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ASSESSMENT OF ECONOMIC IMPACT AND DEVELOPMENT OF A PREDICTOR MODEL FOR TOTAL COST DUE TO ADVERSE DRUG REACTIONS IN CANCER PATIENTS ON CHEMOTHERAPY

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ABSTRACT

The aim of our study was to assess the economic impact of adverse drug reactions (ADRs) on patients due to cancer chemotherapy and develop a predictor model to predict the total cost due to ADRs. Total cost was calculated by taking into account both the direct and indirect cost incurred by the patient due to ADRs. Predictor model was developed to predict the total cost due to ADRs using multivariate regression analysis. A total of 387 patients participated in the study. Mean age of patients was 50.85 ± 11.82 years (95% CI, 49.66-52.03). Out of 387 patients, 51 were admitted to the hospital due to ADR/ADRs. The mean increase in length of stay of patients in hospital due to ADRs was found to be 12.5 days. The total cost due to ADRs in cancer patients on chemotherapy in our study was found to be INR 39,72,737 (≈ 62,568 US$) which included direct and indirect cost of INR 33,25,434 (≈ 52,373 US$) and INR 6,47,303 (≈10,195 US$) respectively. A significant difference was found in the total cost due to ADRs based on the onset of the reaction, severity of ADRs, length of stay of patients in hospital due to ADRs and quality of life scores. In the predictor model, the Coefficient of determination R-square (r^2) was found to be 0.3684.The $F_{(5, 381)} = 44.45$, $p < 0.001$ indicating the overall significance of the regression model. In conclusion, the total cost due to ADRs in cancer patients receiving chemotherapy is huge.

KEYWORDS: Adverse drug reaction, Tertiary care hospital, Direct and Indirect cost, Multivariate regression, Predictor model

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INTRODUCTION

Adverse Drug Reaction (ADR) is defined as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function"[1] .The safe use of medicine is an important issue and the health care professionals, the organization, pharmacists and patients will get benefited by the program which monitors and reports ongoing ADR.[2] ADRs have been considered as an important cause of significant morbidity and mortality and contributes to substantial increase in expense to the patients[3,4]. Cancer is one of the leading causes of morbidity and mortality worldwide. Cancer prevalence in India is estimated to be around 2.0 to 2.5 million, with over 7-8 lakh new cases detected every year and 4-5 lakh cancer deaths per year[5] .The financial burden due to cancer has become an important issue of concern for the purchasers and payers. In 1990, the overall annual costs of cancer diagnosis and treatment in USA was nearly US$ 100 billion as estimated by the National Cancer Institute (NCI). Out of this US$ 27 billion was the direct medical cost, US$ 10 billion was the morbidity cost, and US$ 59 billion was the mortality cost. Recent reports suggest that in USA, around 10% of total health care expenditures go for the direct medical cost of cancer and it amounts US$ 100 billion each year[6] . ADRs are the basic reason for hospitalization and prompts huge expenses to society. As most ADRs never come to clinical attention, the expenses of hospitalization seems as a part of the total costs[7] . ADR related morbidity and mortality have been estimated at US$ 30 billion to US$ 130 billion annually[8] . Costs associated with ADRs are very high as reported by the recent studies. In USA, direct hospital costs have an additional burden of US$ 1.56 to US$ 4 billion per year due to ADRs. This estimate excludes admissions due to ADRs, malpractice and the litigation costs or costs of injuries to patients[9, 10] . The total expense brought about in dealing with all the reported ADRs in a hospital in South India was found to be Rs.76, 564 (US$ 1595) with an average expense of Rs.690 (US$ 15) per ADR[11] . With this background, the aim of our study was to assess the economic impact of ADRs on patients due to cancer chemotherapy and develop a predictor model to predict the total cost due to ADRs.

MATERIALS AND METHODS

The study was carried out for a duration of 3 years (October 2011 to September 2014) in the Department of Radiotherapy and Oncology, Kasturba hospital, Manipal which is a tertiary care multidisciplinary teaching hospital which provides both inpatient and outpatient healthcare services in all specialties. It included 387 patients who developed ADRs due to cancer chemotherapy. Approval to conduct the study was obtained from Institutional Ethics Committee (IEC 169/2011). Patients willing to participate were explained about the study and an informed consent was obtained from them.

