.29 (62.72, 63.87)	
Up to Senior Secondary	2942 (30.1%)	0.693 (0.681, 0.705)		65.76 (65.09, 66.42)	
Graduation & above	1286 (13.1%)	0.735 (0.717, 0.752)		68.68 (67.63, 69.73)	
Wealth Quintile					
Poorest	1958 (20%)	0.744 (0.732, 0.756)	<0.01	65.45 (64.62, 66.28)	0.014
Poor	1960 (20%)	0.707 (0.692, 0.721)		63.82 (62.99, 64.65)	
Middle	1956 (20%)	0.628 (0.611, 0.644)		64.54 (63.77, 65.30)	
Rich	1956 (20%)	0.578 (0.561, 0.596)		63.63 (62.88, 64.38)	
Richest	1957 (20%)	0.619 (0.601, 0.636)		64.19 (63.39, 64.99)	
Marital Status					
Unmarried	895 (9.1%)	0.674 (0.649, 0.699)	<0.01	64.02 (62.74, 65.31)	0.190
Married	7823 (79.9%)	0.659 (0.651, 0.667)		64.46 (64.07, 64.86)	
Separated/Divorced	66 (0.7%)	0.672 (0.596, 0.748)		66.67 (62.85, 70.48)	
Widow/Widower	1003 (10.2%)	0.605 (0.582, 0.627)		63.35 (62.34, 64.37)	
Health insurance					
Not Covered	3993 (40.8%)	0.627 (0.615,0.639)	<0.01	65.26 (64.68,65.84)	<0.01
ABPMJAY	1009 (10.3%)	0.480 (0.455,0.505)		64.63 (63.66, 65.60)	
State Sponsored	3230 (33%)	0.732 (0.722,0.741)		61.77 (61.18,62.36)	
Social Insurance Scheme	568 (5.8%)	0.600 (0.567,0.633)		68.24 (66.87,69.61)	
Private Health Insurance	369 (3.3%)	0.674 (0.638,0.71)		65.86 (63.92,67.8)	
Philanthropist	618 (6.3%)	0.761 (0.738,0.784)		66.64 (65.09,68.18)	
Type of Cancer					
Solid	7618 (78%)	0.639 (0.631, 0.647)	<0.01	63.29 (62.89, 63.68)	<0.01

Haematological	2101 (21.5%)	0.719 (0.705, 0.733)		68.18 (67.36, 68.99)	
Cancer of Unknown Primary Site	42 (0.4%)	0.502 (0.355, 0.649)		58.57 (52.63, 64.51)	
Type of treatment					
Chemotherapy	4304 (50.6%)	0.671 (0.660, 0.681)	<0.01	62.12 (61.61, 62.64)	<0.01
Radiotherapy	347 (4.1%)	0.621 (0.584, 0.658)		59.71 (58.02, 61.40)	
Palliative Care	236 (2.8%)	0.491 (0.433, 0.549)		52.27 (50.14, 54.40)	
Surgery	519 (6.1%)	0.525 (0.493, 0.556)		63.27 (61.98, 64.57)	
Combination therapy*	913 (10.7%)	0.629 (0.606, 0.652)		62.41 (61.33, 63.49)	
Maintenance therapy	179 (2.1%)	0.773 (0.741, 0.806)		72.11 (69.36, 74.85)	
Diagnostic	97 (1.1%)	0.618 (0.538, 0.697)		54.21 (51.06, 57.35)	
Hormone Therapy	238 (2.8%)	0.810 (0.781, 0.839)		72.47 (70.40,74.53)	
Others	1666 (19.6%)	0.787 (0.773, 0.801)		73.13 (72.17, 74.08)	
Cancer Stage					
Carcinoma in Situ	4 (0.1%)	0.877 (0.589, 1.165)	<0.01	75 (47.44, 102.56)	<0.01
Stage I	413 (7.8%)	0.750 (0.723,0.776)		67.07 (65.31, 68.82)	
Stage II	1181 (22.2%)	0.710 (0.694, 0.726)		62.46 (61.48, 63.44)	
Stage III	2165 (40.6%)	0.693 (0.680, 0.706)		63.63 (62.91, 64.34)	
Stage IV	1564 (29.4%)	0.569 (0.549, 0.589)		58.97 (58.17, 59.78)	
Response to Treatment					
Progression/ Disease Free Survival	2402 (29.1%)	0.729 (0.715, 0.742)	<0.01	72.86 (72.13, 73.58)	<0.01
Progressive Diseases	450 (5.5%)	0.568 (0.527, 0.609)		56.99 (55.21, 58.78)	
Ongoing	5394 (65.4%)	0.653 (0.644, 0.662)		61.27 (60.84, 61.71)	
Line to Treatment					
First Line	6817 (83.6%)	0.670 (0.662, 0.678)	0.736	64.43 (64.01, 64.85)	0.044
Second Line	1146 (14.1%)	0.665 (0.644, 0.686)		62.83 (61.79, 63.86)	
Third Line	163 (2%)	0.646 (0.589, 0.704)		65.37 (62.57, 68.17)	
Fourth Line	20 (0.2%)	0.655 (0.472, 0.837)		66.75 (58.60, 74.90)	
Other	5 (0.1%)	0.823 (0.584, 1.063)		71.00 (59.89, 82.11)	
Adverse Effect					
With Adverse Effect	5145 (90.1%)	0.642 (0.633, 0.652)	<0.01	59.62 (59.19, 60.06)	<0.01
Without Adverse Effect	564 (9.9%)	0.840 (0.820, 0.859)		74.51 (73.06, 75.97)	
Total	**9787**	0.655 (0.648,0.662)		64.33 (63.97,64.68)	

**Combination therapy – Chemotherapy + Radiotherapy, Surgery + Radiotherapy, Surgery + Chemotherapy, Surgery + Chemotherapy + Radiotherapy*

Factors influencing health-related quality of life among cancer patients seeking non-hospitalized treatment in India

Results of multiple linear regression implied that even after controlling the socio-demographic variables, HRQOL of patients varies across different categories. The utility score among females was found to be significantly higher than males (B= 0.043). As compared to urban cancer patients, patients belonging to rural and slum areas reported significantly poorer quality of life (B=-0.032 for rural and -0.150 for slum). The utility scores were found to decrease signficantly with increase in level of income. [Table 2]

Table 2: Factors influencing health-related quality of life among cancer patients seeking non-hospitalized treatment in India

Parameter		B	Std. Error	95% Confidence Interval		Sig.
				Lower	Upper	
(Intercept)		.667	.021	.626	.709	.000
Age		-.001	.000	-.002	-.001	.000
Gender Ref Male	Female	.043	.007	.028	.057	.000
Area of Residence (Reference Urban)	Rural	-.032	.008	-.048	-.017	<0.01
	Slum	-.150	.032	-.213	-.088	<0.01
Education Ref No Education	Primary & Middle	.042	.010	.023	.061	<0.01
	Up to Senior Secondary	.085	.010	.065	.105	<0.01
	Graduation & above	.122	.013	.097	.147	<0.01
Wealth Quintile	Poor	-.015	.011	-.037	.006	.168
(Reference- Poorest)	Middle	-.041	.012	-.064	-.019	<0.01
	Rich	-.078	.012	-.102	-.055	<0.01
	Richest	-.079	.012	-.102	-.056	<0.01
Health Insurance (Reference -Not Covered)	ABPMJAY	-.095	.013	-.121	-.070	<0.01
	State Sponsored	.085	.009	.068	.102	<0.01
	Social Insurance Scheme	-.031	.016	-.063	.000	.051
	Private Health Insurance	.027	.019	-.010	.065	.157
	Philanthropist	.075	.015	.046	.104	<0.01
Type of Cancer (Reference-Solid)	Haematological	.051	.009	.033	.070	<0.01
	CUPS	-.111	.056	-.221	-.001	.049
Type of Treatment	Radiotherapy	-.016	.018	-.052	.019	.366
(Reference-Chemotherapy)	Palliative care	-.154	.022	-.196	-.111	<0.01
	Surgery	-.122	.015	-.152	-.093	<0.01
	Combination Therapy	-.009	.012	-.032	.015	.462
	Maintenance Therapy	.095	.025	.045	.144	<0.01
	Diagnostic	-.037	.033	-.102	.028	.265
	Hormone Therapy	.115	.022	.072	.158	<0.01
	Others	.097	.009	.078	.115	<0.01

Socioeconomic variations of the EQ-5D-5L index among hospitalized cancer patients

The mean EQ-5D5L utility score among hospitalized cancer patients was estimated as 0.552 (95% CI: 0.536, 0.567). The mean EQ-VAS score was computed as 55.51 (95% CI: 54.90, 56.13). The mean EQ-5D-5L indices by socioeconomic groups of cancer patients are presented in Table 1. Females were found to have a higher HRQOL (EQ-5D-5L) index (0.556 [95% CI: 0.534-0.578]) compared to males (0.548 [95% CI: 0.526-0.570]). The highest mean EQ-5D-5L score among patients aged 16-30 years was 0.593 [95% CI: 0.546-0.641]. All utility scores were lower in the older age groups i.e. 0.588 [95% CI: 0.559-0.617], 0.540 [95% CI: 0.514-0.65] and 0.504 [95% CI: 0.469-0.539] among patients aged 31-45 years, 45-60 years and above 60 years respectively.

Higher HRQOL was observed among cancer patients of urban and rural areas (0.572 and 0.538 respectively) as compared to those of slum area (0.451). The utility scores were found to increase with increase in level of education (0.444 among illiterates to 0.611 among graduates and post graduates). Furthermore, HRQOL among cancer patients were found to be lowest among richest income groups (0.522) as compared to rich (0.561), middle (0.550), poor (0.557), and poorest income groups (0.568). (Table 3)

The mean EQ-5D-5L utility scores observed for solid, haematological and cancers of unknown primary site were 0.562 [95% CI: 0.545-0.579], 0.506 [95% CI: 0.466-0.547] and 0.604 [95% CI: 0.478-0.729] respectively. The HRQOL decreased with the increase in clinical severity (p value < 0.001). The stage-4 cancer patients had poorest HRQOL (0.464) followed by stage 3 (0.552), stage 2 (0.602) and stage 1 (0.592). The patients in progression free survival state were found to have better quality of life (0.577) as compared to progressive disease patients (0.451). Morever, patients on first line of treatmenet reported higher utility score of 0.562 as compared to subsequent lines of treatment (0.485, 0.455 and 0.451 for second, third and fourt line of trearment). Further, cancer patients with adverse effects were found to have lower quality of life (0.544) as compared to patients with no adverse effects (0.629). Significant differences were observed between mean utility scores across different categories of education, health insurance coverage, type of hospital, duration of hospital, type of treatment, stage of cancer and presence of adverse effects. However, there was no signficant difference

observed between EQ-5D-5L scores according to type of cancer, marital status, age, gender, residential status, wealth quintile, line of treatment . (Table 3)

Table 3: Mean health-related quality of life (HRQoL) score for cancer-related hospitalization

Sociodemographic Category	Sample size N (%)	Mean HRQoL score		Vas Score	
		Mean (95%CIs)	p-value	Mean (95%CIs)	p-value
Age groups					
0-15	158 (6.7%)	0.572 (0.503, 0.641)	0.002	52.25 (50.01, 54.48)	0.058
16-30	271 (11.5%)	0.593 (0.546, 0.641)		56.33 (54.30, 58.36)	
31-45	549 (23.3%)	0.588 (0.559, 0.617)		55.21 (54.03, 56.40)	
45-60	885 (37.5%)	0.540 (0.514, 0.565)		55.99 (55.01, 56.97)	
Above 60	496 (21%)	0.504 (0.469, 0.539)		55.56 (54.13, 57.0)	
Gender					
Male	1197 (50.7%)	0.548 (0.526,0.570)	0.625	55.97 (55.11, 56.83)	0.138
Female	1162 (49.3%)	0.556 (0.534, 0.578)		55.04 (54.15, 55.92)	
Area of Residence					
Urban	1000 (42.4%)	0.572 (0.549, 0.595)	0.043	55.41 (54.39, 56.43)	0.013
Rural	1331 (56.4%)	0.538 (0.517, 0.560)		55.41 (54.64, 56.18)	
Slum	28 (1.2%)	0.451 (0.301, 0.601)		63.93 (59.14, 68.72)	
Education					
No education	378 (16%)	0.444 (0.401, 0.487)	<0.01	55.71 (54.25, 57.17)	<0.01
Primary & Middle	736 (31.2%)	0.538 (0.509, 0.568)		54.29 (53.25, 55.33)	
Up to Senior Secondary	758 (32.1%)	0.580 (0.555, 0.605)		54.67 (53.60, 55.74)	
Graduation & above	487 (20.6%)	0.611 (0.580, 0.643)		58.51 (56.98, 60.03)	
Wealth Quintile					
Poorest	475 (20.1%)	0.568 (0.534, 0.602)	0.395	53.49 (52.14, 54.85)	0.002
Poor	469 (20%)	0.557 (0.524, 0.591)		54.62 (53.28, 55.96)	
Middle	472 (20%)	0.550 (0.516, 0.584)		56.00 (54.66, 57.33)	
Rich	472 (20%)	0.561 (0.526, 0.596)		56.33 (55.04, 57.62)	
Richest	471 (20%)	0.522 (0.483, 0.560)		57.12 (55.58, 58.66)	
Marital Status					
Unmarried	358 (15.2%)	0.588 (0.545, 0.630)	0.002	55.31 (53.60, 57.01)	0.037
Married	1813 (76.9%)	0.554 (0.537, 0.571)		55.23 (54.55, 55.91)	
Separated/Divorced	15 (0.6%)	0.579 (0.318, 0.841)		59.67 (49.28, 70.05)	
Widow/Widower	173 (7.3%)	0.450 (0.384, 0.516)		58.51 (56.03, 60.98)	
Health insurance					

Not Covered	913 (38.7%)	0.502 (0.476, 0.528)	**<0.01**	56.23 (55.12, 57.34)	**<0.01**
ABPMJAY	269 (11.4%)	0.408 (0.354, 0.462)		60.35 (58.80, 61.90)	
State Sponsored	556 (23.6%)	0.642 (0.613, 0.671)		52.45 (51.46,53.43)	
Social Insurance Scheme	230 (9.7%)	0.592(0.551, 0.633)		59.72 (57.79, 61.64)	
Private Health Insurance	241 (10.2%)	0.620(0.581, 0.659)		53.26 (51.28, 55.23)	
Philanthropist	150 (6.4%)	0.608(0.546, 0.671)		50.97 (48.63, 53.30)	
Type of hospital					
Public	729 (30.9%)	0.379 (0.349,0.409)	**<0.01**	61.00 (59.91, 62.09)	**<0.01**
Semi-Private	1630 (69.1%)	0.629 (0.612,0.646)		53.06 (52.34, 53.77)	
Duration of hospitalisation (days)					
1	484 (20.5%)	0.655 (0.636, 0.673)	**<0.01**	50.49 (49.33, 51.64)	**<0.01**
2	270 (11.4%)	0.590 (0.544, 0.636)		63.72 (61.76, 65.68)	
3	274 (11.6%)	0.498 (0.449, 0.546)		61.20 (59.55, 62.85)	
4	290 (12.3%)	0.566 (0.522, 0.611)		57.64 (56.02, 59.27)	
5	342 (14.5%)	0.528 (0.484,0.573)		54.36 (52.79, 55.92)	
>5	699 (29.6%)	0.492 (0.460, 0.525)		53.27 (52.12, 54.41)	
Type of cancer					
Solid	1899 (80.5%)	0.562 (0.545, 0.579)	0.020	55.78 (55.11, 56.46)	0.172
Haematological	444 (18.8%)	0.506 (0.466,0.547)		54.30 (52.78, 55.82)	
Cancer of Unknown Primary Site	16 (0.7%)	0.604 (0.478,0.729)		56.88 (50.21, 63.54)	
Type of treatment					
Chemotherapy	1578 (68.3%	0.571 (0.553,0.590)	<0.01	56.33 (55.6, 57.06)	**<0.01**
Radiotherapy	70 (3.0%)	0.584 (0.496, 0.671)		54.29 (50.96, 57.61)	
Palliative Care	28 (1.2%)	0.202 (0.029, 0.375)		45.54 (39.56, 51.51)	
Surgery	93 (4%)	0.534 (0.454, 0.613)		58.76 (55.83, 61.69)	
Combination therapy*	174 (7.5%)	0.437 (0.374, 0.501)		57.99 (55.51, 60.46)	
Maintenance therapy	7 (0.3%)	0.022 (-0.453, 0.497)		37.14 (14.04, 60.24)	
Diagnostic	98 (%)	0.430 (0.336, 0.523)		51.99 (48.75, 55.23)	
Hormone Therapy	1 (%)	0.488		60.00	
Immunotherapy	21 (0.9%)	0.721 (0.652, 0.791)		51.90 (46.59, 57.22)	
Others	240 (10.4%)	0.608 (0.564, 0.652)		51.35 (49.43, 53.28)	
Cancer Stage					
Carcinoma in Situ	1 (0.1%)	0.737	<0.01	45	0.641
Stage I	87 (5.7%)	0.592 (0.515,0.670)		58.51 (54.9, 62.11)	
Stage II	260 (16.9%)	0.602 (0.557,0.648)		56.77 (55.01, 58.53)	
Stage III	614 (40%)	0.552 (0.522,0.583)		57.90 (56.60, 59.21)	
Stage IV	572 (37.3%)	0.464 (0.428,0.551)		56.99 (55.76, 58.22)	
Response to Treatment					
Progression/ Disease Free Survival	214 (9.4%)	0.577 (0.532,0.622)	0.004	53.11 (50.98,55.23)	0.002
Progressive Diseases	138 (6.1%)	0.451 (0.375,0.527)		52.93 (49.77,56.10)	
Ongoing	1921 (84.5%)	0.557 (0.540,0.574)		56.18 (55.52, 56.84)	

Line to Treatment					
First Line	1980 (87.2%)	0.562 (0.545,0.579)	0.016	55.71 (55.05, 56.37)	0.327
Second Line	229 (10.1%)	0.495 (0.443,0.548)		56.33 (54.17, 58.49)	
Third Line	53 (2.3%)	0.455 (0.337,0.573)		52.08 (47.03,57.12)	
Fourth Line	9 (0.4%)	0.451 (0.066, 0.836)		54.44 (34.81, 74.08)	
Adverse Effect					
With Adverse Effect	1859 (85%)	0.544 (0.526,0.561)	<0.01	56.11 (54.33, 57.89)	0.560
Without Adverse Effect	329 (15%)	0.629 (0.591,0.668)		55.58 (54.90, 56.26)	
Total	2359	0.552 (0.536,0.567)		55.51 (54.90, 56.13)	

