



# **Analysis of the Adverse Drug Reactions and Associated Cost Burden on the Patients in a South Indian Teaching Hospital**

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## **Authors' contributions**

*This work was carried out in collaboration among all authors. Authors MV and PDR have contributed to the conception, design and data collection. Authors PDR and SVS analyzed the data. The manuscript was written by author MV. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Objectives:** To analyse the adverse drug reactions (ADR) and related economic burden on the health care system and health seekers

**Methods:** A prospective observational study was conducted in a South Indian tertiary care teaching hospital from July 2016 – December 2018. ADRs were analyzed for their causality, severity, predictability, and preventability through standard scales and were reported to the Pharmacovigilance Program of India (PvPI) through a specified updated Indian Pharmacopoeia Commission (IPC) suspected ADR reporting form. The total cost burden including both direct and indirect were calculated by assessing the ADR management including the clinical investigations done. The indirect cost was calculated based on the per capita analysis by using the Gross Domestic Product (GDP) of our study area.

**Results:** Among 458 ADRs, 81.88% were reported in Adult population with an almost same incidence in both the genders, majority were probable (41.70%) and Antibiotics were most commonly involved (16.18%). Around 60% ADRs were treated with at least one drug, 27% ADRs required either hospitalization or increased length of Hospitalization. A total of 989164.5 Indian Rupee (INR) was spent by the hospital and the patients for the management of ADRs, of which 79% was direct cost and 21% was indirect cost.

**Conclusion:** In this hospital, 26.88% of patients were identified with ADRs that were associated with high direct costs, due to hospitalization/extended hospitalizations, which resulted in an extra economic burden to the healthcare sector and seekers for the management of ADRs.

*Keywords: Pharmacovigilance; cost burden; causality; analysis; reporting.*

## 1. INTRODUCTION

Medicines were termed as double-edged swords with both beneficial and injurious effects [1-2]. ADRs paved a way for more number of hospital admissions, emergency hospital visits and prolonged hospital stay and, which pose an economic burden to the government and patients [3-14]. In other countries, ADR is the leading cause for hospitalization and mortality, with a substantial economic burden [5,6]. It is early to confirm the complete safety and efficacy of a new drug as such after its commercialization, clinical trials have precincts in the detection of complete safety profile, and it has to be under close watch through a Pharmacovigilance (PV) system. Most of the studies have reported that drug regulatory authorities are receiving less than 10 % of detected ADRs [2-4].

Literature review stated that 4.2-30% of hospital admissions were due to ADRs in the USA and Canada, 5.7-18.8% in Australia, and 2.5-10.6% in Europe [1,6,14]. The prevalence of ADRs among hospitalized patients of England is 3.2%, 4.8% in Germany and in the United States of America (USA) it was 5.6%. Prolonged hospital stay of 8-20 days is also a major consequence of the ADRs [14]. In India, the incidence of ADR is between 5.9 to 22.3%, while deaths due to ADRs account for 1.8%. Admissions due to ADRs accounted for 0.7% of total admissions due to ADRs. The average cost burden of one ADR is INR 690 per patient [15-16].

Another issue with the ADR is the incidence of another reaction to the treatment given to manage the previous ADR, which increases further treatment cost [14].

Analysis of the suspected ADRs in respect to their causality, predictability, preventability, and severity along with relevant clinical data is complex but crucial in assessing the impact of

ADRs on the patient's health and wealth [8-10,17-27]. Though large numbers of studies are available on this concept, there is a wide variation across the countries in cost burden, as it is influenced by countries per capita [6].

Pharmacovigilance is a science and activities related to detection, assessment, understanding, and prevention of adverse events or Drug-related problems [25,28-29]. PV decreases the cost burden by withdrawing the drug from the market or by individualizing drug to specific indications and by providing information to health care professionals and encouraging them towards spontaneous reporting of ADR and rationalizing treatment to minimize ADRs with proper preventive measures [4,25]. By easy identification of Drug-Drug Interaction (DDI) and by providing treatment to ADR at its initial stage and by providing alert cards and detailed clinical registries decreases hospital costs. Therefore, it is an essential component for the health care system to monitor the safety of medicine for achieving a high quality of patient care [17,28]. Hence, healthcare professionals need to know the frequency, magnitude of both beneficial and adverse effects of drugs during clinical use of medicines [29].