Inclusion criteria

- Patients of either sex of any age (except the paediatric age group) who developed ADR/ADRs with chemotherapeutic agents
- Only newly diagnosed cancer patients (fresh cases) who received chemotherapy were selected based on convenience to collect the background data, follow up the patients for any expenses related to ADR, administer the QoL questionnaire and collect any other required information in fresh cases as compared to the established cases (already diagnosed with cancer)

Exclusion criteria

- Patients who developed an ADR due to intentional or accidental poisoning
- ADR to fresh blood/ blood products
- ADR due to overdose
- Patients with drug abuse and intoxication

Hospital based intensive monitoring was carried out in the wards of cancer patients. All patients admitted in the wards were prospectively followed during hospital stay from the day of admission until the day of discharge. Investigator went through the patient records including case sheets, laboratory reports and prescription charts to monitor the ADRs and the details were documented in the patient profile form. Baseline information comprising of demographic data like age, gender of the patient, disease and treatment variables were collected from the patient's record. The direct cost of ADRs that required additional medications, treatment or laboratory monitoring/tests was estimated to determine the expenses incurred by the patient during hospitalization. This included the costs of drugs, syringes, administration, extra nursing and medical care, additional hospital stay and any other additional invasive or noninvasive procedures including laboratory tests. Data pertaining to the cost of extra medications and administration devices was collected from the patient, patient case sheets, nurses and pharmacy, as appropriate. Length of stay of the patient in the hospital due to ADRs was calculated using the data collected from the patient records and interaction with the nurses in the wards of cancer hospital. ADRs that required simple cessation of the suspected drug(s), the cost for treatment was not considered. The indirect cost which included loss of workdays (loss of income for outpatient visit due to ADR/due to hospitalization of the patient) travel, stay, food and other expenses for the patient and their family members because of ADR was calculated by interviewing them. To develop a predictor model for the total cost due to ADRs, various independent variables used in this study included the age group and gender of the patient, site of cancer, onset of reaction, severity and preventability of ADRs, drugs causing ADRs, comorbid conditions, polypharmacy, age as a predisposing factor, organ system (blood, Cardiovascular System (CVS) Central Nervous System (CNS), Peripheral Nervous System (PNS), gastrointestinal, musculoskeletal, renal,

respiratory, sensory, skin and appendages) affected due to ADRs, length of stay of patient in hospital due to ADRs and Quality of Life Scores (QOLS).

Statistical analysis

Data was analyzed using descriptive statistics and results were expressed in percentage, mean and standard deviation (SD). Mean with 95% confidence interval (CI) was used to summarize the age of patients. Mann-Whitney U test was done to find the significance of total cost due to ADRs with all the independent variables in the study. After scoring the data, predictor model was developed to predict the total cost due to ADRs using multivariate regression analysis. Values of $p < 0.05$ were considered to be statistically significant. All analyses were performed using SPSS version 15.

RESULTS

A total number of 387 patients who developed 582 ADRs participated in the study with a mean age 50.85 ± 11.82 years (95% CI, 49.66-52.03).Table 1 shows the demographic characteristics of the patients and type of cancer

Table 1
Demographic characteristics of patients and type of cancer, n = 387

Characteristics	Number of Patients, n (%)
Gender	
Male	171 (44.19)
Female	216 (55.81)
Age group (years)	
21-40	74 (19.12)
41-60	230 (59.43)
61-80	81 (20.93)
>80	2 (0.52)
Type of cancer	
Gastrointestinal	93 (24.0)
Genitourinary	50 (12.90)
Breast	96 (24.80)
Lung	69 (17.80)
Head & Neck	42 (10.90)
Thyroid	9 (2.30)
Lymphoma and leukaemia	14 (3.60)
Myeloma	6 (1.60)
Bone	4 (1.0)
Brain	4 (1.0)