**Combination therapy – Chemotherapy + Radiotherapy, Surgery + Radiotherapy, Surgery + Chemotherapy, Surgery + Chemotherapy + Radiotherapy*

Results of multiple linear regression implied that even after controlling the socio-demographic variables, HRQOL of patients varies across different categories. As compared to urban cancer patients, patients belonging to rural and slum areas reported significantly better quality of life (B=0.039 for rural and 0.065 for slum). [Table 4]

Table 4: Factors influencing health-related quality of life among hospitalized cancer cases in India

Parameter		B	Std. Error	95% Confidence Interval		Sig.
				Lower	Upper	
(Intercept)		.367	.049	.271	.464	.000
Age		-.002	.001	-.003	-.001	.004
Area of Residence (Reference Urban)	Rural	.039	.018	.003	.074	.033
	Slum	.065	.070	-.071	.202	.350
Education Ref No Education	Primary & Middle	.043	.023	-.003	.089	.068
	Up to Senior Secondary	.073	.024	.026	.121	.003
	Graduation & above	.114	.028	.059	.168	.000
Wealth Quintile (Reference- Poorest)	Poor	.026	.024	-.021	.072	.285
	Middle	.060	.024	.012	.108	.014
	Rich	.071	.024	.023	.119	.004
	Richest	.019	.025	-.029	.068	.431
Marital Status (Reference Unmarried)	Married	.010	.028	-.046	.066	.722
	Separated/Divorced	.078	.095	-.108	.264	.412
	Widow/Widower	-.026	.042	-.108	.056	.538
Health Insurance (Reference -Not Covered)	ABPMJAY	-.038	.026	-.090	.013	.142
	State Sponsored	.062	.021	.020	.103	.004
	Social Insurance Scheme	.061	.027	.007	.114	.026
	Private Health Insurance	.028	.029	-.028	.084	.331
	Philanthropist	-.009	.034	-.076	.058	.787
Type of Hospital (Reference Public)	Semi-Private	.237	.020	.198	.276	.000
Number of Days Hospitalised		-.005	.002	-.008	-.002	.001
Type of Cancer (Reference-Solid)	Haematological	-.088	.039	-.165	-.011	.025
	CUPS	.013	.027	-.040	.065	.636
Type of Treatment (Reference-Chemotherapy)	Radiotherapy	-.004	.044	-.089	.082	.931
	Palliative care	-.321	.068	-.455	-.188	.000
	Surgery	-.083	.038	-.158	-.008	.030
	Combination Therapy	-.081	.029	-.137	-.024	.005
	Maintenance Therapy	-.382	.135	-.646	-.118	.005
	Diagnostic	-.106	.040	-.183	-.028	.008
	Hormone Therapy	-.143	.353	-.835	.549	.686
	Immunotherapy	.062	.079	-.093	.217	.431
	Others	.002	.027	-.052	.055	.944

Cancer site specific utility scores among patients seeking non-hospitalized treatment

The stratified analysis was done to compute utility scores according to primary site of cancer. There were significant differences (p value <0.001) observed between utility scores across different cancers. The lowest utility score was estimated for bone cancers (0.305) and highest for leukemia (0.782). Site-specific utility scores stratified on the basis of primary site of cancer among patients seeking non-hospitalized treatment are given in Table 5.

Table 5: Primary-site-specific mean health-related quality of life (HRQoL) score for cancer-related non-hospitalised treatment

Primary site of Cancer	Sample size N (%)	Mean HRQoL score		Vas Score	
		Mean (95%CIs)	p-value	Mean (95%CIs)	p-value
Bladder cancer	74 (0.8%)	0.579(0.498,0.66)	<0.01	64.62(61.02,68.22)	<0.01
Bone cancer	146 (1.5%)	0.305(0.222,0.388)		56.2(53.34,59.05)	
Brain and other nervous system cancers	100 (1.0%)	0.555(0.467,0.643)		62.77(59.58,65.96)	
Breast cancer	2303 (23.6%)	0.72(0.709,0.732)		67.7(67.03,68.38)	
Cancer of unknown primary site	44 (0.5%)	0.52(0.376,0.664)		58.41(52.3,64.52)	
Cervical and Uterine cancers	654 (6.7%)	0.613(0.583,0.643)		65.34(63.94,66.74)	
Colorectal cancer	457 (4.7%)	0.616(0.584,0.648)		58.24(56.76,59.72)	
Head and Neck cancer	454 (4.7%)	0.581(0.547,0.615)		62.35(60.87,63.84)	
Oral cancer	658 (6.7%)	0.584(0.555,0.612)		62.72(61.49,63.94)	
Kidney and ureter cancer	65 (0.7%)	0.551(0.453,0.65)		58.45(54.19,62.7)	
Leukemia	1167 (12%)	0.782(0.766,0.798)		70.95(69.86,72.04)	
Lung cancer	743 (7.6%)	0.58(0.55,0.609)		60.95(59.63,62.26)	
Lymphoma	434 (4.4%)	0.651(0.616,0.686)		64.69(62.93,66.44)	
Multiple Myeloma	347 (3.6%)	0.63(0.591,0.668)		65.84(63.92,67.76)	
Ovarian cancer	745 (7.6%)	0.701(0.676,0.726)		65.68(64.21,67.15)	
Pancreatic and Biliary cancers	365 (3.7%)	0.576(0.537,0.614)		54.16(52.74,55.58)	
Prostate cancer	118 (1.2%)	0.624(0.556,0.692)		60.17(57.09,63.25)	
Penile cancer	25 (0.3%)	0.529(0.352,0.706)		64.92(57.81,72.03)	
Skin cancer	36 (0.4%)	0.343(0.153,0.532)		59.31(54.09,64.52)	
Soft tissue tumors	63 (0.6%)	0.564(0.462,0.666)		54.44(49.94,58.95)	
Testicular cancer	81 (0.8%)	0.703(0.618,0.788)		62.89(58.33,67.45)	
Upper GI tract cancers	500 (5.1%)	0.64(0.612,0.668)		57.57(56.26,58.87)	
Other hematological cancers (exc. Lymphomas and Leukemia)	151 (1.5%)	0.633(0.577,0.689)		61.95(58.98,64.93)	
Other cancers	32 (0.3%)	0.804(0.731,0.877)		67.19(60.08,74.29)	

Cancer site specific utility scores among hospitalized cancer patients

The stratified analysis was done to compute utility scores according to primary site of cancer. There were significant differences (p value <0.001) observed between utility

scores across different categories of cancers. The lowest utility score was estimated for cancers of brain and other nervus system (0.326) and highest for testicular cancers (0.771). Site-specific utility scores stratified on the basis of primary site of cancer among hospitalized cases is given in Table 6.

Table 6: Primary-site-specific mean health-related quality of life (HRQoL) score for cancer-related treatment

Primary site of Cancer	Sample size N (%)	Mean HRQoL score		Vas Score	
		Mean (95%CIs)	p-value	Mean (95%CIs)	p-value
Bladder cancer	19 (0.8%)	0.579(0.371,0.788)	<0.01	56.84(49.51,64.17)	<0.01
Bone cancer	73 (3.2%)	0.392(0.271,0.513)		54(50.6,57.4)	
Brain and other nervous system cancers	24 (1%)	0.326(0.127,0.525)		47.5(39.29,55.71)	
Breast cancer	309 (13.1%)	0.648(0.614,0.682)		56.8(55.07,58.52)	
Cancer of unknown primary site	17 (0.7%)	0.624(0.499,0.749)		57.06(50.82,63.29)	
Cervical and Uterine cancers	130 (5.5%)	0.55(0.486,0.615)		58.12(55.66,60.57)	
Colorectal cancer	264 (11.2%)	0.595(0.554,0.636)		56.41(54.75,58.07)	
Head and Neck cancer (excluding Oral cavity)	112 (4.7%)	0.533(0.461,0.605)		57.81(55.01,60.62)	
Oral cancer	201 (8.5%)	0.507(0.462,0.552)		58.76(56.72,60.79)	
Kidney and ureter cancer	18 (0.8%)	0.637(0.493,0.782)		57.22(49.44,65)	
Leukemia	196 (8.3%)	0.562(0.508,0.616)		53.65(51.63,55.66)	
Lung cancer	144 (6.1%)	0.488(0.416,0.56)		54.55(52.09,57.01)	
Lymphoma	166 (7%)	0.562(0.494,0.63)		58.1(55.62,60.59)	
Multiple Myeloma	71 (3%)	0.255(0.145,0.365)		49.3(44.77,53.82)	
Ovarian cancer	163 (6.9%)	0.586(0.531,0.641)		54.17(51.65,56.69)	
Pancreatic and Biliary cancers	92 (3.9%)	0.499(0.425,0.572)		51.58(48.58,54.58)	
Prostate cancer	21 (0.9%)	0.54(0.35,0.729)		54.29(48.98,59.59)	
Penile cancer	9 (0.4%)	0.327(-0.091,0.745)		57.78(45.91,69.64)	
Skin cancer	10 (0.4%)	0.289(-0.06,0.639)		56(47.11,64.89)	
Soft tissue tumors	28 (1.2%)	0.532(0.364,0.7)		54.29(48.94,59.63)	
Testicular cancer	59 (2.5%)	0.771(0.702,0.84)		57.97(53.19,62.75)	
Upper GI tract cancers	203 (8.6%)	0.579(0.527,0.631)		53.23(51.25,55.21)	
Other hematological cancers (exc. Lymphomas and Leukemia)	12 (0.5%)	0.229 (-0.083,0.541)		40.83(31.66,50)	
Other cancers	16 (0.7%)	0.601(0.414,0.787)		53.13(46.83,59.42)	

Discussion

Universal Health Coverage (UHC) is a longstanding tenet of global health and has, in recent years become the overarching framework for policies and investments in health globally and nationally [40]. Financial risk protection (FRP) is a key component of UHC, which is defined as access to all needed quality health services without financial hardship [41]. In order to realize UHC, cancer services must be included in benefit packages and sustainably financed through public resources for protecting the cancer patients against financial toxicity. Financial toxicity has been shown to affect access to cancer care, leading to delay or foregoing cancer care, bankruptcy, poor quality of life and poor survival [42] [43]. Therefore, it is important to acknowledge financial toxicity as an important outcome of clinical condition impacting cancer patients, as well as to identify the most actionable and effective interventions to prevent financial hardship, in order to deliver UHC by 2030 [44].

Once the Governments commit to the aspirational goal of financing health services to provide universal coverage, health care systems face the challenge of fiscal sustainability in the context of scarce resources. This becomes even more evident in the context of oncology due to high cost of care. As a result, decisions regarding priority setting become inevitable. It is thus no surprise that two out of the initial thirteen studies commissioned by HTAIn are focussed on evaluating strategies for cancer screening and prevention in India [45]. Moreover, a large multi-centric study is being carried out to determine the value-based pricing guidelines for anticancer drugs [14].

It is also worthwhile to mention that National Cancer Grid (NCG) in collaboration with National Health Agency (NHA), India have signed a memorandum of Understanding (MOU) to strengthen delivery of cancer services under Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (ABPM-JAY) with common objectives to reduce cancer burden, ensure uniform standards of patient care towards effective and efficient patient-centric care, improve access to cancer services and ensure FRP [46] [47]. These agencies also support the use of HTA in informing policy decisions and thereby achieving the sustainable development goals on the pathway to attain UHC. However, the lack of cost data represents a major evidence barrier in the journey toward UHC-oriented health policy decisions in India. In particular, in setting reimbursement package rates, the limited availability of cost information is seen as a significant concern [11] [48] [49].

Several countries have established such databases of health care costs [49] [50]. India has also created a national database of health system costs [10] [48]. However, none of these national databases have a specific focus on cancer. Moreover, due to being a generic database of cost, it does not provide disaggregated data on cost by the type of disease, and level of severity. Finally, the existing database contains only estimates of health system cost, while nearly 68% of the total health expenditure in India is financed out-of-pocket by households. As a result, the present study estimates would be a significant value addition. Since the study aims to determine the patient care costs which will help in determining provider payment rates, conduct cost-effectiveness analyses for value based care, the study has chosen to include public hospitals. The patient care costs derived from data collected from these public hospitals can be aggregated with health system costs estimated in another national costing study conducted in public hospitals to compute the overall societal cost of cancer care in India [48]. Although, the present study has no private hospital as such but three hospitals in our sample have category of patients who are provided care at prices similar to the prices of the most pure private hospitals in tier 2 and 3 cities of India. The study provides comprehensive estimate of economic burden attributable to cancer in India. Using the distribution of cancers as per National Cancer Registry Program [51], and the total sample of 12,148 cancer patients recruited in this study, we estimate that our study sample are sufficient to provide valid estimates of OOPE, CHE and HRQOL for top 3, 6 and 12 cancers respectively in India, with a 5% margin of error and 95% CI. However, at 10% margin of error and 95% CI, our study would be powered to give valid estimates of OOPE, CHE and HRQOL for top 11, 17 and 20 cancers respectively in India as shown in Table 7.

Table 7: Estimated sample size for OOPE, HRQOL and CHE at 5% and 10% margin of error

Margin of Error	Sample size	Number of cancers with valid estimates

	OOPE	CHE	HRQOL	OOPE	CHE	HRQOL
5%	1690	845	398	3	6	12
10%	422	211	99	11	17	20

Further, several countries have published their value-sets for different health states using the EQ5D5L [52] [53] [54]. The HTAIn in India has also recently completed a study and will shortly publish its own value set [29]. However, it is not possible to cross-walk the health state with the individual cancer patients and their stage and type of treatment. On the other hand, the HTA study precisely requires information on the latter. As a result the present study would add significantly to the existing evidence base by providing stage-specific, and severity-specific estimates of utility score for cancer patients.

The overall burden of cancer in terms of health outcomes, such as mortality and morbidity, is evidently high globally and in India [55]. In addition to the growing disease burden, high economic burden (both health system cost and OOPE) associated with cancer-related diagnostic and treatment modalities have been reported in both developed and developing countries. Pertaining to the exponential costs incurred by patients on cancer treatment, it has become important to ascertain the economic consequences in terms of OOPE, health care burden, CHE, and impoverishment resulting from seeking cancer treatment.

In India, where enrolment in health insurance schemes is low, majority of the cost is paid by the patients out of their own pocket. The cost incurred on cancer treatment includes the cost of medical services availed (direct cost) and loss of wages (indirect cost) [56]. Due to high cost associated with cancer treatment, a substantial proportion of cancer patients faces financial toxicity [57-59].Therefore, ascertaining these cost estimates will help in strategising the mitigation of the financial consequences of cancer treatment. In addition, robust research that assesses the high direct medical and diagnostic costs is imperative to inform value-based standard treatment guidelines and priority-based allocation of healthcare funds [60]. Many studies have been conducted in the past wherein researchers have made an attempt to estimate the OOPE on cancer. However, most of these studies are either single centric or focus on only one type of cancer. In studies that include all cancer types, either the sample size is small or the study estimates

only the direct medical costs associated with cancer treatment. We conducted this study to estimate the OOPE and financial toxicity associated with the treatment of cancer.

Our study fills the aforementioned gaps in the existing literature by collecting primary data from seven different sites across different parts of India. In addition, data on both direct medical and non-medical cost was elicited. Indirect cost was also recorded from a subset of the total sample. A total of 9787 cancer patients were recruited and OOPE data was recorded on non-hospitalised treatment. Similarly, OOPE on hospitalisation was elicited from 2736 patients. The data was further stratified based on type of cancer, stage of cancer, type of treatment, line of treatment, response to treatment, and so on. The total annual direct OOPE on cancer treatment was found to be INR 3,33,408 (INR 57,553 for hospitalisation and INR 3,49,497 for non-hospitalised treatment). The mean and standard error (SE) per-visit OOPE for non-hospitalised treatment was found to be INR 8,053 (143.7). The annual mean direct OOPE on hospitalisation was found to be INR 57,553 (2953.4). In a systematic review conducted by Dhankhar A et al, (2021), the OOPE on hospitalisation was reported as INR 83,396 [61]. This study has pooled all the studies reporting estimates on economic burden of cancer irrespective of study design. Ther is a high hetergenity in the studies used in this systematic review and metanayses owing to varied sample size, methodological approaches used for comoutation of direct OOPE, study area, patient charateristics etc. The direct OOPE was reported as INR 2653 for a reference period of 15 days in the same study. Similarly, a recent secondary analysis of nationally represntative data of national sample survey organization (NSSO) 75th round conducted by Yadav et al. (2021) reported a relatively lower annual total direct OOPE on cancer (INR 17, 701) [62]. It should noted that NSSO has a very small sample size of merely 256 cancer patients and thus findings cannot be generalizable to the nation.

Another study conducted by Maurya et al. (2021) reported OOPE of INR 24,372 for non-hospitalized care among head and neck, breast, and cervical cancer patients in India [63]. Singh et al. (2020) reported the mean OOPE of INR 34,741 due to hospitalisation among cervical cancer patients [64]. This variation in the estimates across different studies can be attributed to the fact that most studies conducted on economic burden of cancer have been single-centric, have small sample size, high heterogeneity and varied methodological approaches for calculating direct and indirect OOPE, and report total cost of treatment without mentioning the reference time period for which OOPE data was

elicited. Also, most studies focus on one or two cancer categories only. For those reporting all cancer types, the number of patients recruited under different categories gets further reduced. However, our study was conducted across six states of India where large cancer institutes are situated that witness a high footfall of patients from the neighbouring states also, thus making it a representative national sample. Also, the present study collects data on twenty-four cancer categories having a adequate sample size under each category.

We also determined the factors affecting OOPE on cancer treatment. It was found that for both hospitalisation and non-hospitalised treatment, OOPE was significantly affected by the wealth quintile of the patient and the status of health insurance coverage. Patients belonging to richest income groups incurred highest OOPE as compared to patients from the poorest wealth quintiles. Similar results were reported by Singh et al (2020) wherein OOPE increased with increase in evel of icome (highest among richest income groups). However, the results were statistically insignificant [64]. Further, the study conducted by Maurya et al. (2021) reported an opposite trend [63]. In their study, the OOPE incurred on cancer treatment was the highest among patients of lowest socio-economic status and least among patients from the upper socio-economic class. This variation in the reported outcomes could stem from the difference in the type of socio-economic classification used to assess the economic outcomes. In our study, wealth quintiles were created using the patients' annual consumption expenditure as proxy of income. Most studies also reported that OOPE on cancer treatment was significantly high among patients who were not covered under any health insurance scheme. These results were in line with the findings of our study.