The clinical pharmacist has a major role in lowering health care costs by reviewing the drug therapy of patients. The minimization of irrational prescriptions can lessen the drug cost and also the risk of adverse effects.

In India, very few studies have concentrated on ADR caused hospitalization and/or prolongation of the hospitalization and costs associated with ADRs. The present study was envisaged to Assess the severity of ADRs and evaluation of Costs associated with ADRs and its impact on the economy and the need of Pharmacovigilance, role of health care professionals in minimizing the occurrence of ADRs and its burden on patients.

## 2. METHODOLOGY

A Prospective observational study was performed over a period of two and half year from July 2016 to December 2018 at Government General Hospital at Kadapa, Andhra Pradesh, India.

### 2.1 The Functioning of ADR Reporting System

As part of our research, all the health care professionals within the hospital are being encouraged regarding Spontaneous Reporting of ADRs. All the received suspected ADR reporting forms are being scrutinized and reports which meet the Pharmacovigilance Program of India (PvPI) criteria [17] are being reported to PVPI.

### 2.2 Data Evaluation

All the suspected ADRs were categorized based on their causality, preventability, seriousness, severity and other characteristics like the class of the drug involved, the system involved, management and outcome of the ADRs. We have used World Health Organization (WHO) Causality assessment scale, PvPI seriousness criteria [17], Hartwig and Siegel Severity Assessment Scale [26] and the modified Schumock and Thornton preventability scale [11].

The key part is assessing the management and economic burden of an ADR on the patient and the hospital, which contributes both, direct and indirect costs. As the study site is a government health care centre, the majority of the cost was barred by the government from the hospital budget.

The overall socio-economic burden includes direct, indirect and hidden costs. However, hidden costs representing pain, sadness and depression were not considered in the present study.

### 2.3 Measurement of Direct Costs

Medical costs such as a physician, laboratory, nursing care charges, and drug charges (including drug delivery devices) for the total duration of hospitalization and the extended duration of hospitalization due to the occurrence of the ADR were calculated.

### 2.4 Measurement of Indirect Costs

Apart from the direct costs, there are other indirect costs incurred by ADRs, which includes, loss of working hours/ loss of their daily earnings of the patients/ and their caregivers. Indirect costs were calculated using the human capital approach [22] i.e., by taking districts per capita income over the specified time period. The formula is as follows: Lost income due to Hospitalization = Number of days in hospital X Per capita GDP of Kadapa district /365. Lost income from accompanying Hospitalized patient = Number of days in attendance X Per capita GDP of Kadapa district /365. Lost income for an outpatient = Number of outpatient visits due to ADR X Per capita GDP of Kadapa district /730. Per Capita Income of the Kadapa district for the year, 2017-18 was Rs.1, 25, 319 and 2016-17's Per Capita Income was Rs.1, 08, 716, which was taken from Performance Appraisal and District Economic Scenario 2017-18 by Andhra Pradesh government [30].

### 2.5 Data Sources

The patients who have developed ADRs during the hospital stay or admitted with ADRs were identified and followed throughout their hospital stay. The data regarding the demographics, reaction date, and its description, suspected drug/s, co-morbidities, past medical and medication history, concomitant drug/s, and previous allergies was collected through direct interview with the patient and their caretaker. Details of the ADR treatment and its outcome, and other details necessary for the evaluation were collected from the concerned physician and through the evaluation of patient medical records.

### 2.6 Statistics

Descriptive statistics includes Mean, Standard Deviation and Percentages were applied in analyzing the results.

## 3. RESULTS

A total of 458 suspected ADRs from different departments were analysed and reported to PvPI. The mean Standard Deviation (SD) age of the total study patients is 42.45 ( $\pm$  18.56) years, Female patients average (SD) age is 40.98 ( $\pm$  17.89) years and in Males, it is 44.15 ( $\pm$  19.21) years.

Of total patients, 106 (23.14 %) were admitted/consulted with ADR and remaining were developed ADRs during their hospital stay.

### 3.1 Data Evaluation Based on the Demographics of the Patients

#### 3.1.1 Gender and age

More than half of the of the study subjects were males (53.71%). the majority of the patients were adults 82 %, Table 1 explains the demographics of the study population.