The patients who participated in this study were on various drugs/drug combinations. Most commonly used individual drugs were cisplatin, capecitabine and paclitaxel. Of the drug combinations, paclitaxel + carboplatin and doxorubicin + cyclophosphamide were most frequently used. Most of the reported ADRs (524) had latent onset (> 2 days) followed by 41 which were sub-acute (between 1-24 hours) and only 17 had an acute onset (within 60 minutes) of reaction. Severity of ADRs were assessed using Hartwig scale[12] . In our study, moderate (level 3) type reaction was the most observed followed by mild (level 1) and mild (level 2). Moderate (level 4a, 4b) and severe (level 5) were less observed and there were no severe (level 6) ADRs. 23 ADRs (severe level 7) lead to the death of the patient. Based on modified Schumock and Thornton [13], it was found that most of the ADRs were not preventable (470), some were probably preventable (107) and very few were definitely preventable (5). It was found that 126 patients were on polypharmacy, 101 had comorbid condition and 83 patients were above 60 years of age. In some patients, more than one predisposing factor was observed. Patients on cisplatin reported the highest number of ADRs followed by capecitabine and paclitaxel. Of the drug combinations, patients on paclitaxel + carboplatin showed highest number of ADRs followed by doxorubicin + cyclophosphamide. Commonly affected organ systems due to ADRs were blood, skin and appendages, gastrointestinal system, CNS and PNS.Based on the QOLS, our study showed that 16.54% had poor global health status/QOL, 72.35% had average and 11.11% had a high global health status/QOL. Table 2 shows the length of stay of patients in hospital due to adverse drug reactions. Out of 387 patients, 51 were admitted to the hospital due to ADR/ADRs. The mean increase in length of stay of patients in hospital due to ADRs was found to be 12.5 days.

Table 2
Length of stay of patients in hospital due to ADRs in cancer patients on chemotherapy

Length of stay in hospital (number of days)	Frequency (n= 51)
1-10	25
11-20	9
21-30	9
31-40	2
41-50	2
51-60	1
61-70	2
>70	1

Table 3 shows the amount of money spent by the patient due to ADRs in cancer patients on chemotherapy. The total cost due to ADRs in cancer patients on chemotherapy in our study was found to be INR 39,72,737 (≈ 62,568 US$) which included direct and indirect cost of INR 33,25,434 (≈ 52,373 US$) and INR 6,47,303 (≈10,195 US$) respectively.

Table 3
Direct cost, indirect cost and total cost due to ADRs in cancer patients on chemotherapy

Direct cost	Amount in Rupees	Indirect cost	Amount in Rupees
Professional charges	5,57,905.48	Loss of work days	3,43,053.00
Nursing charges	3,15,361.74	Travel, stay and other expenses for the family	3,04,250.00
Administrative charges	24,046.00		
Bed charges/ Hospital stay	84,420.00		
Laboratory investigations	9,04,432.91		
Drugs and surgical supply	14,39,267.39		
Total cost (in Rupees)	**33,25,433.52**		**6,47,303.00**

(n = 387, number of ADRs = 582)

1US$ = 63.49 INR In our study, significant differences were found in the total cost due to ADRs based on the onset of reaction, severity of ADRs, length of stay of patients in hospital due to ADRs and QOLS.

Figure 1
Box plot showing the relationship between onset of reaction and the total cost (in INR) due to ADRs

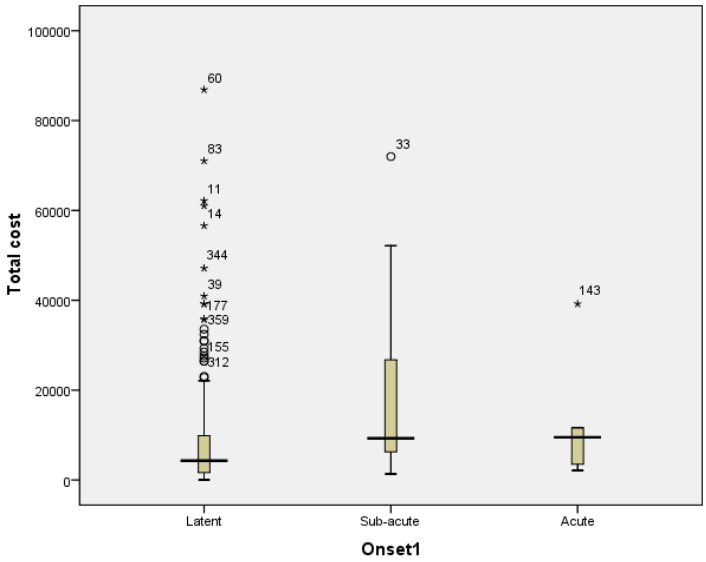


Figure 1 depicts the median and IQR of total cost due to ADRs according to the onset of reaction. There is a variation in the median score between acute, sub-acute and latent onset of reactions thus showing a significant difference in the median total cost across different onset of reactions (p = 0.001).