In our study, salary or savings were the major (74.3%) source of financing cancer treatment, followed by borrowing money without interest from relatives/friends, borrowing money with interest, selling of assets, health insurance, and other sources. Similar findings were reported by Nair et al. (2016) [65]. However, Wadasadawala et al. (2020) reported that most patients reported borrowing money as major source of financing, followed by savings, charity from NGOs/philanthropists, and salary/household income [66]. Singh et al. (2020) reported that 30% of the patients borrowed money for financing their cancer treatment [64].

The results of our study also reveal that the overall prevalence of catastrophic health expenditure among cancer patients was found to be 84% due to non-hospitalised

treatment and 28.5% due to hospitalisation at a threshold of 40% of non-food consumption expenditure. The prevalence of impoverishment was also found to be high among cancer patients; approximately 67% were impoverished due to non-hospitalised treatment and 17% due to hospitalisation. Yadav et al. (2021) reported 44.2% prevalence of CHE at 10% threshold for iutpatient care and 70% for inpatient care [62]. Maurya et al. (2021) reported 61.6% CHE for non-hospitalised treatment [63]. Singh et al. (2020) reported 62% prevalence of CHE at 40% threshold for hospitalisation. These findings are consistent with present study estimates [64].

For both hospitalisation and non-hospitalised treatment, the odds of CHE and impoverishment were low for insured patients as well as for those in the higher wealth quintiles. Singh et al. (2020) reported similar trends. In their study, CHE was highest among patients from low-income quintile [64]. Other studies also reported that for hospitalisation, the odds of CHE and impoverishment were higher for patients seeking treatment in private hospitals than those getting treated at public hospitals. These findings are comparable to the results of our study wherein, hospitalisation in private hospitals was significantly associated with higher odds of CHE and impoverishment. Our study also found that as the duration of hospitalisation increased, the prevalence of CHE and impoverishment increased significantly.

Our study findings emphasise that a high amount of OOPE incurred on cancer treatment hints at strengthening the capacity of existing public health sector. Secondly, in context of Universal Health Coverage (UHC), financial risk protection for cancer treatment needs expansion. High rates of catastrophic health expenditure and impoverishment due to cancer treatment make it imperative to enhance coverage of risk pooling mechanisms for reducing reliance on OOP payments. Although, various publicly sponsored health insurance schemes have been launched across India, under which treatment of cancer is an integral component, there is a need to strictly revise the design and height of health benefit packages of these schemes, for preventing delays in seeking care, financial toxicity, poor quality of life and patient survival. Finally, there is a need to focus on cancer prevention strategies in the form of screening programmes, for detection of cancer lesions in the early or pre-cancerous stage, and minimal radical treatment to reduce economic burden due to cancer.

Future Applications of database of health care costs and HRQOL

The national database developed as part of this study will serve as unique Indian data repository of cost of cancer care as well as HRQOL. This database would be the sole evidence-based resource on OOPE estimates (both direct and indirect costs), which along with the health system costs, can be used to inform the provider payment rates for cancer specific health benefit packages under various national and state level publically financed health insurance schemes. Further, the estimated OOPE and HRQOL by site, stage and treatment approach will aid in robust cost-effectiveness analysis of screening and treatment strategies for cancer control in India. Currently, there are few published and readily accessible cost data in India particularly on cancer to inform HTA and insurance design. The present study is going to be a first step in providing easily accessible reference cost and HRQOL data on cancer for India. The study findings will be available through the National health system cost database besides publishing as peer reviewed papers [10].

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Chapter-11: Estimation of indirect costs due to loss of productivity among cancer patients

Introduction

The cost of cancer treatment has gone up because of increased need of sophisticated infrastructure, investigations requiring high technology, late presentation, and costly drugs. [1] The overall societal burden of cancer not only consists of the substantial direct medical expenditures associated with the disease, but also the indirect costs, such as hours of work forgone by the patient due to hospitalization and time required for seeking treatment.[2]

Indirect costs due to loss of productivity and the individual's contribution to the economy constitutes a substantial proportion of the total societal costs associated with cancer and need to be emphasized upon for understanding the complete picture of the economic burden of cancer. To accurately analyze the societal cost of this disease, economic evaluations of cancer must incorporate both direct and indirect costs. In fact, there is limited evidence to inform policymaking regarding socioeconomic dimensions of the disease which can further disallow discussions on health financing mechanisms. [3]

Therefore, with this motivation, we analyze the value of hours of lost productivity that an individual could have contributed to had they not been sick. Most patients experience a drop in their income while undergoing cancer-related diagnosis and treatment. During treatment, indirect cost is a major contributing factor of the economic burden on patients, increasing their financial stress and can even drive many families to economic catastrophes. [1,4,5]

Productivity losses caused by disease (excluding mortality costs), whether long-term or short-term, are collectively known as morbidity costs and are best estimated by analyzing morbidity patterns in a representative sample of the population. Indirect costs are not financially eminent like expenses on a balance sheet instead they have to be computed using guiding principles for calculating the value of work and productivity. Additional indirect costs include the time a patient and/or family members spend visiting physicians, other health professionals, and hospitalized persons, and time lost from work by family members when someone in the family is ill. Unwanted job changes and loss of opportunities for promotion and education due to illness may reduce productivity and result in additional indirect cost.

The most common approach to the computation of indirect costs of illness is the human capital method and that was chosen for this study. [6] It is based on the discounted value

of earnings forgone as a result of premature morbidity and mortality. It is assumed that the worth to society of an individual's life is measured by the production potential, which in a competitive labor market is usually calculated as the present discounted value of expected labor earnings. Human capital valuation rests on the assumption that earnings reflect productivity. That is not to say that each employee receives the value of his personal contribution to output, but that each receives the value of output added by the marginal or last-hired worker. [7,8] In this study, data was collected from various government and private health facilities of five states of India and 2,577 people were enquired in detail about their annual expenditures, composition of the family, hours of activities forgone that they could have participated in, such as household chores, professional work, childcare, social work, and leisure and the involvement of caregiver to help them with the same. In addition to this, the caregivers were also enquired about their productivity hours they had to forgo while caring for the patients. Since the data was collected from patients who are currently undergoing treatment, it presents indirect cost estimates reflecting morbidity due to cancer, and not premature mortality or workforce departure.

The unfortunate burden of the indirect cost usually seen is that the patients/their caregivers spend it from their own savings, but at a later stage, they start selling their assets and ultimately landed-up borrowing money for their treatment. [6] Overall, this study aims to highlight the importance of examining indirect costs when considering the economic impact of illness, including a range of productivity cost subcomponents in such estimates, choosing the costing perspective carefully, and being explicit about assumptions that underpin the methods.

Review of Literature

For estimating the indirect cost, a literature search was done to find various approaches. The most widely used and validated approaches include the Human Capital Approach (HCA), Friction Cost Approach (FCA), Output-based Approach, Prevalence-based Approach, and Willingness-to-pay Approach.[8,9,10.11] Out of these approaches, most of the literature addressed Human Capital Approach and Friction Cost approach as the conclusive and reliable methods for generating estimates that represent loss of productivity. HCA assumes that an individual produces a stream of output over lifetime and generates labour earnings that reflect productive capacity. [8] Estimation of indirect cost requires applying a relevant wage rate to time forgone from productive activity. This approach uses the reported time of forgone activities while seeking cancer treatment and tending to the patient. Therefore, to fulfil the objectives of the study, HCA was considered most suited approach for estimating indirect costs. [11]

Methodology

The estimation of indirect cost due to loss of productivity of patients and their caregivers was done to encompass the societal perspective of economic burden of cancer. The morbidity element of the indirect costs was captured by enquiring patient and their caregivers about the lost hours of their productive time due to cancer treatment for ten activities – household work, childcare activities, professional work, voluntary work, social work, seeking work, attending school, physical workout, leisure activities and others. Indirect cost estimates were computed for a sample of 2,576 patients and their caregivers from five states of India. After taking the informed consent from patients, data regarding the number of hours forgone by patients while seeking cancer treatment and by their caregivers while tending to the patients was recorded. These hours reflect the time that could have been spent by patients or caregivers on various activities mentioned above. Further, the number of hours of paid activities delegated to another individual by the patient or caregiver was also recorded. For calculating the indirect cost, total hours forgone by patients were converted into work days and relevant standardised wage rates [National Sample Survey 2011-16, (68th round) – 'Household Consumer Expenditure' and 'Employment and Unemployment'] were applied to estimate the loss of productivity.[12] The wage rates provided in the report consider an ideal work day to be of eight hours.

For conducting a robust analysis, we selected the wage rates that were stratified by (i) area of residence and gender, and (ii) level of education. For generating cost estimates of caregivers, their daily wage rates were calculated based on the income reported by them. These wage rates were used in the analysis wherein the 2011-12 years values are used.[12] Usage of standard real wages that have been most cited in the context of Indian productivity studies aids comparison without the effect of inflation.

In addition, daily wage rates for patients were also computed by taking annual household expenditure as proxy for their annual income. Based on the number of family members, equi-size values were computed for households to further derive the patients' annual income. [13] The annual consumption expenditure and equi-size value were used to estimate the proportional distribution of per capita consumption expenditure among family members based on the WHO handbook on Tuberculosis Patients Cost Surveys.(2) This method was guided by the fact that an individual drives the expenses from the income itself. Hence, the daily wage rates derived from this method are justified.

Indirect cost was then calculated as the product of daily wage rates (calculated using the three criteria mentioned above) and total number of work days (total hours forgone in a month divided by ideal work hours per day) for the patient. For caregivers, monthly income was used to generate daily wage rates and the product of hours forgone and daily/monthly wage rates represented the indirect cost. Furthermore, the amount paid by the caregiver for activities delegated to an alternative worker were also added to the loss of productivity of the caregivers. Mean and median indirect cost and their counterpart measures of dispersion [standard deviation (SD) and interquartile range (IQR)] were computed for all the categories of indirect cost estimation in Microsoft Excel.

Results

The gradient of indirect cost using different daily wage rate criteria are presented in Table 1.

TABLE 1: Indirect costs of patients and their caregivers on the basis of different criteria

Criteria	Sample size	Daily Wage rates (INR)*	Mean (SD) indirect cost	95% CI	Median (IQR) indirect cost
INDIRECT COST OF PATIENTS					
Level of education					
Low Education	1056	81	2014.67 (1185.27)	1943.1 - 2086.24	1822.5 (1215)
Middle school	888	105	2943.52 (1609.62)	2837.51 - 3049.53	2756.25 (1575)
Senior Secondary	286	167	4630.02 (2539.14)	4334.46 - 4925.58	5010 (2505)
Graduation and above	346	390	11038.92 (6186.41)	10384.77 - 11693.07	11700 (5850)
Area of Residence and Gender					
Rural Male	738	108	2904.11 (1821.73)	2772.46 - 3035.76	2835 (2430)
Rural Female	988	68	1750.98 (925.8)	1693.18 - 1808.78	1530 (765)
Urban Male	319	232	6749.91 (4199.76)	6287.28 - 7212.54	6960 (5220)
Urban Female	531	180	4852.63 (2393.54)	4648.58 - 5056.68	5400 (2025)
Per capita consumption expenditure					
Indirect cost per day	2577	7489.41	7489.41 (6285.81)	7246.56 - 7732.26	6273.36 (6323.65)
INDIRECT COST OF CAREGIVERS					
Self-reported income					
Monthly income	2577		39,379.02 (57483.76)	39304.5 - 39453.54	26760.0 (39775.63)
Daily wage rate	2577		1312.63 (1928.13)	1238.11 - 1387.15	892.0 (1325.85)

**Wages rates (INR) are quoted from Indian Labour Organisation (ILO) Asia-Pacific Working Paper Series – Towards an India Wage Report (2017). The wage rates were estimated for 2010-2012 considering an ideal work day to be of eight hours.*

Socio-demographic profile of patients:

Indirect cost data were elicited from a total of 2,576 patients out of a sample size of 9,787. The patients belonged to all age groups. Majority patients were female (n=1519, 58.96 %) and 41.03% were males (n=1057). A large proportion (67%) of patients hailed from rural areas (n=1726) and the remaining 33% were from urban areas (n=850). Most patients had attained a lower educational status (n=1056, 41%) followed by middle school education (n=888, 34.6%), graduation and above (n=346, 13.3%), and the secondary school education (n=286, 11.1%). Majority (68.5%) of the patients reported that the number of hours was mostly forgone on household activities followed by professional work (24.5%).

Indirect cost incurred by patient while seeking treatment

Based on the level of education

The results of the stratified analysis showed that the indirect cost increased with increasing level of education. It was found to be the highest among patients with graduation or higher level of education [mean: INR 11,038.92 (95% CI: 10,384.77 – 11,693.07); median 11,700 (IQR: 5,850)] followed by those with up to senior secondary education [mean: INR 4,630.02 (95% CI: 4,334.46 – 4,925.58); median 5,010 (IQR: 2,505), middle school education [mean: INR 2,943.52 (95% CI 2,837.51 – 3,049.53); median 2756.25 (IQR: 1575)], and the lowest among patients with low educational status [mean: INR 2,014.67 (95% CI: 1943.1 - 2086.24); median: INR 1,822.50 (IQR: 1215), respectively.

Based on the area of residence and gender

Due to the variation in the wage rates based on this criterion, the financial setback due to loss of productivity was observed to be the highest among urban males [INR 6,750 (95% CI: 6287.28 - 7212.54); median: INR 6960 (IQR 5220)] followed by urban females [mean: INR 4852.63 (95% CI: 4648.58 – 5056.68); median: 5400 (IQR: 2025)], rural males [mean: INR 2904.11 (95% CI: 2772.46 – 3035.76); median 2835 (2430)] and the least among rural females [mean: INR 1750.98 (95% CI: 1693.18); median 1530 (IQR: 765)].

Based on annual consumption expenditure

The overall mean indirect cost by taking annual consumption as proxy for patient income, for all patients was INR 7,489 (95% CI: 7246.56 - 7732.26) with a median loss of productivity of INR 6,273 (IQR: 6323.65) with 50% of the population ranging between INR 3,468 and INR 9,791.

Indirect cost incurred by caregivers based on self-reported income

The income reported by the caregivers of the patients was used to calculate the monthly mean indirect cost due to caregiving, which was found to be INR 39,379.02 (95% CI: 39304.5 – 39453.54) [median: INR 26,760 (IQR: 39775.63)]. The total indirect mean OOPE was estimated as INR 8,802 (standard error=134.8)

Discussion

The imputed value of forgone productivity when patients' labour services become less efficient on account of morbidity or premature mortality is widely regarded as indirect cost. Indirect costs result from output lost because of cessation or reduction of productivity due to morbidity and mortality. The usual components of output-loss are earnings and the imputed market value of forgone activities. In the past, it has been argued upon whether the cost of morbidity and mortality due to illness is an individual's output or an individual's output minus his or her consumption. [14,15,16] Concern is usually with the total cost of illness to society, not just the output an individual contributes in excess of consumption. Economists generally agree that consumption should not be deducted. [17]

The human capital approach assesses the burden of illness in terms of the flow of goods and services which are either diverted from alternative uses to provide medical care and other needs of the ill (direct costs) or forgone because of work-time loss and loss of output measured by earnings paid for work, plus wage supplements such as employer contributions for social insurance, private pensions, and welfare funds (indirect costs).[18] In cases such as housekeeping, where work is not reimbursed, estimates of the value of those services are made, usually by either the market value or opportunity-cost approach.[19] In the market value approach, the services provided by the housekeeper are valued according to the estimated cost of replacing these services with labor from the market place.[20] The opportunity-cost value of a housekeeper's services is the wage the housekeeper could earn if working.[19]

In this study, we computed the total and stratified indirect cost using the human capital approach in an attempt to bridge the limitation of using one standard wage rate across all genders and educational statuses. Data was collected both from the patient and their caregivers as both had incurred the losses of production time. For the patients, the highest wage loss was found in the category of individuals with graduate or post graduate degree. This could be accounted to the fact that their daily wage rates are higher (INR 390) as compared to others for the higher degree of contribution to work and exclusivity of their labour. Estimation of indirect cost stratified by gender and area of residence reveals that the wage losses were highest in urban areas than rural areas. The difference in the indirect cost associated with area of residence is pertaining to the difference in wage rates in rural and urban areas. Further, males incurred a higher indirect cost as compared to females. It should be noted that the wage loss seen among females was not due to fewer number of hours forgone but due to low daily wage rates of INR 180 for urban and INR 68 for rural females.

The caregivers' reported income was used in the evaluation of the loss of production value and was found to be INR 39,379 (SD: INR 57,843). The measure of dispersion is so vast owing to the variability of the sample population in terms of age, occupational status, geographical differences, etc. Higher indirect cost among caregivers can be attributed to the fact that most caregivers belong to the young and productive age groups. The variation in the estimates also results from the differences in the income of caregivers, number of hours forgone, and availability or applicability of alternative worker.

One of the strengths of the study is that it considers the relevant standardized wage rates for different categories of area of residence, gender, and level of educational status of the individual - that exist in the economy circa 2010-12 (with the base year of 2004-05 wages) discounted for the inflation. The standard wages allow a textured evaluation of the human capital production value based on the nuances of different wage rates based for different categories. Therefore, it was possible to estimate the average loss of productivity for each category. Inherently, Human Capital Approach is one of controversy- the argument is that the calculation of expected earnings misses on the subtleties of human existence and principles of rationality fail to capture the same. [21] Despite that the analysis aims to bridge the gap by addressing wage disparity and the phenomenon of payment of services of the forgone hours by the individual as a

component of the indirect cost which otherwise has not been accounted for in other studies yet. The wage discrimination must be carefully considered as it does not directly reflect the difference in level of productivity by the different groups, but the cost of hours forgone alone based on standardized wages so far. The study acknowledges the use of daily wage rates derived from the figures of monthly household consumption expenditure. The computation was done by equi-size distribution of the consumption expenditure based on the number of family members and the size of contribution to the same. This attempt addresses the limitation of real income data of the patients.

Conclusion

The overall burden of cancer consists of the substantial direct medical expenditures associated with the disease, but also incorporates societal indirect costs, such as hours of work forgone by the patient due to hospitalization and time required for treatment. Indirect costs due to loss of productivity and the individual's contribution to the economy constitutes a substantial proportion of the total societal costs associated with cancer and reveals the complete picture of the economic burden of cancer. To accurately analyze the financial burden and toxicity of cancer, economic evaluations must incorporate both direct and indirect costs. According to our study, the average indirect cost due to loss of production by the caregiver runs higher as compared to the patients. This is because better health status and activities forgone by the caregiver account for greater loss of productivity as opposed to the morbidity restricting the full labor participation by the patients. The economic burden of cancer is a bane and calls for the need of improving the systems around health financing to prevent these costs plummet the impoverishment due to the disease burden.