**Table 1. Demographics of the study population**

Parameter	Total N=458	Percentage (%)
<b>Gender</b>		
Male	212	46.29
Female	246	53.71
<b>Age</b>		
Paediatrics (0-11 Years)	26	5.68
Adolescents (12-17 Years)	18	3.93
Adults (18-65 Years)	375	81.88
Geriatrics (>66 Years)	39	8.52

#### 3.2 Department Wise Distribution

We observed that 51.74% of the total ADRs were experienced by the patients in the general medicine department, followed by Dermatology (19.21%), Psychiatry (18.78%), Paediatrics (3.93%), obstetrics and Gynaecology (1.31%), General surgery (1.09%), and other departments (4%).

#### 3.3 Analysis of ADRs

We have analyzed the ADRs by using various scales. The detailed information was presented in Table 2.

#### 3.4 Drug Class

The most common drugs responsible for the ADRs are presented with their WHO- Anatomical Therapeutical Chemical Classification (ATC) drug codes. Nearly 78 (16.81%) ADRs were from antibiotics, of which 20 ADRs with ceftriaxone (J01DD04) and 11 ADRs with augumentin (J01CR02); antipsychotics were accounted for 68 (14.84%) ADRs, of them 24 ADRs were with olanzapine (N05AH03), and 20 with risperidone (N05AX08); analgesics and antipyretics were accounted for 57 (12.44%)

ADRs, of which 23 ADRs with diclofenac (M01AB05) and 12 with paracetamol (N02BE01); antihypertensives and anti-inflammatory drugs (corticosteroids) were involved in 43 (9.39%) ADRs each, in which prednisolone (A07EA01, D07AA01, R01AD02) involved in 19 ADRs, dexamethasone (D07AB19, A01AC02) in 12 ADRs, amlodipine (C08CA01) involved in 19 ADRs and furosemide (C03CA01) in 10 ADRs; anticonvulsants were involved in 33 (7.21%) ADRs, of which 17 were because of Phenytoin (N03AB02) and 10 with sodium valproate (N03AG01); anti-retrovirals were involved in 24 (5.24%) ADRs; anti-diabetics in 17 (3.71%) ADRs in which metformin (A10BA02) was involved in 10 ADRs, glimepiride (A10BB12) in 4 ADRs; anti-ulcer and antacids in 17 (3.71%) ADRs of them pantoprazole (A02BC02) was involved in 10 ADRs.

#### 3.5 System Organ Class (SOC) Involved in the Reactions

We have classified all the ADRs according to the system organ involved and it is illustrated in Table 3.

#### 3.6 Management of ADRs

The detailed information on the management of ADRs has been depicted in Table 4.

#### 3.7 Outcome of the Reactions

Patients were followed till they discharge from hospital to assess the outcome of the reaction, 134 (29.35%) patients were recovered from the reaction and 136 (29.69%) were at the recovering at the time of discharge, 48 (10.48%) patients were not recovered and 1 (0.22%) patient's outcome was considered to be fatal.

#### 3.8 Cost Analysis

We have made an attempt to estimate the cost implicated in the management of the ADRs, which include both direct and indirect costs. The Cost Analysis of the total ADRs was mentioned in Table 5.

#### 3.9 Direct Cost

The direct cost was calculated through the analysis of medical care, nursing care, clinical investigation; the indirect cost was assessed based on per-capita approach.

Out of 458 ADRs, 274 (59.83%) were treated with at least one drug and the total cost was INR

**Table 2. Analysis of ADRs**

<b>Parameter</b>	<b>Number of ADRsN=458</b>	<b>Percentage(%)</b>
<b>Causality</b>		
Certain	43	9.39
Possible	162	35.37
Probable	191	41.70
Un-assessable	53	11.57
Unclassifiable	5	1.09
Unconditional	4	0.87
<b>Seriousness</b>		
Death	1	0.22
Disability	1	0.22
Hospitalization/ prolonged	137	29.91
Life-threatening	6	1.31
Other medically important	8	1.74
Required intervention to prevent permanent impairment/damage	143	31.22
Non-serious	162	35.37
<b>Severity</b>		
Mild	235	51.31
Moderate	181	39.52
Severe	42	9.17
<b>Preventability</b>		
Not preventable	39	8.52
Definitely preventable	187	40.83
Probably preventable	232	50.66

**Table 3. Distribution of ADRs as per the System Organ Class (SOC)**

<b>SOC</b>	<b>Number of ADRsN=458</b>	<b>Percentage(%)</b>
Central Nervous System	98	21.40
Skin	84	18.34
Gastrointestinal System	83	18.12
Immune system	76	16.59
Cardiovascular System	53	11.57
Endocrine system	34	7.42
Renal system	22	4.80
Hepatic system	17	3.71
Respiratory system	16	3.49
Muscle system	13	2.84
Generalised body system	3	0.66