Onset of reaction	Median	Interquartile range (IQR)
Latent	4305.23	(1648, 9868)
Sub-acute	9261.63	(6258. 27981)
Acute	9502.52	(2825, 25394)

Figure 2
Box plot showing the relationship between severity of ADRs and the total cost due to ADRs

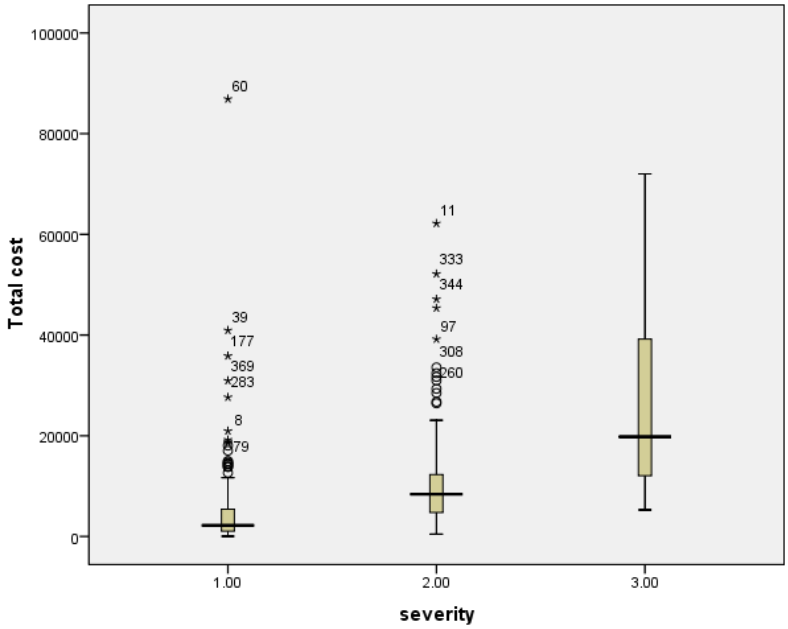
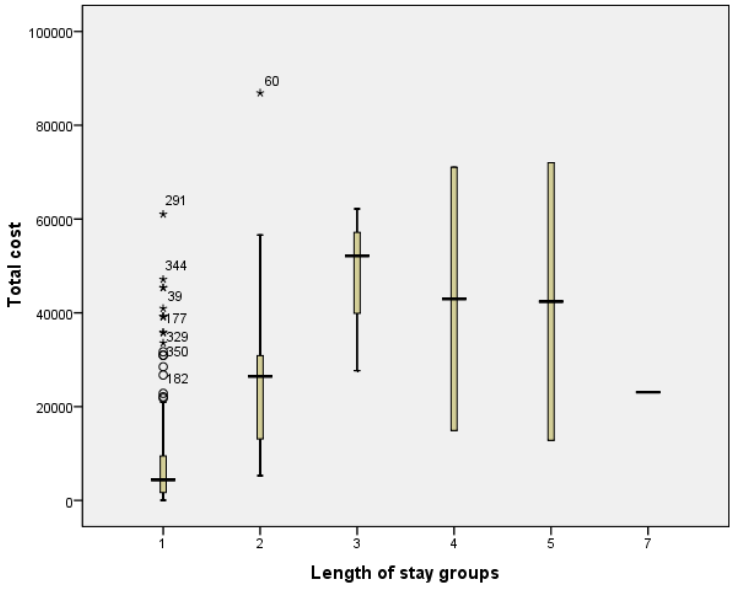


Figure 2 depicts the median and IQR of total cost due to ADRs according to the severity of ADRs. The median score between mild (1), moderate (2) and severe (3) ADRs are significantly different. It is observed that there is significant difference in the median total cost between mild and moderate, mild and severe as well as moderate and severe (p = 0.001). Hence, there is a linear relationship between total cost and severity of ADRs.