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SECTION-C: Assessment of impact of price regulation on sales/volumes of anticancer drugs in India

Chapter 12: Impact of price and trade margin regulation on cancer medicine in India

Introduction

In 2016, cancers accounted for 5 percent of the total Disability Adjusted Life Years (DALYs) and, over 8 percent of the total deaths in India. Both the number of deaths due to cancer as well as new cancer cases doubled between 1990 and 2016 (1). Besides the humongous disease burden, cancer also places significant socio-economic burden on patients and their families. Several cancer patients in the country have been known to travel long distances in order to access health care. Resource constrained Indians face several hardships in accessing treatment leading to overwhelming social and economic consequences resulting in impoverishment of families and exacerbation of societal inequality (2).

The average out of pocket expenditure for cancer patients is in fact 2.5 times that for other diseases (3,4). On an average inpatient care for cancer in private facilities entails about three times higher out of pocket spending compared to care in public facilities. Borrowings, sales of existing assets and contributions from friends and relatives have been found to be sources of financing cancer treatment of some 40 percent of hospitalised cases. Further, over 60 percent of the households receiving treatment in the private sector end up spending more than 20 percent of their annual per capita household expenditure (5).

Impoverishment of households as a result of out-of-pocket expenditure on medicines in India has been reported in previous studies (6). Price regulation of medicines is therefore crucial in the country and goes back several decades. The World Health Organization too recommends the use of different mechanisms for price regulation such as health technology assessment, external reference pricing, regulating mark-ups in the supply chain among others (7). The most recent policy in the country, the National Pharmaceutical Pricing Policy (NPPP), 2012 (8) was notified by the National Pharmaceutical Pricing Authority (NPPA) in order to control prices of essential medicines which are defined as medicines listed on the National List of Essential Medicines (NLEM) using a market-based formula. The market based formula, uses a simple average of prices

to retailers (PTR) of brands of a formulation with market share greater than or equal to one percent and allowing 16 percent retail margin.

The Drug Price Control Order (DPCO), 2013 (9) was subsequently notified to implement the provisions of NPPP, 2012 for drugs including those used for cancer treatment on the NLEM, 2011. The NLEM is a dynamic list and was revised in 2015. Some new anti-cancer medicines or new formulations (additional strengths and dosage forms) of existing medicines were added to the list and some anti-cancer formulations on the earlier list were removed. In addition, in February, 2019, the NPPA invoked para 19 of DPCO, 2013 and notified another 42 anti-cancer drugs for 30% trade margin cap through a 'Trade Margin Rationalization Approach' (10).

Literature suggests that while policies involving direct price control are effective in reducing prices and controlling expenditures, they may not lead to a reduction in medicine expenditures in the long run since manufacturers are able to figure out ways to increase sales of formulations outside price regulation (11). A recent study found that despite the attempts to regulate prices as well as trade margins of some anti-cancer medicines in India, their prices have remained high and that there is considerable variation in the prices of the same medicines marketed by different manufacturers. The study also observed that anti-cancer medicines priced lower are not necessarily purchased more (12).

These observations raise questions on the effectiveness of policies aimed at reducing medicines prices and expenditure in increasing consumption as was reported in previous studies (13,14,15). A study found that manufacturers engage in pricing coordination in order to avoid price-cap regulation by increasing the average price of the regulated formulation in the time period prior to regulation (16). Some pharmaceutical companies are known to have left certain product categories after the implementation of price regulation came into existence (17). The objective of the present study was therefore to ascertain the impact of price and trade margin regulation on the sales of anti-cancer medicines in the private retail market in India.

Methods

Data

Pharmaceutical market dataset, PharmaTrac was obtained from AIOCD AWACS[1] for the 72-month period from January, 2015 to December, 2020. PharmaTrac data was collected from a panel of 9000 stockists across 30 different regions of the country and extrapolated to reflect the overall medicine sales (value and volume) in the Indian private-sector retail segment. Medicines are classified and arranged in the dataset based on the Anatomical Therapeutic Chemical (ATC) classification of the European Pharmaceutical Market Research Association (EphMRA). This classification was employed to identify retail sales market in Indian private sector for anti-cancer medicines.

The medicines for which trade margins were regulated as well as those for which celling prices were notified by the NPPA were identified within the dataset. Each medicine was treated as an individual market for the purpose of this analysis. The list of medicines under trade margin and price regulation were obtained from the NPPA notification on trade margin regulation and the NLEM, 2015 respectively. The dates of notification of price ceilings for medicines in NLEM, 2015 were obtained from the NPPA website.

Study period

While the study period for assessing the impact of price regulation was January, 2015 to December, 2020, the period for assessing the impact of trade margin regulation was August, 2017 to December, 2020.

Interventions under study

Medicines on the National list of Essential medicines (NLEM), 2015 are under price regulation. The principles and implementation process of the price regulation can be found on the NPPA website. The date of notification of the ceiling price for anti-cancer medicines was considered the intervention of interest. It must be noted that for multiple strengths and dosage forms of the same medicines under NLEM, 2015, multiple dates for price ceiling notifications were identified on the NPPA website. We used interrupted time

[1] AIOCD Pharmasofttech AWACS Pvt. Ltd. is a market research company set up as a joint venture between All Indian Origin Chemists and Distributors Ltd. (AIOCD Ltd.) and Trikaal Mediinfotech Pvt. Ltd. AWACS stands for Airborne Warning And Control System.

series design to evaluate the impact of the interventions. The data was accordingly organised into two segments- pre- and post-intervention. The pre-intervention period was from January, 2015 until the month(s) in which price ceilings were notified.
The individual months or the window of months for notification were excluded including the 45 day period allowed under the policy for implementation of the notified ceiling prices. The period following the implementation period was the post-intervention period until December, 2020. To avoid the confounding influence of the regulation of cancer medicines under NLEM, 2011, we ensured that this analysis was carried out for only those medicines (strengths and dosage forms) that were newly added into NLEM, 2015. We were able to identify 19 such medicines in PharmaTrac data which were included in NLEM, 2015 and therefor price regulated for the first time and for which we were able to identify the dates of notification of ceiling price on the NPPA website.

In addition, under para 19 of DPCO, 2013 the National Pharmaceutical Pricing Authority (NPPA) also released a gazette notification regulating the trade margins of 42 essential anti-cancer drugs in India. The trade margins regulation policy was made legally effective from 8th March 2019. Therefore, the period before Mar-2019 (August, 2017 to February, 2019) was considered as pre-intervention period and post intervention period was March, 2019 onwards until December, 2020.

Research design

Interrupted time series, a quasi-experimental research design will be used to capture the impact of price and trade margin regulation on anti-cancer drug sales in India. A reference market outside regulation was used as control group to further strengthen our research design. The control group for each regulated cancer medicine was identified on the basis of their use on the site of cancer. The control was therefore identified as a cancer drug used on the same type of cancer but not under regulation.

Statistical analysis

We performed interrupted time series analysis to detect the pre-intervention trend, post-intervention level and trend change relative to the pre-intervention level and trend of anti-cancer medicines with trade margins regulation. The dependent variable (Y_t) appeared as 'logarithm of sales volume' of anti-cancer medicines. 'Time' appeared as an independent variable. A least square regression line was fitted to the two segments of the

continuous variable time for the pre- and post-intervention period and two binary variables were introduced to estimate the immediate level change (variable name: intervention) as well as trend change (variable name: time after intervention) after the intervention in the outcome variable (see equation 1 below). The variable 'intervention' was assigned as a binary variable taking the value '0' for the pre-intervention period and the value '1' for the post-intervention period, whereas time after intervention was a continuous variable for the post-intervention period. The segmented regression analysis helped us statistically determine the change in the intercept and the slope coefficients between the pre- and post-intervention periods.

Equation 1:

$$Y_t = \alpha + \beta 1 \text{ time t} + \beta 2 \text{ intervention t} + \beta 3 \text{ time after intervention t} + \epsilon_t$$

A counterfactual was introduced into the model, i.e. the trend in the sales in the post-intervention period had the trade-margins on anti-cancer medicines not been regulated. This was done by assuming that the pre-intervention trend would have continued in the post-intervention period had the intervention not been implemented. The model was checked for autocorrelation with the help of Durbin-Watson statistic, autocorrelation (ac) and partial autocorrelation (pac) estimates and plots of the residuals and appropriate adjustment were made to the model. The analysis was carried out using the statistical software, STATA version 14.

Outcomes

The outcome variables for studying the impact of price and trade margins regulation on cancer medicine sales in the private sector was the sales volume – a proxy for consumption of medicines - of anti-cancer medicines under regulation. The dataset provides the number of units/packs sold as well as the pack sizes. The two were multiplied to obtain the number of standard units (SUs) which were in the form of number of tablets, vials, bottles etc. sold in the market.

Sensitivity Analysis

As part of sensitivity analysis, we ran our model with unregulated comparison groups to control for time varying confounders and other policies that may be impacting intervention and control groups. For this, we considered the difference between the sales of the two medicines as the dependent variable and performed the analysis on the same

lines as described above. We were able to run the analysis with the control group for 10 of the 17 medicines under study for impact of price regulation. We were unable to identify suitable control groups for 1 medicine under price regulation. For 6 additional price-regulated medicines, the control group identified did not have sufficient data points in the pre- and/or post-intervention period.

To study the impact of trade margin regulation we were able to undertake the analysis for 26 medicines. Out of 26 medicines under study we were able to run the analysis with a comparison group for 18 medicines. We were unable to identify suitable control groups for 2 medicines under trade margin regulation. For 6 additional medicines, the control group identified did not have sufficient data points in pre- and/or post intervention period so were excluded from the analysis. The findings of the sensitivity analysis are presented as annexures.

Limitation

Sales data collected from the stockists was used as a proxy for consumption of anti-cancer medicines might not accurately represent the consumption. Further, PharmaTrac did not have sufficient data points for us to be able to carry out the analysis on Ifosamide, cancer drugs newly added in NLEM, 2015. PharmaTrac did not have sufficient data points to the run the ITS analysis on cladribine, clofarbine, dasatinib, mitoxantrone, Olaparib, eribulin mesylate and plerixafor, drugs under Trade margin regulation.

Results

Anti-cancer market in India

Anti-cancer medicines worth INR 28.81 billion were sold in the private retail market in India in the year 2020 up from INR 23.39 billion in the year 2015 (see table A). As of 2020, 13.48 percent of the total anti-cancer medicine market comprised medicines which were under both NLEM, 2011 and NLEM, 2015 and hence price regulated since 2013. Anti-cancer formulations accounting for an additional 4.14 percent of the sales which were under NLEM, 2011 were left out of NLEM, 2015. Formulations with sales amounting to 24.61 percent of the market were added to NLEM, 2015 and therefore brought under price regulation for the first time following the notification of the revised list. 27.33 percent of the anti-cancer market was under trade margin regulation in 2020; 23.43

percent of the market was under trade margin regulation alone and an additional 3.16 percent of the market was under trade margin and price regulation (NLEM, 2015) both and 0.74 percent of the market was brought under trade margin regulation after being removed from the NLEM. 30.44 percent of the market in terms of sales value was neither price nor trade margin regulated in 2020.

Table A: Anti-cancer medicine market in India

	2015	2016	2017	2018	2019	2020
Trade margin regulated only* (%)	21.53	22.23	26.14	28.56	26.91	23.43
NLEM 2011 only (%)	3.99	4.09	5.25	5.14	5.34	4.14
NLEM 2015 only (%)	24.34	24.02	26.77	24.53	23.76	24.61
NLEM 11 and NLEM 15 (%)	27.08	23.09	14.54	11.29	11.53	13.48
NLEM 2011 and trade margin regulated (%)	0.57	0.54	0.76	1.08	1.10	0.74
NLEM 2015 and trade margin regulated (%)	4.99	5.52	5.15	4.38	3.73	3.16
Others (%)**	17.49	20.51	21.39	25.02	27.63	30.44
Total anti-cancer drug market (INR billion)	**23.39**	**23.74**	**25.31**	**27.68**	**29.76**	**28.81**

Notes: * trade margin regulation was notified in 2019; ** others refer to those anti-cancer medicines which were outside the NLEM, 2015, NLEM 2011 and trade margin regulation

Impact of price regulation on sales of cancer medicines

Our analysis suggests that post intervention (NPPA notification on ceiling prices, 2016 - 2017), of total 17 cancer medicines under study, 7 medicines (Capecitabine, Asparaginase, Gefitinib, Mycophenolate Mofetil, Tacrolimus, Trustuzumab, Temozolamide) witnessed both an immediate and sustained increase in sales in the post-intervention period, 3 medicines (Bicalutamide, Dacarbazine, Etoposide) witnessed an immediate increase in sales followed by a sustained decline, 6 medicines (Arsenic trioxide, Chlorambucil, Docetaxel, Letrozol, Methotrexate, Cyclosporin) witnessed an immediate and sustained decline in sales and 1 medicine (Pegylated interferon alpha 2B) witnessed an immediate decline followed by a sustained increase in sales (See table 1). See table 1a (annexure) for the summary. The formulations of these 17 medicines under study for determining the impact of price regulation accounted for 24.45 % of the sales in the anti-cancer medicines market in 2020 in value terms.

Table 1: Cancer medicines with immediate increase followed by a sustained increase post-intervention

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Capecitabine	**Coefficient**	-.021	.516	.028	12.585	0.797
	P value (95% CI)	0.191 (-0.054, 0.011)	0.004 (0.175, 0.856)	0.087 (-0.004, 0.062)	0.000 (12.265, 12.905)	
Asparaginase	**Coefficient**	-.054	.590	.089	7.778	0.514
	P value (95% CI)	0.295 (-0.157, 0.048)	0.257 (-0.439, 1.620)	0.091 (-0.014, 0.193)	0.000 (6.815, 8.741)	
Trustuzumab	**Coefficient**	-.021	.949	.026	7.372	0.935
	P value (95% CI)	0.213 (-0.055, 0.012)	0.000 (0.557, 1.342)	0.125 (-0.007, 0.061)	0.000 (7.022, 7.721)	
Temozolide	**Coefficient**	-.071	.755	.064	10.517	0.894
	P value (95% CI)	0.005 (-0.121, 0.021)	0.004 (0.245, 1.264)	0.013 (0.014, 0.115)	0.000 (10.045, 10.988)	
Gefitinib	**Coefficient**	-.068	.413	.068	14.210	0.292
	P value (95% CI)	0.000 (-0.095, -0.041)	0.002 (0.161, 0.666)	0.000 (0.041, 0.095)	0.000 (13.967, 14.454)	
Mycophenolate mofetil	**Coefficient**	.004	.014	.006	13.558	0.983
	P value (95% CI)	0.737 (-0.019, 0.027)	0.904 (-0.227, 0.256)	0.587 (-0.017, 0.030)	0.000 (13.334, 13.783)	
Tacrolimus	**Coefficient**	-.014	.035	.022	14.230	0.988
	P value (95% CI)	0.268 (-0.041, 0.011)	0.803 (-0.245, 0.316)	0.098 (-0.004, 0.049)	0.000 (13.975, 14.485)	

In table 1 we present cancer medicines which showed positive effect of the intervention in terms of sales volumes. The average monthly sales of Capecitabine witnessed an immediate rise by 51.6% (p=0.00) in the post intervention period followed by a sustained positive rise to the tune of 2.8% (p=0.08) in comparison to the pre-intervention period. Also, the average monthly sales for Asparaginase witnessed a highly insignificant immediate rise to the tune of 59% (p=0.26) in the post-intervention period followed by a sustained rise of 8.9% (p=0.09).

The average monthly sales of Trustuzumab saw a sharp immediate and highly significant increase by 94.9% (p=0.00) in the post-intervention period followed by a sustained increase by 2.6% (p=0.12). The average monthly sales of Temozolomide witnessed an

immediate and sustained increase in the post-intervention period by 75.5% (p=0.00) and 6.4% (p=0.01) respectively. The average monthly sales of Gefitinib witnessed a significant immediate and sustained increase by 41.3% (p=00) and 6.8% (p=0.00) respectively in the post-intervention period in comparison to the pre-intervention period. However, the average monthly sales of Mycophenolate Mofetil and Tacrolimus witnessed a small and insignificant immediate and sustained increase in the post-intervention period.

Table 2: Cancer medicines with immediate increase followed by a sustained decline in the post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Bicalutamide	Coefficient	.005	.098	-.004	13.445	0.989
	P value (95% CI)	0.321 (-0.005, 0.015)	0.050 (0.000, 0.196)	0.415 (-0.014, 0.006)	0.000 (13.352, 13.53)	
Dacarbazine	Coefficient	.026	.757	-.037	7.365	0.161
	P value (95% CI)	0.712 (-0.115, 0.168)	0.288 (-0.655, 2.170)	0.608 (-0.181, 0.106)	0.000 (6.038, 8.691)	
Etoposide	Coefficient	.057	.569	-.097	7.737	0.530
	P value (95% CI)	0.282 (-0.047, 0.162)	0.657 (-1.981, 3.121)	0.119 (-0.220, 0.025)	0.000 (5.809, 9.66)	

Table 2 shows present medicines which experienced an immediate increase followed by sustained decline in terms of sales volume. The average monthly sales of Bicautamide witnessed an immediate rise of 9.8% (p=0.05) followed by a slight sustained but highly insignificant drop of 0.4% (p=0.4) in the post-intervention period in comparison to the pre-intervention period. The average monthly sales of Dacarbazine witnessed an insignificant immediate increase of 75.7% (p=0.29) followed by a sustained but highly insignificant reduction of 3.7% (p=0.61) in the post-intervention period in comparison to the pre-intervention period. Similarly, the average monthly sales of Etoposide witnessed a highly insignificant but immediate rise by 56.9% in the post intervention period in comparison to the pre-intervention period followed by a sustained decline by 9.7% (p=0.12).