Severity of ADRs	Median	Interquartile range (IQR)
Mild (1)	2195	(1050, 5475)
Moderate (2)	8392.38	(4725, 12360)
Severe (3)	19810.88	(11583, 39205)

Figure 3
Box plot showing the relationship between length of stay in hospital and the total cost due to ADRs



1 – 0 to 15 days
2 – 16 to 30 days
3 – 31 to 45 days
4 – 46 to 60 days
5 – 61 to 75 days
6 – 76 to 90 days
7 – 91 to 105 days

Figure 3 depicts the median and IQR of total cost due to ADRs according to length of stay of the patients in hospital. It is observed that there is significant difference in the median total cost across the group of patients based on length of stay of the patients in hospital (p = 0.001).

Length of stay in hospital (in days)	Median	Interquartile range (IQR)
1	4397.52	(1648, 9502)
2	26453.05	(12703, 31662)
3	52147.92	(27647, 62182)
4	42974.87	(14910, 71039)
5	42407.08	(12819, 71994)
7	23060.13	(23060, 23060)

Figure 4
Box plot showing the relationship between QOLS and the total cost due to ADRs

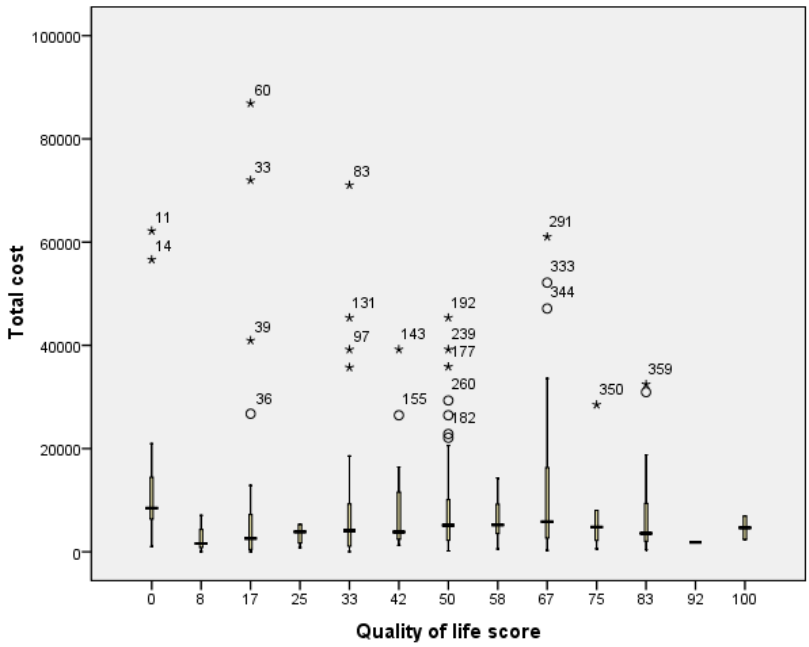


Figure 4 depicts the median and IQR of total cost due to ADRs according to QOLS. It is observed that there is significant difference in the median total cost between the patients with different QOLS (p = 0.030).

Quality of life scores	Median	Interquartile range (IQR)
0	8473.6	(5792, 14549)
8.33	1605	(50, 7045)
16.67	2582.5	(435, 7678)
25	3881.11	(1262, 5329)
33.33	4114.1	(1088, 9486)
41.87	3832.38	(2382, 12414)
50	5136.94	(2227, 10093)
58.33	5227.9	(3012, 9912)
66.67	5833.04	(2551, 16564)
75	4795.79	(1796, 13151)
83.33	3570.38	(2013, 9620)
91.67	1847.5	(1847, 1847)
100	4648.74	(2381, 6916)

Predictor model for total cost due to adverse drug reactions

Table 4
Total cost predictor model

```
Call:
lm(formula = log totalcost ~ CVS + Lengthofstay + QOLS + severe_1,
    data = TempDF)

Residuals:
    Min      1Q  Median      3Q     Max
-3.5777 -0.5918  0.0536  0.6520  3.3956
Coefficients:
                    Estimate Std. Error t value Pr(>|t|)
(Intercept)         7.124718   0.150480  47.347  < 2e-16 ***
CVS[T.yes]         -1.523447   0.561354  -2.714  0.00695 **
Lengthofstay        0.030436   0.006721   4.529 7.95e-06 ***
QOLS                0.010951   0.002654   4.126 4.53e-05 ***
severe_1[T.moderate]  1.255975   0.119144  10.542  < 2e-16 ***
severe_1[T.severe]    1.835507   0.274586   6.685 8.25e-11 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 1.116 on 381 degrees of freedom
Multiple R-squared:  0.3684,    Adjusted R-squared:  0.3601
F-statistic: 44.45 on 5 and 381 DF,  p-value: < 2.2e-16
```