Table 3: Cancer medicines with immediate and sustained decline in the post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Arsenic Trioxide	Coefficient	0.031	-.245	-.034	7.012	0.134
	P value (95% CI)	0.043 (0.001, 0.062)	0.507 (-0.981, 0.489)	0.071 (-0.071, 0.003)	0.000 (6.449, 7.575)	
Chlorambucil	Coefficient	.143	-.511	-.150	9.301	0.575
	P value (95% CI)	0.064 (-0.008, 0.294)	0.515 (-2.070, 1.048)	0.056 (-0.303, 0.003)	0.000 (7.861, 10.741)	
Docetaxel	Coefficient	.066	-.358	-.057	7.825	0.221
	P value (95% CI)	0.014 (.013, 0.118)	0.153 (-0.854, 0.136)	0.034 (-0.110, -0.004)	0.000 (7.347, 8.304)	
Letrozole	Coefficient	.067	-.101	-.039	12.877	0.962
	P value (95% CI)	0.016 (0.012, 0.122)	0.765 (-0.771, 0.569)	0.166 (-0.095, 0.016)	0.000 (12.305, 13.449)	
Methotrexate	Coefficient	0.044	-0.341	-0.044	9.477	0.273
	P value (95% CI)	0.000 (0.026, 0.062)	0.000 (-0.510, -0.173)	0.000 (-0.062, -0.026)	0.000 (9.314, 9.639)	
Cyclosporin	Coefficient	.119	-.434	-.111	7.018	0.662
	P value (95% CI)	0.013 (.026, 0.211)	0.538 (-1.83, 0.967)	0.027 (-0.210, -0.013)	0.000 (5.86, 8.168)	

***In cyclosporin 10 months' time period was taken as intervention period**

Medicines which were observed to have negative effect of the intervention in terms of sales volumes are presented in table 3. The NPPA notified the price ceiling for Arsenic Trioxide in July, 2017 after which the average monthly sales of the medicine witnessed an immediate but highly insignificant drop to the tune of 24.5% (p=0.51). This was followed by a sustained rise in average monthly sales by 3.4% (p=0.07) in comparison to the pre-intervention period. Similarly,

The average monthly sales of Chlorambucil witnessed an immediate but highly insignificant drop to the tune of 51% (p=0.5) followed by s sustained drop of 15% (p=0.06). The average monthly sales of Docetaxel witnessed a sharp sudden, but highly insignificant decline by 35.8% (p=0.15) followed by a sustained decline of 5.7% (p=0.03) in the post-intervention period in comparison to the pre-intervention period. The average monthly sales of Letrozole and cyclosporin witnessed a highly insignificant immediate decline followed by an insignificant sustained decline in the post-intervention period when compared with the pre-intervention period. The average monthly sales of Methotrexate witnessed a highly significant immediate and sustained decline in the post-

intervention period when compared with the pre-intervention period to the tune of 34% (p=0.00) and 4.4% (p=0.00) respectively.

Table 4: Cancer medicines with sudden decline followed by a sustained increase in the post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
PEGYLATED INTERFERON ALPHA 2B	Coefficient	-.118	-.205	.063	8.806	0.594
	P value (95% CI)	0.036 (-.228, -.0077)	0.725 (-1.372, 0.960)	0.269 (-0.050, 0.176)	0.000 (7.73, 9.872)	

***10 months' time period was taken as intervention period**

The average monthly sales of Pegylated Interferon Alpha 2B witnessed an immediate decline in sales followed by a sustained rise in the post-intervention period in comparison to the pre-intervention period. The level and trend change were however both statistically insignificant.

Impact of trade margin regulation on sales of cancer medicines

Our analysis suggests that post intervention (NPPA notification on trade margin cap), of total 26 cancer medicines 2 medicines (Erlotinib, Pegfilgrastim) witnessed both an immediate and sustained increase in sales in the post intervention period, 10 medicines (Bevacizumab, Crizotinib, Sunitinib, Pomalidomide, Azacitidine, Decitabine, Epirubicin, Mitomycin, Exemestane, Cabazitaxel) witnessed an immediate increase in sales followed by sustained decline, 5 medicines (Osimertinib, Carfilzomib, Everolimus, Enzalutamide, Triptorelin) witnessed an immediate and sustained decline in sales and 9 medicine (Irnotecan, Lenolidomine, Regorfenib, Lapatinib, Pemetrexed, Bendamustine, Fulvestrant, Estramustine, Nilotinib) witnessed an immediate decline followed by a sustained increase in the sales (see annexure table 5). These 26 medicines under study for the impact of trade margin regulation accounted for 21.42 percent of the sales in the anti-cancer drugs market in India in 2020 in value terms.

Table 5: Cancer medicines immediate increase followed by a sustained increase in the post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Erlotinib	Coefficient	.002	.216	.006	12.661	0.975
	P value (95%ci)	0.775 (-0.013, 0.018)	0.068 (-0.016, 0.448)	0.508 (-0.013, 0.027)	0.000 (12.483, 12.838)	
Pegfilgrastim	Coefficient	-.016	.011	.051	8.872	0.644
	P value (95%ci)	0.035 (-0.031, -0.001)	0.914 (-0.201, 0.223)	0.000 (0.031, 0.070)	0.000 (8.709, 9.035)	

In table 5 we present cancer medicines which showed positive effect of the intervention in terms of sales volumes. The average monthly sales of Erlotinib witnessed a small and insignificant immediate rise of 21.6% (p=0.07) followed by sustained rise of 0.6% (p=0.5) in the post-intervention period in comparison to the pre-intervention period. The monthly average sales of Pegfilgrastim witnessed a highly insignificant immediate rise by 1.1% (p=0.91) in the post intervention period followed by a significant sustained positive rise to the tune of 5.1% (p=0.00) in comparison to the pre-intervention period.

Table 6: Cancer medicines with immediate increase followed by a sustained decline in the post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Bevacizumab	Coefficient	.019	.487	-.012	7.824	0.880
	P value (95% CI)	0.005 (0.006, 0.033)	0.000 (0.299, 0.675)	0.133 (-0.029, 0.004)	0.000 (7.680, 7.969)	
Crizotinib	Coefficient	.146	.330	-.151	6.480	0.880
	P value (95% CI)	0.000 (0.111, 0.181)	0.187 (-0.168, 0.828)	0.000 (-0.195, -0.106)	0.000 (6.098, 6.861)	
Sunitinib	Coefficient	.052	.190	-.108	7.709	0.726
	P value (95% CI)	0.000 (0.034, 0.071)	0.147 (-0.070, 0.450)	0.000 (-0.131, -0.084)	0.000 (7.509, 7.909)	
Pomalidomide	Coefficient	.012	.095	-.021	10.328	0.958
	P value (95% CI)	0.215 (-0.007, 0.032)	0.506 (-0.194, 0.386)	0.096 (-0.047, 0.004)	0.000 (10.106, 10.549)	
Azacitidine	Coefficient	-.001	.548	-.019	7.508	0.780
	P value (95% CI)	0.961 (-0.044, 0.042)	0.088 (-0.086, 1.184)	0.483 (-0.076, 0.036)	0.000 (7.024, 7.992)	
Decitabine	Coefficient	-.011	.164	-.080	6.593	0.721
	P value (95% CI)	0.545 (-0.048, 0.026)	0.533 (-0.364, 0.693)	0.002 (-0.128, -0.032)	0.000 (6.187, 7.000)	
Epirubicin	Coefficient	-.020	.020	-.030	9.264	0.904

	P value (95% CI)	0.241 (-0.054, 0.014)	0.934 (-0.479, 0.521)	0.171 (-0.075, 0.013)	0.000 (8.882, 9.645)	
Mitomycin	**Coefficient**	.012	.760	-.014	9.046	0.620
	P value (95% CI)	0.440 (-0.019, 0.044)	0.002 (0.306, 1.215)	0.481 (-0.055, 0.026)	0.000 (8.697, 9.395)	
Exemestane	**Coefficient**	.015	.039	-.012	11.547	0.420
	P value (95% CI)	0.025 (0.002, 0.027)	0.662 (-0.143, 0.222)	0.150 (-0.028, 0.004)	0.000 (11.406, 11.688)	
Cabazitaxel	**Coefficient**	-.002	.018	-.009	4.354	0.543
	P value (95% CI)	0.928 (-0.062, 0.056)	0.966 (-0.849, 0.885)	0.797 (-0.086, 0.066)	0.000 (3.695, 5.013)	

Table 6 presents cancer medicines which demonstrated immediate increase followed by sustained decline in the post intervention period. The average monthly sales of Bevacizumab witnessed a highly significant immediate increase of 48.7% (p=0.00) followed by a sustained but insignificant reduction of 1.2% (p=0.13) in the post-intervention period in comparison to the pre-intervention period. The average monthly sales of Crizotinib witnessed an immediate increase by 33% (p=0.19) followed by a sustained reduction by 15.1% (p=0.00) in the post-intervention period compared with the pre-intervention period. Similarly, the average monthly sales of Sunitinib witnessed an insignificant but immediate rise by 19% (p=0.15) in the post intervention period in comparison to the pre-intervention period followed by a sustained decline by 10.8% (p=0.00). The average monthly sales of Pomalidomide witnessed a highly insignificant but immediate rise by the tune of 9.5% (p=0.51) in the post intervention period in comparison to the pre-intervention period followed by a sustained reduction of 2.1% (p=0.1). The average monthly sales of Azacitidine witnessed an insignificant immediate rise of 54.8% (p=0.09) followed by a sustained but highly insignificant decline of 1.9% (p=0.48) in the post-intervention.

The average monthly sales of Decitabine witnessed a highly insignificant immediate increase of 16.4% (p=0.53) followed by a significant sustained reduction of 8% (p=0.00) in the post-intervention. The average monthly sales of Epirubicin witnessed a highly insignificant immediate rise by 2% in the post intervention period in comparison to the pre-intervention period followed by a sustained decline by 3% (p=0.17). The average monthly sales of Mitomycin witnessed an immediate but highly significant increase to the tune of 76% (p=0.00) followed by sustained drop of 1.4% (p=0.48). The average monthly sales of Exemestane witnessed an immediate but highly insignificant increase to the tune

of 3.9% (p=0.66) followed by sustained drop of 1.2% (p=0.15). Similarly, the average monthly sales of Cabazitaxel witnessed an immediate but highly insignificant increase to the tune of 1.8% (p=0.97) followed by sustained drop of 0.9% (p=0.80).

Table 7: Cancer medicine with Immediate and sustained decline in the post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Osimertinib	Coefficient	.172	-.202	-.153	4.337	0.834
	P value (95% CI)	0.000 (0.131, 0.214)	0.486 (-0.787, 0.381)	0.000 (-0.206, -0.100)	0.000 (3.888, 4.787)	
Carfilzomib	Coefficient	.009	-.117	-.002	6.51	0.088
	P value (95% CI)	0.224 (-0.006, 0.025)	0.216 (-0.306, 0.071)	0.803 (-0.021, 0.016)	0.000 (6.366, 6.667)	
Everolimus	Coefficient	.025	-.457	-.042	10.086	0.466
	P value (95% CI)	0.042 (0.000, 0.051)	0.013 (-0.810, -0.104)	0.010 (-0.074, -0.010)	0.000 (9.815, 10.357)	
Enzalutamide	Coefficient	.069	-.331	-.028	8.71	0.748
	P value (95% CI)	0.000 (0.040, 0.098)	0.063 (-0.681, 0.018)	0.108 (-0.062, 0.006)	0.000 (8.435, 8.994)	
Triptorelin	Coefficient	.015	-.022	-.016	8.959	0.979
	P value (95% CI)	0.165 (-0.006, 0.037)	0.890 (-0.351, 0.306)	0.251 (-0.044, 0.012)	0.000 (8.711, 9.208)	

In table 7 we present cancer medicines which showed negative effect of the intervention in terms of sales volumes. The average monthly sales of Osimertinib witnessed an insignificant immediate decline in the post-intervention period when compared with the pre-intervention period to the tune of 20.2% (p=0.49) followed by highly significant sustained decline by 15.3% (p=0.00).

The average monthly sales of Carfilzomib and Enzalutamide witnessed an insignificant immediate and sustained decline in the post-intervention period when compared with the pre-intervention period. The average monthly sales of Everolimus witnessed a significant immediate and sustained decline in the post-intervention period when compared with the pre-intervention period to the tune of 45.7% (p=0.01) and 4.2% (p=0.01) respectively. Similarly, the average monthly sales of Triptorelin witnessed an insignificant immediate and sustained decline in the post-intervention period when compared with the pre-intervention period to the tune of 2.2% (p=0.9) and 1.6% (p=0.25) respectively.

Table 8: Cancer medicines with sudden decline followed by a sustained increase in post intervention period

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
Irnotecan	Coefficient	.008	-.174	.045	7.133	0.368
	P value (95% CI)	0.690 (-0.035, 0.052)	0.570 (-0.791, 0.442)	0.110 (-0.010, 0.101)	0.000 (6.659, 7.607)	
Lenolidomide	Coefficient	-.005	-.173	.039	12.668	0.964
	P value (95% CI)	0.567 (-0.024, 0.013)	0.206 (-0.445, 0.099)	0.002 (0.014, 0.063)	0.000 (12.459, 12.876)	
Regorafenib	Coefficient	-.073	-.045	.057	10.886	0.602
	P value (95% CI)	0.001 (-0.112, -0.033)	0.869 (-0.600, 0.509)	0.027 (0.006, 0.107)	0.000 (10.460, 11.313)	
Lapatinib	Coefficient	-.037	-.585	.021	10.500	0.865
	P value (95% CI)	0.019 (-0.068, -0.006)	0.010 (-1.024, -0.145)	0.283 (-0.018, 0.060)	0.000 (10.164, 10.837)	
Pemetrexed	Coefficient	-.006	-.221	.030	8.680	0.857
	P value (95% CI)	0.478 (-0.023, 0.011)	0.076 (-0.465, 0.023)	0.008 (0.008, 0.052)	0.000 (8.492, 8.868)	
Bendamustine	Coefficient	-.003	-.030	.006	7.769	0.936
	P value (95% CI)	0.887 (-0.049, 0.042)	0.931 (-0.741, 0.680)	0.831 (-0.053, 0.065)	0.000 (7.236, 8.302)	
Fulvestrant	Coefficient	.008	-.159	.005	7.261	0.245
	P value (95% CI)	0.208 (-0.004, 0.020)	0.082 (-0.340, 0.021)	0.474 (-0.010, 0.022)	0.000 (7.122, 7.400)	
Estramustine	Coefficient	-.158	-2.697	0.185	9.942	0.8637
	P value (95% CI)	0.002 (-.250, -0.066)	0.000 (-3.978, -1.416)	0.021 (0.030, 0.340)	0.000 (9.056, 10.829)	
Nilotinib	Coefficient	0.057	-0.707	0.026	5.183	0.366
	P value (95% CI)	0.424 (-0.088, 0.204)	0.156 (-1.704, 0.288)	0.729 (-0.128, 0.181)	0.000 (4.274, 6.091)	

Table 8 presents cancer medicines which show immediate decline followed by sustained increase in the post intervention period. The average monthly sales of Irnotecan witnessed a highly insignificant immediate decline by 17.4% (p=0.57) followed by an insignificant sustained increase by 4.5% (p=0.11) in the post-intervention.

The average monthly sales of Lenalidomide and Regorafenib witnessed an insignificant but immediate decline in the post intervention period followed by a sustained increase. The average monthly sales of Lapatinib witnessed a significant immediate decline by 58.5% (p=0.01) followed by an insignificant sustained increase by 2.1% (p=0.28) in the post-intervention. The average monthly sales of Pemetrexed witnessed an insignificant immediate decline by 22.1% (p=0.08) followed by a significant sustained increase by 3% (p=0.01) in the post-intervention.

The average monthly sales of Bendamustine and Nilotinib witnessed a highly insignificant immediate decline) followed by an insignificant sustained increase. Also, the average monthly sales of Fulvestrant witnessed an insignificant immediate decline by 15.9% in the post intervention period followed by a sustained increase by 0.5% (p=0.47). The average monthly sales of Estramustine witnessed a highly significant immediate decline by 269.7%% in the post intervention period followed by a sustained increase by 18.5% (p=0.02).

Discussion

Utilising nationally representative private sector medicine sales data and robust econometric methods, this study is the first study to the best of our knowledge to report the impact of both price and trade margin regulation polices on the anti-cancer drug market. The most notably effect observed was an immediate as well as sustained decline in the sales volume of 6 (35%) of the 17 price regulated medicines and 5 (19%) of the 26 trade margin of regulated medicines under study in the post-intervention period in comparison to the pre-intervention period. An immediate increase followed by a sustained decline in sales volume was observed for 3 (18%) price regulated medicines and 10 (38%) trade margin regulated medicines under study in the post intervention period. 7 (41%) medicines under price regulation and 2 (8%) medicines under trade margin regulation witnessed both an immediate and sustained increase in sales in the post-intervention period. 1 (6%) medicine under price regulation and 9 (35%) medicines under trade margin regulation witnessed an immediate decline followed by a sustained increase in sales in the post-intervention period.

The markets for different anti-cancer medicines demonstrated widely varying effects of the two policies of price and trade margin regulation. Literature on market definitions (18) suggests that since patients cannot substitute the medicines prescribed to them with available alternatives owing to information asymmetry, individual medicines should be studied as distinct markets. This resonates even more for medicines used to treat cancer, a highly specialised disease condition. We therefore undertook separate analysis for each individual medicine, and observed considerable heterogeneity in the findings.

The findings can however be explained in terms of substitution effect but from the point of view of prescribers. The preferences of prescribers could have shifted in the interest

of the patient as they would have chosen to prescribe the drugs under regulation instead of equally effective alternatives as they were made available at lower prices leading to an increase in sales- both immediate and sustained. On the other hand prescribers could be influenced by the marketing practices of pharmaceutical companies and therefore prescribe equally effective alternative drugs outside the ambit of regulation even though they may be priced higher. For commercial reasons in order to generate higher revenues for pharmaceutical companies as well as hospitals, higher priced drugs may be pushed leading to an immediate as well as sustained decline in sales of price regulated drugs.

Chaudhuri, S. (2019) argued that simply fixing price cap on drugs does not make them more accessible. Only the dose forms and strengths of molecules specifically identified in the NLEM are price-controlled under DPCO, 2013. This allows companies to promote various dosage forms, strengths, and competing molecules, restricting the supply of price-controlled pharmaceuticals thereby defeating the primary goal of price control. Sahay and Jaykumar (2016) noted that price ceilings may prove effective in lowering all pharmaceutical prices, however the accompanying pricing pressure may counterintuitively, result in low-cost goods being phased out of the market. If a considerable section of the population relies on these low-cost pharmaceuticals, consumer welfare may suffer despite the reduction in prices.

Fickweiler et al., (2017) (19) noted that the relationships between physicians and pharmaceutical companies, as well as the acceptance of gifts from the companies' sales representatives have been found to influence the prescribing behaviour of physicians and are likely to contribute to irrational prescribing of the company's medicine.

The demand for essential and life-saving medicines are relatively price inelastic. Doctors prescribe such medicines irrespective of their prices and patients buy them in the absence of alternatives and in turn sometimes incur debts. . Vincent Rajkumar (2020) (20) argued that the fact that therapies for critical diseases are not luxury commodities, but are required by vulnerable patients seeking to improve their quality of life or extend their lives, keeps prescription drug prices high. Patients and their families are also willing to pay any price to save or prolong life in the case of critical conditions. Some drugs are indispensable for treatment of particular cancers and any price reduction for these drugs should lead to an immediate and sustained increase in sales. This was noticed for drugs such as Trastuzumab, but surprisingly not for Letrozole

Standards of care are routinely updated and may have changed as a result of drugs with improved effectiveness being made available in the market and therefore led to prescription of drugs outside price regulation which may have led to an immediate increase followed by a sustained decline in sales of certain drugs under study.

Differences in the effects of the policies may be explained in terms of the type of use for individual drugs i.e. whether a drug is used for curative or palliative care use. Prescriber as well as patient attitudes may vary depending on the use. Drugs meant for treatment may be perceived as essential and therefore witness increase in sales as a result of price reduction as against those meant for palliative care use. Similarly, drugs used for single indication may not see much increase in sales as a result of price reduction as their markets may not have significant growth potential in comparison to drugs meant for multiple indications. Initial price of a drug may also be an indicator of the impact of regulation. For drugs with higher prices before price regulation was implemented may be expected to have a larger impact in sales as compared to lower priced drugs brought under regulation.

Bhaskarabhatla et al. (2016) pointed out that the flaws in policy design are compounded by shortcomings in implementation. Due to a lack of price information, the ceiling price for 102 of the 652 formulations has not been determined. Firms that violate price-cap regulations have also been punished ineffectively. The NPPA lacks a local presence and relies on others to monitor prices at the state level, such as the Department of Pharmaceuticals, restricting its ability to monitor and enforce the legislation.
Interrupted time series analysis, which is regarded in literature as the strongest, quasi-experimental research design meant for the evaluation of longitudinal effects of interventions (21), is increasingly being used in drug utilization research (22). We therefore chose this research design for our study and as part of sensitivity analysis we further strengthened it by adding relevant control groups for select medicines.

Kaur, Jain and Bhatnagar (23) in their paper studying the trend in utilization of oncology services under Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (PM-JAY), India's government-funded health insurance scheme launched in September 2018 noted that 9 percent of the total claims submitted and 34 percent of all submitted claims for tertiary care were for oncology segment till July, 2019 across 26 states and union territories. Our study which focuses solely on the private marker for cancer medicines, was unable to

factor in the impact of Ayushman Bharat PM-JAY on the utilisation of cancer medicines through the public sector and its spillover effect on the private market. More research is needed in this arena.

ANNEXURES

Annexure table 1: Summary findings of Price regulated anti-cancer medicines without control

Impact of Price Regulation on sales of anti-cancer medicines	Number of medicines	Medicine names

Immediate increase followed by a sustained decline	3	BICALUTAMIDE, DACARBAZINE, ETOPOSIDE
Immediate increase followed by a sustained increase	7	CAPECITABINE, ASPARAGINASE, GEFITINIB, MYCOPHENOATE MOFETIL, TACROLIMUS, TRUSTUZUMAB, TEMOZOLAMIDE
Immediate decline followed by a sustained decline	6	ARSENIC TRIOXIDE, CHLORAMBUCIL, DOCETAXEL, LETROZOL, METHOTREXATE, CYCLOSPORIN
Immediate decline followed by a sustained increase	1	PEGYLATED INTERFERON ALPHA 2B
Total medicines under study	**17**	

Annexure table 2: Cancer medicines with immediate increase followed by a sustained increase post intervention with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
CAPECITABINE with TEGAFUR + URACIL as control	**Coefficient**	-0.025	0.542	0.032	12.600	0.536
	P value (95% CI)	0.066 (-0.052, 0.001)	0.000 (0.268, 0.816)	0.020 (0.005, 0.059)	0.000 (12.339, 12.860)	
ASPARAGINASE with METHOTREXATE + FOLIC ACID as control	**Coefficient**	-0.010	-.003	0.021	14.110	0.742
	P value (95% CI)	0.139 (0.023, 0.003)	0.956 (0.129, 0.122)	0.003 (.007, 0.034)	0.000 (13.988, 14.232)	
GEFITINIB with AXITINIB as control	**Coefficient**	-0.025	0.229	0.024	13.768	0.049
	P value (95% CI)	0.093 (-0.054, 0.004)	0.108 (-0.051, 0.511)	0.110 (-0.005, 0.054)	0.000 (13.499, 14.038)	
MYCOPHENOLATE with SIROLIMUS as control	**Coefficient**	-0.005	0.072	0.016	13.599	0.736
	P value (95% CI)	0.510 (-0.021, 0.010)	0.342 (-0.078, 0.223)	0.042 (0.000, 0.033)	0.000 (13.453, 13.745)	
TACROLIMUS with SIROLIMUS as control	**Coefficient**	-0.013	0.094	0.019	14.172	0.434
	P value (95% CI)	0.101 (-0.029, 0.002)	0.215 (-0.056, 0.244)	0.019 (0.003, 0.035)	0.000 (14.026, 14.317)	

Annexure table 3: Cancer medicines with immediate increase followed by a sustained decline in the post intervention period with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
BICALUTAMIDE with ABIRATERONE ACETATE as control	Coefficient	-0.002	-0.103	-0.002	13.441	0.406
	P value (95% CI)	0.818 (0.021, 0.016)	0.254 (.282, 0.075)	0.769 (-.022, 0.016)	0.000 (13.268, 13.614)	
ETOPOSIDE with CARBOPLATIN as control	Coefficient	0.075	-0.207	-0.084	7.710	0.252
	P value (95% CI)	0.000 (0.034, 0.116)	0.608 (-1.011, 0.596)	0.000 (-0.130, -0.038)	0.000 (7.055, 8.364)	

* Instead of log of the difference of sales volume, the difference of sales volume was used as the dependent variable- ETOPOSIDE

Annexure table 4: Cancer medicines with immediate and sustained decline in the post intervention period with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
LETROZOLE with ANASTROZOLE as control	Coefficient	43263.28	339645.8	-98.511	-109264.9	0.809
	P value (95% CI)	0.143 (-14980.8, 101507.4)	0.220 (-208579.6, 887871.1)	0.997 (-58928.02 58731)	0.682 (-638827.6 420297.8)	
METHOTREXATE with MYCOPHENOLATE SODIUM as control	Coefficient	-0.024	0.972	0.020	10.435	0.231
	P value (95% CI)	0.468 (-0.090, 0.042	0.003 (0.347, 1.598)	0.541 (-0.046, 0.087)	0.000 (9.831, 11.039)	
CYCLOSPORIN with SIROLIMUS as control	Coefficient	282.617	-20988.46	-491.364	28125.04	0.5595
	P value (95% CI)	0.501 (-553.63, 1118.86)	0.000 (-31760.07 - 10216.86)	0.264 (-1362.86 380.13)	0.000 (18590.34, 37659.73)	

*Instead of log of the difference of sales volume, the difference of sales volume was used as the dependent variable- LETROZOLE

Annexure table 5: Summary findings of Trade Margin regulated anti-cancer medicines without control

Impact of Price Regulation on sales of anti-cancer medicines	Number of medicines	Medicine names
Immediate increase followed by a sustained decline	10	**BEVACIZUMAB, CRIZOTINIB, SUNITINIB, POMALIDOMIDE, AZACITIDINE, DECITABINE, EPIRUBICIN, MITOMYCIN, EXEMESTANE, CABAZITAXEL**
Immediate increase followed by a sustained increase	2	**ERLOTINIB, PEGFILGRASTIM**
Immediate decline followed by a sustained decline	5	**OSIMERTINIB, CARFILZOMIB, EVEROLIMUS, ENZALUTAMIDE, TRIPTORELIN**
Immediate decline followed by a sustained increase	9	**IRNOTECAN, LENOLIDOMIDE, REGORAFENIB, LAPATINIB, PEMETREXED, BENDAMUSTINE, FULVESTRANT, ESTRAMUSTINE, NILOTINIB**
Total medicines under study	26	

Annexure table 6: Cancer medicines with immediate increase followed by a sustained decline in the post intervention period with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
SUNITINIB with AXATINIB as control	Coefficient	12.027	1668.419	-186.627	1271.34	0.498
	P value (95% CI)	0.751 (-64.259, 88.315)	0.003 (593.945, 2742.892)	0.000 (-284.002, -89.253)	0.004 (445.583, 2097.11)	
POMALIDOMIDE with DARATUMUMAB as control	Coefficient	.0018	.166	-.0126	10.485	0.123
	P value (95% CI)	0.910 (-.031, 0.034)	0.186 (-.084, 0.417)	0.469 (-.0481, 0.022)	0.000 (10.260, 10.710)	
AZACITIDINE with FLUDARABINE as control	Coefficient	84.462	2014.818	-91.8563	-1278.503	0.663
	P value (95% CI)	0.078 (-10.011, 178.936)	0.005 (666.401, 3363.235)	0.142 (-216.065, 32.353)	0.016 (-2301.12, -255.886)	
DECITABINE with FLUDARABINE as control	Coefficient	-67.95	-381.50	29.17	2312.144	0.837
	P value (95% CI)	0.000 (-99.862, -36.050)	0.098 (-836.897, 73.892)	0.167 (-12.770, 71.127)	0.000 (1966.78, 2657.508)	
EPIRUBICIN with CARBOPLATIN as control	Coefficient	.0361	-.129	-.044	10.051	0.288
	P value (95% CI)	0.002 (0.014, 0.057)	0.385 (-.429, 0.169)	0.002 (-.071, -0.016)	0.000 (9.820, 10.281)	
MITOMYCIN with CETUXIMAB as control	Coefficient	.002	.898	-.006	9.019	0.589
	P value (95% CI)	0.874 (-.032, 0.038)	0.001 (0.397, 1.398)	0.759 (-0.052, 0.038)	0.000 (8.634, 9.404)	
EXEMESTANE with PALBOCICLIB as control	Coefficient	.0138	.0239	-.01071	11.515	0.361
	P value (95% CI)	0.039 (0.000, 0.026)	0.795 (-0.161, 0.208)	0.203 (-0.027, 0.006)	0.000 (11.373, 11.657)	
CABAZITAXEL with ABIRATERONE ACETATE as control	Coefficient	.0086	.2423	-.0364	12.695	0.621
	P value (95% CI)	0.080 (-0.001, 0.018)	0.001 (0.105, 0.378)	0.000 (-.048, -0.024)	0.000 (12.590, 12.800)	

* Instead of log of the difference of sales volume, the difference of sales volume was used as the dependent variable: SUNITINIB, AZACATADINE, DECITABINE

Annexure table 7: Cancer medicines immediate and sustained increase with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
ERLOTINIB with AFATINIB as control	Coefficient	-.008	.230	.015	12.763	0.578
	P value (95% CI)	0.700 (-.054, .037)	0.025 (0.032, 0.427)	0.496 (-.030, 0.0621)	0.000 (12.55, 12.967)	
PEGFILGRASTIM with SARGRAMOSTIM as control	Coefficient	-.021	.017	.064	8.844	0.569
	P value (95% CI)	0.033 (-.040, -0.001)	0.903 (-.264, 0.299)	0.000 (.037, 0.090)	0.000 (8.633, 9.055)	

Annexure table 8: Cancer medicine with immediate and sustained decline in the post intervention period with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
OSIMERTINIB with AFATINIB as control	Coefficient	81.285	5218.81	-897.454	337.571	0.6017
	P value (95% CI)	0.915 (-1475.933 1638.505)	0.123 (-1521.148 11958.77)	0.254 (-2482.73 687.824)	0.921 (-6626.523 7301.666)	
CARFILZOMIB with DARATUMUMAB as control	Coefficient	-.0084	-.8290	.0534	6.398	0.417
	P value (95% CI)	0.806 (-0.078, 0.061)	0.003 (-1.361, -0.296)	0.156 (-0.021, 0.128)	0.000 (5.922, 6.874)	
EVEROLIMUS with AXATINIB as control	Coefficient	.021	-.489	-.038	10.042	0.460
	P value (95% CI)	0.126 (-0.006, 0.049)	0.017 (-.886, -0.092)	0.035 (-.074, -0.0028)	0.000 (9.737, 10.348)	
ENZALUTAMIDE with ABIRATERONE ACETATE as control	Coefficient	-.0001	.306	-.0321	12.770	0.688
	P value (95% CI)	0.975 (-.011, 0.011)	0.000 (0.163, 0.448)	0.000 (-0.046, -0.018)	0.000 (12.656, 12.884)	
TRIPTORELIN with ABIRATERONE	Coefficient	.008	.245	-.036	12.670	0.6175
	P value (95% CI)	0.091 (-0.001, 0.018)	0.001 (0.106, 0.385)	0.000 (-0.049, -0.024)	0.000 (12.562, 12.77)	

ACETATE as control						

*instead of log of the difference of sales volume, the difference of sales volume was used as the dependent variable: OSIMERTINIB

Annexure table 9: Cancer medicines with immediate decline followed by a sustained increase in post intervention period with control

Cancer medicine		Time	Intervention (level change)	Time after intervention (trend change)	Constant	R2
LENOLIDOMIDE with DARATUMUMAB as control	**Coefficient**	.0111	-.241	.0215	12.523	0.586
	P value (95% CI)	0.478 (-0.020, 0.043)	0.050 (-0.482, 0.000)	0.206 (-.012, 0.055)	0.000 (12.307, 12.739)	
FULVESTRANT with PALBOCICLIB as control	**Coefficient**	.052	.356	-.053	7.609	0.676
	P value (95% CI)	0.001 (0.023, 0.081)	0.088 (-0.055, 0.768)	0.006 (-0.091, -0.016)	0.000 (7.292, 7.925)	
ESTRAMUSTINE with ABIRATERONE ACETATE as control	**Coefficient**	0.013	0.211	-0.052	12.647	0.526
	P value (95% CI)	0.036 (0.0009, 0.026)	0.020 (0.0354, 0.386)	0.000 (-0.0739, -0.0314)	0.000 (12.526, 12.769)	

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SECTION-D: Assessment of impact of price regulation on insurance claims under Punjab Cancer Raahat Kosh Yojana

Chapter 13: Effect of price regulation of anti-cancer drugs on insurance claims in a northern state of India – a payer's perspective

Introduction

With increasing longevity, burden of cancers is on the rise very strongly. Though many forms of this previously deadly disease are now considered curable, the treatment entails multiple surgeries, chemotherapy, radiotherapy and palliative care. All of these make cancer an expensive disease to manage and cure. There's wide range of evidence on the catastrophic health expenditure caused by cancers, approximating the value to be between 21% to 68% across population groups.(1–6)

Various attempts towards addressing this challenge have been made through public provisioning and prescription practices. One possible solution is price regulation which refers to the policy of setting prices by a government agency, legal statute or regulatory authority. Under this policy, minimum and/or maximum prices may be set. There are 2 broad mechanisms to control the prices of drugs in India, market based and cost- based. Currently, the DPCO uses the market-based pricing mechanism where-in the ceiling price is calculated by taking the simple average of prices of brands which have more than 1% of market share total market turnover of the respective drug. Another method is cost-based pricing which accounts for the cost of active pharmaceutical ingredient, cost of excipients, cost of labour and overheads, cost of packaging and also the cost of duties applicable. The market-based method is currently in practice.(7)

Price regulation for ensuring reasonable maximum retail price (MRP) can be achieved by keeping the trade margin at a rational level along the supply chain. Trade margin is the difference between the price at which the manufacturers sell to trade and the price to patients, i.e., MRP. Therefore, on 27th February, 2019, National Pharmaceutical Pricing Authority (NPPA) had put 42 anti-cancer drugs under 30% trade margin cap.(8) Consequently, manufacturers and hospitals revised MRP of these drugs (all strengths and dosage forms, whether individual or in combination, irrespective of dosage strength, dosage form and /or route of administration), to be effective from 8th March, 2019, based on the Trade Margin (TM) formula. National Pharmaceutical Pricing Authority (NPPA) is

the umbrella body which is responsible for regulating and fixing prices of essential drugs, expanding the national list of essential medicines (NLEM), and regulating the price increase of non-essential medicines which are not under the DPCO.(9)

This ambitious step of government has the potential of putting long-lasting impact on the cancer-care arena of India comprising of not only patients, pharmaceutical industry and price regulators, but insurance providers as well. Assessing the magnitude of this impact is essential for supporting, refining and furthering this attempt not for cancers alone, but other similarly high economic burden diseases as well. Unfortunately, the existing evidence in this regard is unsubstantial, crude, rudimentary and indirect.

Therefore, this study aimed to assess the impact of price regulation of anti- cancer drugs on amounts of claims sought from insurers for treatment of cancers. The practice of using insurance claims data for testing medical resource utilization and treatment costs is well established.(10–12)

There are two possible perspectives in economic evaluations i.e., societal and payers. The societal perspective includes the impact of an intervention on the patients or target population. The payer's perspective focuses on the impact on the provider. Here, the payer's side cost has been analysed which is the government in this scenario.

Material and methods

Mukh Mantri Cancer Rahat Kosh (Chief Minister Cancer Relief Fund), a state health insurance scheme in Punjab, offers an insurance cover of up to Rs. 1.50 Lakhs per patient for cancer treatment in 9 public and 9 empanelled private hospitals of Punjab. The beneficiaries of the scheme include Punjab resident cancer patients except government employees, ESI (Employees State Insurance) employees and their dependents, those with any facility of medical reimbursement or health insurance.(13)

Data source: Secondary data from claims paid to beneficiaries of Mukh Mantri Cancer Rahat Kosh scheme from October 2018 to September 2021.

Pre and post intervention period: The price regulation policy was made legally effective from 8th March 2019. Therefore, the period before March 2019 (October 2018 to March 2019) was considered as pre-intervention period and post intervention period included the data on insurance claims after March 2019 (April 2019 to September 2021).

Data analysis: The data received was reviewed for completeness, coded and recoded in Microsoft Excel. After cleaning data for accuracy, consistency and completeness, 10586 insurance claims were analysed with help of R software.

Statistical analysis: Data has been described as proportions and percentages. Continuous data has been described as mean & standard deviation (SD) or Median & interquartile range (IQR). The change in the amount of insurance claims between pre- and post-intervention period was assessed with the help of statistical tests, namely, Mann-Whitney U and Kruskal Wallis tests of association. Control variables taken were public/private health facility, level of health facility and cancers with/ without usage of newly price regulated drugs. The influence of control variables on the amount of insurance claims was also assessed using generalized linear regression modelling. Difference in difference analysis was performed for medication claim amount in cancers with and without usage of price regulated drugs, with respect to pre- and post-intervention period.

RESULTS

Claims of 10586 beneficiaries were analysed with 79.9% beneficiaries from post-intervention period (Table 1). Majority of the patients were being treated in private healthcare facilities (67.2%) and at medical college level (64.2%).