Model is as follows

$$Log(total\ cost) = 7.12 - (1.5 \times CVS) + (0.03 \times length\ of\ stay) + (0.011 \times QOLS) + (1.3 \times moderate\ severity) + (1.84 \times severe\ severity)$$

The Coefficient of determination R-square (r^2) was found to be 0.3684 indicating that 36.84% of the variation in the "total cost" is explained by the independent variables (ADRs related to CVS, length of stay of patient in hospital due to ADRs, QOLS and severity of ADRs) included in the model.
The $F_{(5, 381)} = 44.45$, $p < 0.001$ indicating the overall significance of the regression model.

DISCUSSION

In our study, the total cost due to ADRs was found to be significantly different based on the severity of ADRs, i.e. mild, moderate and severe. The median total cost for mild, moderate and severe ADRs was found to be Rs.2195, Rs.8392 and Rs.19811 respectively thus showing a linear relation between total cost and severity of ADRs. Furthermore, a study in Canada reported that for patients with mild ADRs the cost was US$ 235 per person and the average cost for those with severe ADRs was US$ 691. Patients admitted to hospital with severe ADRs cost an average US$ 7529 per person during their hospital stay [14] . In the present study, out of 387 patients who reported a total of 582 ADRs, 51 (13.18%) were admitted to the hospital due to ADR/ADRs which is similar to a study conducted in Spain where 43 (14.78%) toxicity episodes caused hospital admission out of 291 patients who developed 491 ADRs[15] . The mean increase in length of stay of patients in hospital due to ADRs in our study was found to be 12.5 days. A study at Brigham and Women's Hospital and Massachusetts General Hospital found that on an average ADEs increased the length of stay by as much as 4.6 days [10] . Another study reported that ADRs lead to an average increase in length of stay in hospital by 3.15 days[16] . A study by Patel et al reported the median hospital stay of patients with ADRs to be 5 days[17] . The total cost due to ADRs in cancer patients on chemotherapy in our study was found to be INR 39, 72,737 (≈ 62,568 US$) which included direct and indirect cost of INR 33, 25,434 (≈ 52,373 US$) and INR 6, 47,303 (≈10,195 US$) respectively. This is analogous to studies in India and New Jersey where the total hospitalization cost due to ADRs was found to be INR 15,67,397 (US$ 36,451) for 317 ADRs and 22,775 US$ for 131 patients respectively[18, 19] . Another study conducted in inpatient setting found the cost to be 2,262 US$ per ADR[9]. Predictor model for total cost due to ADRs was developed with the collected data. In this model, the coefficient of determination R-square (r^2) was found to be 0.3684 indicating that 36.84% of the variation in the "total cost" is explained by the independent variables included in the model. The model included several independent variables as predictors which include ADRs affecting CVS, length of stay of patients in the hospital due to ADRs, QOLS, moderate and severe level of severity of ADRs. Among them, severe level of severity alone explained 18.4% of variation in the total cost. The $F_{(5, 381)}$ was found to be 44.45, $p < 0.001$ indicating the overall significance of the regression model. One of the limitation of the study is that the predictor model developed were not validated due to unavailability of the adequate sample. Therefore, one of the major challenge in this area of research is focusing on developing the predictor models which require large sample size. Since time is a constraint, long-term research is required to draw authentic and reliable conclusions.

CONCLUSION

The present study showed that the total cost due to ADRs in cancer patients receiving chemotherapy is huge. Thus, measures need to be put into place to reduce the economic burden on the patient due to ADRs which can also improve the QOL of the patients. The predictor model for total cost due to ADRs explained 36.84% of variation in the total cost. The model included several independent variables as predictors amongst which severe level of severity alone explained 18.4% of variation in the total cost.

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