Table 1: Demographic and treatment profile of study subjects

Gender	**Frequency (%)**
Female	6105 (57.7)
Male	4481 (42.3)
Type of health facility	
Government	3467 (32.8)
Private	7119 (67.2)
Level of health facility	
Specialized Cancer hospital	3069 (29.0)
Medical College & Hospital	6799 (64.2)
Others (Civil or multi-speciality hospitals)	718 (6.8)
Period of observation	
Before price regulation	2119 (20.1)
Post price regulation	8467 (79.9)

Table 2: Distribution of insurance claims stratified by cancer site

Cancer category	Frequency (%)
Gastrointestinal	1514 (14.3)
Endocrinal	704 (6.7)
Hepatobiliary	558 (5.3)
Haematological	1038 (9.8)
Musculoskeletal	271 (2.6)
Neurological	233 (2.2)
Head & Neck	1369 (12.9)
Breast	2388 (22.6)
Gastrointestinal	863 (8.2)
Endocrinal	814 (7.7)
Urinary system	360 (3.4)
Lung	280 (2.6)
Skin	93 (0.9)
Unknown primary	101 (1.0)
Total	10586

Table 3: Mean utilization amount for complete treatment and medications

Cost	Mean	Standard deviation	Median	IQR	Range
Utilization Amount	117692.01	44167.515	150000	75000 - 150000	15 - 150000
Medication Amount	16327.52	28133.936	117	117 – 21718.50	0 - 150000

On an average, Rs. 117692 were claimed out of the maximum cover of Rs. 1.5 lakhs. Utilization amount Claims for medications formed 13.87% of the total amount utilized. (Table 3)

Table 3: Factors influencing medication claim amount

Factors	N (%)	Mean ± SD of Medication Amount	P value	Beta Coefficients	P value
Cancers where price regulated drug is NOT used	5324	13294.09 ± 24704.89	0.000	Reference	0.000
Cancers where price regulated drug is used	5262	19396.70 ± 30923.41		6099.50	
Before price regulation	2119	24745.39 ± 31959.93	0.000	Reference	0.000
Post price regulation	8467	14220.82 ± 26681.76		-8047.74	
Government Hospital	3467	2310.41 ± 12392.47	0.000	Reference	0.000
Private Hospital	7119	23153.95 ± 30983.22		21235.92	
Specialized Cancer hospital	3069	21906.37 ± 30818.99	0.000	Reference	
Medical College & Hospital	6799	14416.78 ± 27168.38		-569.76	0.333
Others (Civil or multi-speciality hospitals)	718	10590.72 ± 20557.55		-14549.95	0.000

Likelihood ratio chi-square – 1847.16; df – 5; Sig. – 0.000

Claims for medications were found to be significantly lower among patients post-price regulation, those attending public hospitals or with cancers where the price regulated drugs were not used. The amount was significantly higher in patients attending specialized cancer hospital and medical colleges. (Table 4)

Table 4: Difference in medication amount in cancers with and without usage of price regulated drugs, for pre- and post-intervention period

	Estimates in INR	P value
Intercept	31010	0.000
Cancers where price regulated drug is NOT used	Reference	0.000
Cancers where price regulated drug is used	9358	
Before price regulation	Reference	0.000
Post price regulation	-9894	
Difference in difference	-1697	0.207

Residual standard error: 27640 on 10582 degrees of freedom; Multiple R-squared: 0.03509 Adjusted R-squared: 0.03482; F-statistic: 128.3; p-value: 0.000

A difference-in-difference analyses (DID) was performed to observe the effect of price regulation on the difference between medication claim amounts for cancers with and without usage of price regulated drugs. The difference decreased post-intervention, although it was not found to be statistically significant. (Table 4, Fig. 1)

The equation of DID is as follows: **Medication amount = Constant + b1*post price regulation + b2*cancer with price regulated drug usage + b3*interaction**

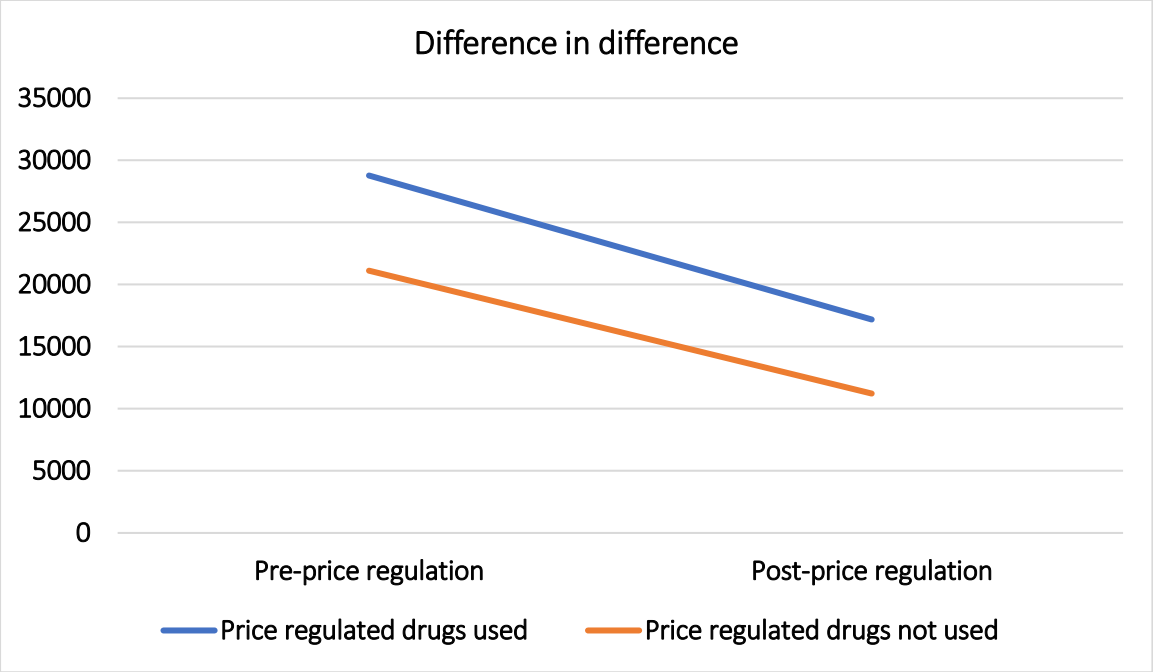

Figure 1: Difference in medication amount in cancers with and without usage of price regulated drugs, for pre- and post-intervention period

Discussion

An analysis of 10,586 insurance claims paid under the Mukh Mantri Cancer Rahat Kosh (Chief Minister Cancer Relief Fund) was performed. The proportion of females was approximately equal to males, which is in line with the general prevalence pattern of cancers.(14)

20% of the records were from pre-price regulation period while 80% data were from introduction of the initiative onwards, as the detailing required for data analysis was present only from a few months earlier to the point of intervention. The possible reasons for this might be the wave of digitalization currently progressing in India and the targeted supervision, monitoring and rejuvenated energy, in terms of man, money as well as material that go hand-in-hand with the entry of any new scheme and reform.

The beneficiaries of the scheme claimed a good fraction (average 78%) of the total available cover, with many tapping into the whole ₹ 150,000/- (USD 1930). This shows the adequacy of the amount of monetary insurance provided to each patient. It is worth mentioning at this point that the same amount of protection is offered to the beneficiaries of Pradhan Mantri Jan Arogya Yojana (commonly known as Ayushman Bharat) as well.

Cost of medications formed approximately 14% of the total claim amounts which is a noteworthy figure. National Pharmaceutical Pricing Authority (NPPA) put a 30% trade margin cap on retail of 42 crucial anti-cancer drugs in February 2019. The drugs selected for price regulation were the ones which posed a remarkably higher burden on insurance claim payers. This is conveyed by the statistically significant difference in medication amount claimed by patients with and without the cancers where price regulated drugs are routinely used.

This measure of NPPA brought about a statistically significant reduction in the amounts of claims filled for medications by the cancer patients. The overall utilization amount was also significantly decreased implying the absence of any compensatory rise of user charges for other services by the private sector.

As shown in Table 3, medication claim was higher in private hospitals as compared to government hospitals. The cost of medications was also significantly more for patients getting treated from specialized cancer hospitals and hospitals with medical colleges. These differences in cost remained significant even after adjusting for cancers with or

without price regulated drug usage and period of observation. Therefore, the difference made by price regulation was not substantial enough to overpower the divide between government and private hospitals, general hospitals and specialized, tertiary care treatment. Although, the difference in medication cost between specialized cancer hospitals and medical colleges which was statistically significant in bivariate analysis became not significant on applying regression model. This implies that price regulation was effective in vanishing the difference in medication associated economic burden between specialized cancer hospitals and medical colleges.

In concordance, the difference in the sums claimed for cancers whither the concerned drugs are and are not employed, declined after price regulation. However, this difference in difference was not found to be statistically significant. In a study from Israel, price regulation as a cost-regulating mechanism was found to have no association with healthcare costs.(15) On the contrary, average daily cost of antibiotics declined rapidly after government price regulation in China.(16) Similarly, Korean price cut program helped in immediate reduction of anti-diabetic medication cost.(12) On the other hand, even extensive price controls could not contain the growth of antihyperlipidemic agents in South Korea.(17)

One possible explanation of this study's results can be reduced marketing of the price-controlled drugs by pharmaceutical companies due to declining profits. These results convey that the government's efforts for reducing the economic burden of cancer-care by keeping the trade margin at a rational level, are definitely yielding momentous outcomes, although further refinement of the endeavour is recommended. Further research can be done on the contribution of individual anti-cancer drugs, out of the regulated 42, on reduction in spending on medications. Studying utilization and sales trends of these drugs can help recognize the ones having little or no impact, to be replaced by others with the potential to bring about significant reduction in the economic burden of cancer treatment.(18)

This study has some limitations. Insurance claims data under Mukh Mantri Cancer Rahat Kosh does not include individual drugs and treatments done for each patient.

Conclusion

Patients claimed a good portion of the total insurance cover under the Cancer relief fund. The choice of drugs for price regulation is appropriate and in line with the target of reducing burden on insurance claim payers. NPPA eliminated the gap in medication claims between specialized cancer hospitals and medical colleges with hospitals by putting trade margin cap on retail of 42 crucial anti-cancer drugs. This step has also brought about a significant difference in the overall cancer medication claims. However, this difference was not significant when the cancers were segregated by use of the price regulated drugs. These results convey that the government's efforts for reducing the economic burden of cancer-care by keeping the trade margin at a rational level, are definitely yielding momentous outcomes, although further refinement of the endeavour is recommended. Also, other factors which have led to the overall decline in medication claims even in cancers without use of price regulated drugs, need to be explored for future policy planning.

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SECTION-E: Data collection tools

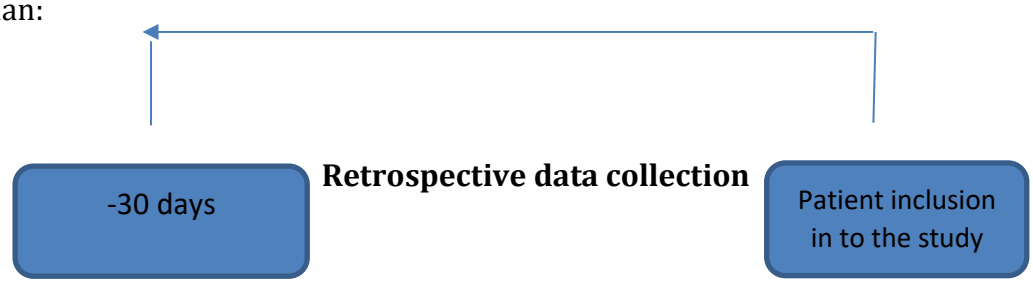
Annexure- I

Case Definitions

A. NEWLY DIAGNOSED CASE:

Newly diagnosed case is defined as a patient who has received a diagnosis of malignancy (histopathology proven) in ≤ 45 days prior to study inclusion and who has not received any cancer directed treatment plan.

Data collection plan:

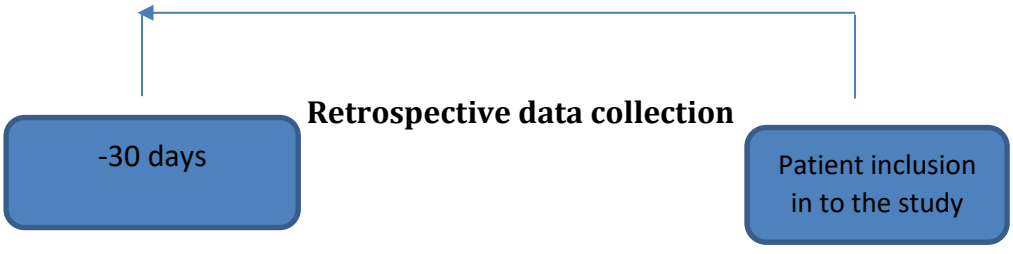


B. ON TREATMENT CASE:

On treatment case is defined as those who are receiving any form of cancer directed treatment at the first time of study inclusion or within prior to the 1 year of study inclusion.

Data collection plan:

i. Retrospective data collection: If the last visit of the patient is ≤30 days, retrospective data on out-of-pocket expenditure incurred for non-hospitalised treatment in the past 1 month or since last visit (whichever is less) will be collected along with assessment of health related quality of life (HRQOL).

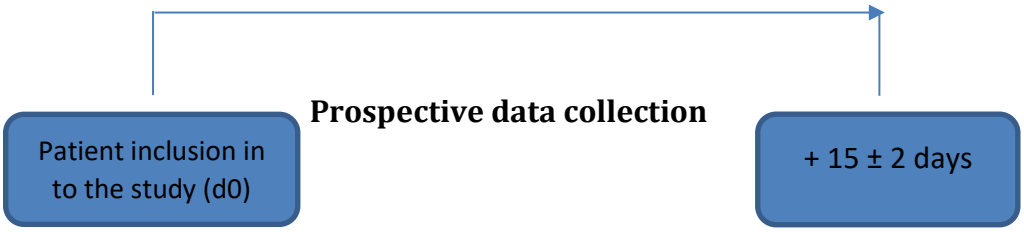


C. <u>FOLLOW-UP CASE:</u>

Follow-up case are those patients who have been diagnosed more than one year prior to study inclusion and are not receiving a planned cancer treatment at the time of study inclusion.

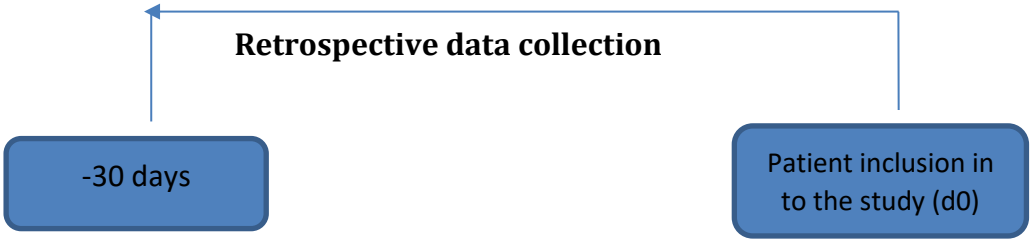
Data collection plan:

1) Prospective data collection: If the last visit of the patient is ≥30 days, prospective data will be collected after + 15 ± 2 days

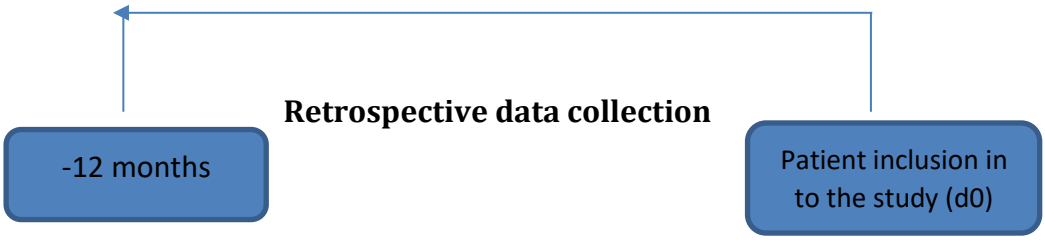


2) Retrospective data collection:

ii. If the last visit of the patient is ≤ 30 days, retrospective data on out-of-pocket expenditure incurred for non-hospitalised treatment in the past 1 month or since the last visit (whichever is less) will be collected along with the assessment of HRQOL.



ii) All the out-of-pocket expenditures incurred for the utilization of inpatient services due to cancer in the past 12 months prior to the inclusion into the study. This is applicable to all the three types of patients-newly diagnosed, on-treatment cases and follow-up cases.



Inpatients/hospitalised cases:

In-patients are defined as those patients who have been **hospitalized overnight** and they will be categorised as per their definition of the type of cases as newly diagnosed, on-treatment and follow-up cases

*** Details of the case types and the elements of data collection:**

S. No.	Case type	Cancer diagnosis	Cancer treatment	Type of data collection	Time period for data collection	Elements of data collection
Non-hospitalized cases						
1	Newly diagnosed	≤ 45 days prior to study inclusion	Should not have happened	Retrospective data	-30 days from study inclusion	1 – 7
2	On-treatment	Any time prior to study inclusion	Yes; last cancer treatment of any type, within 12 months of	a) Prospective data (applicable to patients with prior visit > 30 days)	+ 15 ± 2 days from study inclusion	1 – 7

			study inclusion	b) Retrospective component (applicable to patients with prior visit ≤ 30 days)	-30 days from study inclusion	1 – 7
				c) Retrospective data to capture information related to hospitalization (applicable to all patients on treatment)	-12 months from study inclusion	1 – 8
3	Follow-up treatment	Any time prior to study inclusion	Completed cancer treatment more than 12 months of study inclusion and are visiting hospital for follow-up	a) Prospective data (applicable to patients with prior visit > 30 days)	+ 15 ± 2 days from study inclusion	1 – 7
				b) Retrospective component (applicable to patients with last visit ≤ 30 days)	-30 days from study inclusion	1 – 7
				c) Retrospective data to capture	-12 months from study inclusion	1 – 8

				information related to hospitalization (applicable to all patients on treatment)		
4	Inpatients (categorized into as per their definition of the type of cases as newly diagnosed, on-treatment & follow-up cases)	Patients will be interviewed daily till discharge to collect information on daily expenses incurred on hospitalization including inpatient stay in cancer ward/HDU/ICU/surgical procedure in inpatient setting etc. during last one year. However, rest of the information such as socio-demographic characteristics, consumption expenditure, clinical information and HRQOL will be recorded on the day of recruitment				

Elements of data collection: *Consultation charges-1, Lab investigations/Diagnostics-2, Drug costs-3, Day care charges-4, Radiation charges-5, Transportation charges-6, Health related quality of life-7, Hospitalization charges-8*

Annexure-II

Data collection tool for direct expenditure due to non-hospitalized treatment

SECTION-A: GENERAL INFORMATION

CR No…….. Patient ID: ___ ___ /____ /___ ___ ___ ___

Name of the Department……. Dept. Registration No (if applicable)……..

Name of the clinic (if applicable) …….. Date of Interview ----/----/----

1) Name of Patient ……..…….....
2) Name of care-giver (if patient is not the respondent)……..
3) Contact No. of respondent
   Home_____Mobile-1_____Mobile-2_____
4) Gender :
   a) Male b) Female
5) Age of Patient in year ☐ month ☐
6) Religion :
   a) Hindu b) Muslim c) Sikh
   d) Christian f) Others
7) Area of residence :
   a) Urban b) Slum c) Rural
8) Educational status :
   a) Illiterate b) Primary c) Middle
   d) Matric e) Senior secondary f) Graduation
   g) Post graduation
9) Marital Status :
   a) Unmarried b) Married
   c) Separated/Divorced d) Widow/Widower
10) Financial benefit scheme :
   a) Ayushman Bharat PradhanMantari Jan ArogyaYojana (AB-PMJAY) b) Other centrally sponsored schemes b) State government sponsored c) Government/PSU

as an employer d) Employer supported (other than govt./PSU) health protection e) Voluntary private insurance f) Philanthropists/NGO's/trusts g) Others. Specify……..h) Not covered

11) Total number of family members……..
12) Total number of family members aged >10 years……..
13) Total number of family members aged <10 years……..

SECTION B: OUT OF POCKET EXPENDITURE

A) .How much was the expenditure incurred on non-hospitalized treatment since the last visit (in INR). [Fill this section after 15 days if last visit was more than a month ago		**B). In regard to the above expenditure incurred, what was the source of finance?**	
Expenditure Head	**Amount (in INR)**	**Source**	**Amount (in INR)**
Travelling cost		Salary/Savings	
Medicines		Selling of assets	
Lab tests/ Diagnostics		Borrowed from relatives/friends without interest	
User fees/Hospital charges (File charges)		Borrowed with interest	
Informal payment		Health insurance	
Boarding/Lodging		Any other (specify)	
Food			
Other			
Total			

C. Please provide information related to any hospitalization occurred due to cancer during last one year

Hospital admission	Type of hospital (Public/Private)	Reason of hospitalization	Number of days of admission	Total OOPE for an episode of hospitalization
1				
2				
3				
4				
5				
6				

SECTION C: EQ-5D-5L tool for estimation of health-related quality of life. Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems in bathing or dressing myself ❑

I have slight problems in bathing or dressing myself ❑

I have moderate problems in bathing or dressing myself ❑

I have severe problems in bathing or dressing myself ❑

I am unable to bathe or dress myself ❑

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities) ❑

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

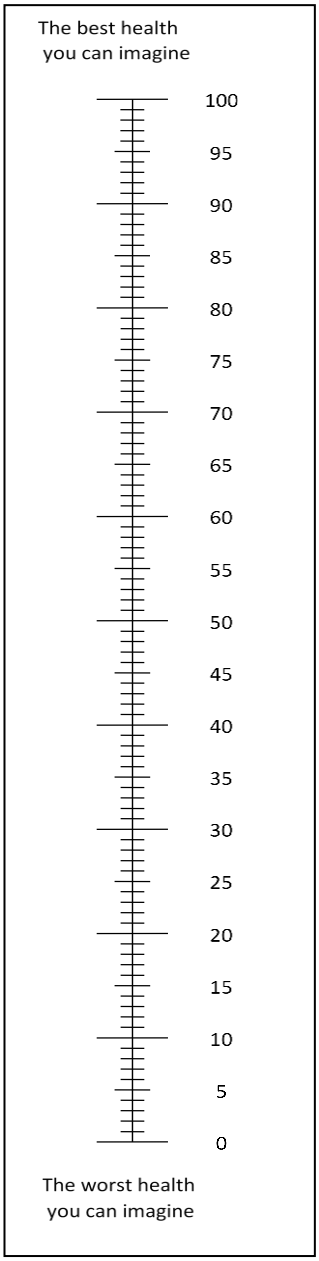
I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑



We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Mark an X on the scale to indicate how your health is TODAY.

SECTION-D

CONSUMPTION EXPENDITURE

How much does your family spend per month on following items?	Expense		
	7 days	30 days	365 days
i. Food purchased/home production: ration (Cereals, pulses, edible oil, bread etc.), Fruits and vegetables, Milk, Milk products, Beverages etc.			
ii. Education (Books, newspaper, fees)			
iii. Health			
iv. Bills (Electricity, telephone, water, Equated monthly installment –EMI etc.)			
v. Conveyance, fuel			
vi. Rents			
vii. Clothing, Footwear, bedding, curtains etc.			
viii. Entertainment (Cable, cinema, sports, recreation & hobbies)			
ix. Personal effects (Watch, mobile phone, spectacles, toiletries, jewelry)			
x. Consumer services (Domestic help, cook, sweeper, barber, tailor, priest, beautician)			
xi. Pan, Tobacco, alcohol or any other intoxicants			
xii. Miscellaneous (household appliances, furniture, crockery, animals, or any family function)			

SECTION E: CLINICAL PROFILE OF CANCER PATIENTS

	Patient ID:	__ __ /___ /__ __ __ __
	Date of Diagnosis	
	Start Date of treatment	

1.	Basis of Diagnosis (multiple select)	○ Clinical ○ Radiology (X-ray, USG, MRI,CT, PET) ○ Endoscopy ○ Histology ○ Cytology (FNAC/fluid cytology) ○ Peripheral blood immunophenotyping ○ Bone Marrow examination ○ Others, specify…… ○ Unknown/No information
2.	Primary Site	
3.	TNM Classification	
4.	Stage (single select)	○ In situ ○ Localization (T1) ○ Direct Extension (T2+) ○ Regional lymph node involvement (N+) ○ Direct extension with regional lymph node involvement(T+N+) ○ Distant metastasis(M+) ○ Unknown/No information ○ Not applicable
5.	Site specific staging	
6.	Histology	
7.	Final Diagnosis ICD-O 3 Classification	
8.	Final Diagnosis ICD-10 Classification	

9.	Treatment obtained since last visit (multiple select)	o Surgery o Radiotherapy o Brachytherapy o Chemotherapy o Chemotherapy+ Radiation o Surgery +Radiotherapy o Surgery +Chemotherapy o Surgery + Chemotherapy +Radiotherapy o Chemo-radiotherapy o Palliative Care o Unknown/No information o Others, specify……..
10.	Completion of Treatment (single Select)	o Complete o Ongoing o Not started yet o Refused further treatment o Unknown/No information
11.	Adverse effect of treatment (select multiple options)	o Nausea o Vomiting o Diarrhoea o Mucositis o Hair loss o Fatigue o Weight loss o Anemia o Neutropenia o Febrile Neutropenia o Infections, not related to neutropenia o Deep Vein Thrombosis o Cardiac Complication

		○ Second malignancy ○ Any other, please specify
12.	Response to treatment	○ Complete response ○ Very good partial response (applicable only for Multiple Myeloma) ○ Ongoing response ○ Partial response ○ Stable disease ○ Progressive disease ○ Minimal residual disease status negative (optional)
13.	Line of treatment	○ First line ○ Second line ○ Third line ○ Fourth line ○ If any other, specify……
14.	If on Chemotherapy, then ***current*** regimen/medication	

Reason of hospitalization: Chemotherapy (1) /radiotherapy (2) /adverse event(3) /surgery (4)/others 5) , specify……

Annexure-III

Data Collection Tool for direct expenditure due to hospitalization

SECTION-A: GENERAL INFORMATION

CR No…… Patient ID: ___ ___ /____ /___ ___ ___ ___

Name of the Dept …….. Dept. Registration No (if applicable)……..

Name of the Clinic (if applicable) …… Date of Interview ----/----/----

1) Name of the Patient ……
2) Name of the care-giver (if patient is not the respondent)……..
3) Contact No. of respondent
   Home_____Mobile-1_____Mobile-2_____
4) Gender:
   a) Male b) Female
5) Age of Patient in year ☐ months ☐
6) Religion:
   a) Hindu b) Muslim c) Sikh
   d) Christian e) Others
7) Area of residence:
   a) Urban b) Slum c) Rural
8) Educational status:
   a) Illiterate b) Primary c) Middle
   d) Matric e) Senior secondary f) Graduation
   g) Post graduation
9) Marital Status:
   a) Unmarried b) Married
   c) Separated/Divorced d) Widow/Widower
10) Financial benefit scheme*: ……
11) Total number of family members……..
12) Total number of family members aged >10 years……..
13) Total number of family members aged <10 years……..

** 1-Ayushman Bharat Pradhan Mantari Jan ArogyaYojana (AB-PMJAY), 2-Other centrally sponsored schemes, 3- State government sponsored, 4- Government/PSU as an employer, 5-Employer supported (other than govt./PSU) health protection, 6-Voluntary private insurance, 7-Philanthropists/NGO's/trusts, 8-Others, specify in Q.10, 9-Not covered*

SECTION B: OUT OF POCKET EXPENDITURE

I. In regard to the expenditure incurred on hospitalization (See II), what was the source of finance*?

Source	**Amount in INR**
Salary/Savings	
Selling of assets	
Borrowed from relatives/friends without interest	
Borrowed with interest	
Health insurance	
Any other (specify)	

Fill this section after filling Part II on next page

II. How much you spend on hospitalized care during last 24 hours (Day-wise)*

Expenditure Head	**Day**								
	1	2	3	4	5	6	7	8	9
Travelling cost									
Medicines									
Lab tests/ Diagnostics									
Procedure/Surgery									
User fees/Bed charges									
Informal payment									
Boarding/Lodging/Food									
Others									
Total									
Expenditure Head	10	11	12	13	14	15	16	17	18
Travelling cost									
Medicines									
Lab tests/ Diagnostics									
Procedure/Surgery									
User fees/Bed charges									
Informal payment									
Boarding/Lodging/Food									

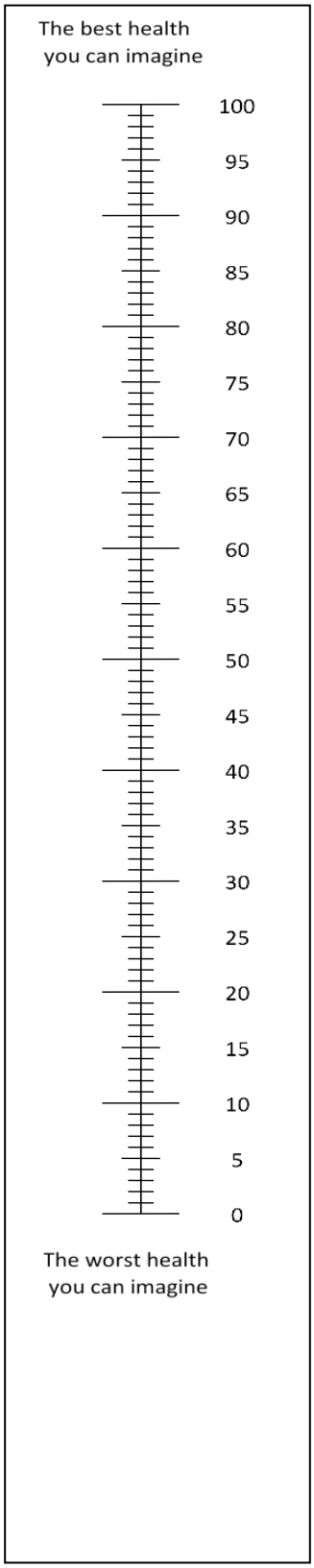
Others									
Total									
Expenditure Head	19	20	21	22	23	24	25	26	27
Travelling cost									
Medicines									
Lab tests/ Diagnostics									
Procedure/Surgery									
User fees/Bed charges									
Informal payment									
Boarding/Lodging/Food									
Others									
Total									

**Fill this section for all days of admission till the patient is discharged*

SECTION C: EQ-5D-5L TOOL FOR ESTIMATION OF HEALTH-RELATED QUALITY OF LIFE

Under each heading, please tick the ONE box that best describes your health TODAY

We would like to know how good or bad your health is TODAY.
This scale is numbered from 0 to 100.
100 means the best health you can imagine.
0 means the worst health you can imagine.
Mark an X on the scale to indicate how your health is TODAY.



MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems in bathing or dressing myself ❑

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I have moderate problems in bathing or dressing myself ❑

I have severe problems in bathing or dressing myself ❑

I am unable to bathe or dress myself ❑

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities) ❑

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

SECTION-D CONSUMPTION EXPENDITURE

How much does your family spend on following items?		Expense		
		7 days	30 days	365 days
xiii.	Food purchased/home production: ration (Cereals, pulses, edible oil, bread etc.), Fruits and vegetables, Milk, Milk products, Beverages etc.			
xiv.	Education (Books, newspaper, fees)			
xv.	Health			
xvi.	Bills (Electricity, telephone, water, EMI etc.)			
xvii.	Conveyance, fuel			
xviii.	Rents			
xix.	Entertainment (Cable, cinema, sports, recreation & hobbies)			
xx.	Consumer services (Domestic help, cook, sweeper, barber, tailor, priest, beautician)			
xxi.	Pan, Tobacco, alcohol or any other intoxicants			
xxii.	Clothing, Footwear, bedding, curtains etc.			
xxiii.	Personal items (Watch, mobile phone, spectacles, toiletries, jewelry)			
xxiv.	Miscellaneous (household appliances, furniture, crockery, animals, or any family function)			

SECTION E: CLINICAL PROFILE OF CANCER PATIENTS

	Patient ID:	___ ___ /___ /__ __ __ __
	Date of Diagnosis	
	Start Date of treatment	
1.	Basis of Diagnosis (multiple select)	o Clinical o Radiology (X-ray, USG, MRI,CT, PET) o Endoscopy o Histology o Cytology (FNAC/fluid cytology) o Peripheral blood immunophenotyping o Bone Marrow examination o Others, specify…… o Unknown/No information
2.	Primary Site	
3.	TNM Classification	
4.	Stage(single select)	o In situ o Localization (T1) o Direct Extension (T2+) o Regional lymph node involvement (N+) o Direct extension with regional lymph node involvement(T+N+) o Distant metastasis(M+) o Unknown/No information o Not applicable
5.	Site specific staging	
6.	Histology	
7.	Final Diagnosis ICD-O 3 Classification	
8.	Final Diagnosis ICD-10 Classification	

9.	Treatment obtained since last visit (multiple select)	○ Surgery ○ Radiotherapy ○ Brachytherapy ○ Chemotherapy ○ Chemotherapy+ Radiotherapy ○ Surgery +Radiotherapy ○ Surgery +Chemotherapy ○ Surgery + Chemotherapy +Radio ○ Chemo-radiotherapy ○ Palliative Care ○ Unknown/No information ○ Others, specify……..
10.	Completion of Treatment (single Select)	○ Complete ○ Ongoing ○ Not started yet ○ Refused further treatment ○ Unknown/No information
11.	Adverse effect of treatment (select multiple options)	○ Nausea ○ Vomiting ○ Diarrhoea ○ Mucositis ○ Hair loss ○ Fatigue ○ Weight loss ○ Anemia ○ Neutropenia ○ Febrile Neutropenia ○ Infections, not related to neutropenia ○ Deep Vein Thrombosis ○ Cardiac Complication

		○ Second malignancy ○ If any other, specify……..
12.	Response to treatment	○ Complete response ○ Very good partial response ○ Ongoing response ○ Partial response ○ Stable disease ○ Progressive disease ○ Minimal residual disease status negative (optional)
13.	Line of treatment	○ First line ○ Second line ○ Third line ○ Fourth line ○ If any other, specify……..
14.	If on Chemotherapy, then ***current*** regimen/medication	

Annexure-IV

Data Collection Tool for Indirect expenditure due to treatment

Patient Details:

1. What would you have being doing otherwise if you were not taking treatment? (Multiple response allowed)

   Time spent (in hours) on:

   1 day 1 week 1 month

Household activities	____	____	____
Childcare	____	____	____
Professional work	____	____	____
Voluntary work	____	____	____
Leisure activities	____	____	____
Attending School/University	____	____	____
Seeking work	____	____	____
Social work	____	____	____
Physical workout	____	____	____
Other (specify)	____	____	____

2. Did other people take over and perform your usual household tasks during your hospital stay? If yes, fill the appropriate option, there can be more than one answer

	Yes/No/NA	Paid/Unpaid	No. of hours
Household activities	____	____	____
Childcare	____	____	____
Professional work	____	____	____
Voluntary work	____	____	____
Leisure activities	____	____	____
Attending School/University	____	____	____
Seeking work	____	____	____
Social work	____	____	____
Physical workout	____	____	____
Other (specify)	____	____	____

Caregivers:

	Caregiver 1	Caregiver 2	Caregiver 3
Relation with patient			
Address			
Contact No.			
No. of visits (per day)			

Total duration of Hospital stay (In hours)			
Employment status (Yes/No)			
Nature of employment (Give codes as mentioned in the end of tool)			
Monthly Gross Income of Caregiver (In Rs)			
Time spent daily (hours) on:			
Household activities			
Hours forgone due to care-giving			
Alternative			
No. of hours (alternative)			
Payment to alternative paid worker (In Rs)			
Childcare			
Hours forgone due to care-giving			
Alternative			
No. of hours (alternative)			
Payment to alternative paid worker (In Rs)			
Professional work			
Hours forgone due to care-giving			
Alternative			
No. of hours (alternative)			
Payment to alternative paid worker (In Rs)			
Voluntary work			
Hours forgone due to care-giving			
Alternative			
No. of hours (alternative)			

Payment to alternative paid worker (In Rs)			
Leisure activities			
Hours forgone due to care-giving			
Attending School/university			
Hours forgone due to care-giving			
Seeking work			
Hours forgone due to care-giving			
Social work			
Hours forgone due to care-giving			
Alternative			
No. of hours (alternative)			
Physical workout			
Hours forgone due to care-giving			
Other (specify)			
Hours forgone due to care-giving			
Alternative			
No. of hours (alternative)			

**Alternative Worker;* Yes (Paid) =1, Yes (Unpaid) =2, No=3, Not Applicable (NA) =4

Employment Status; Cultivator=1, Agricultural wage labourer=2, Non-agricultural wage labourer=3, Own account worker=4, Employer=5, Unpaid family worker=6, Regular salaried/Wage employee=7,Unemployed=8, Rentier/Pensioner/Other remittance recipient=9, Not able to work due to disability=10, Too old to work=11, Others=12