**Table 4. Management of ADRs**

<b>Management</b>	<b>Number of ADRs(n=458)</b>	<b>Percentage(%)</b>
Treated	274	59.83
Drug withdrew	257	56.11
Substituted with another drug	8	1.75
No change	146	31.88
Dose reduced	100	21.83
No information	9	1.97

**Table 5. Cost Analysis of the total ADRs**

	<b>Total Amount Spent in INR</b>	<b>Amount spent by the Govt Hospital in INR (%)</b>	<b>Amount spent by the patient in INR (%)</b>
<b>Direct costs</b>			
Hospital Charges	683100.00	683100.00 (100%)	00
Ambulatory care charges	9200.00	9200.00 (100%)	00
Investigation cost	35770	32020 (89.52%)	3750 (10.48%)
Medication cost	54630.79	37113.15 (67.93%)	17517.64 (32.06%)
<b>Indirect Costs</b>			
Inpatient*	199090.00	00	199090.00
Outpatient <sup>‡</sup>	7373.70	00	7373.70
<b>Total</b>	<b>989164.5</b>	<b>761433.15 (76.977%)</b>	<b>227731.34 (23.023%)</b>

\*Lost income due to Hospitalization = Number of days in hospital X Per capita GDP of Kadapa district /365.

\*Lost income from accompanying Hospitalized patient = Number of days in attendance X Per capita GDP of Kadapa district /365.

<sup>‡</sup>Lost income for an outpatient = Number of outpatient visits X Per capita GDP Kadapa district /730.

54630.79 with an average of INR 185.68 was spent on medicines/drugs. Of the total cost INR, 37113.15 (67.93%) was spent by the hospital and INR 17517.64 (32.06%) was borne by the patient.

A total of 123 (26.86%) patients have either hospitalized/prolonged their hospitalization due to ADRs. Expenditure on hospital charges (bed charges, doctor's visiting charges, and nursing charges) was 683100.00 INR with a mean of INR 5553.66 ( $\pm$  5218.43) per patient cost for hospitalization. Overall 46 (10.04%) patients with ADRs were consulted and received ambulatory care, the total expenditure was INR 9200.00. Overall 100 (21.83%) patients underwent investigational procedures as part of ADR management and the amount spent on the investigations was INR 35770.00.

### 3.10 Indirect Costs

A total of 621 working days with an average of 5.05 ( $\pm$ 4.74) days for each inpatient has been lost which resulted in the loss of income of the patients and/or their caretakers. And 46 outpatients have lost 23 working days. A total income of INR 206463.7 was lost by 169 patients because of ADRs.

## 4. DISCUSSION

ADRs are one of the sources that place the burden of extra cost on patients, patient's caretakers and the health care system. In our study, the majority (76.85%) of the ADRs were developed during the in-patient treatment course. And in 23.14% of cases, ADR is the reason for a hospital visit, KJ Patel et al. [13] and

Sivasankaran P et al. [2] have also reported the similar results.

Study findings show that females (53.71%) were more affected to ADRs than males (46.29%) which may be due to their physiological characteristics, as well as genetic/metabolic and hormonal differences and our study results were supported by Lucca JM et al. [6] and Chen Wu et al., [10]. The occurrence of ADR according to sex is coincidental and doesn't play any significant role.

The occurrence of ADRs is significantly more (81.88%) in adults than other populations, this is due to the reason that adult consultations were more than others and another reason may be the identification of ADRs in adults is unproblematic and these group people can express their health problems than paediatrics and geriatrics. Studies conducted by Akhideno PE et al. [9], Anum Saqib et al., [5], Lobo et al., [4] and KJ Patel et al. [13] also reported that adults were affected with more ADRs. In support to this, we observed the majority of ADRs in the general medicine (51.74%), where the rate of consultation is more when compared to other departments, Rajeshreddy SGSV et al. [7] reported that the majority (45%) of ADRs were reported in General Medicine and Lobo et al. [4] reported as 22 % of the ADRs were from the same department. R J Lihite et al. [11] have reported that the majority ADRs were reported from the department of Dermatology and very few from General medicine department.

In causality assessment, the majority of the ADRs were probably (41.70%) and possibly (35.37%) related to the drug. Assessing the

relationship between the drug and the reaction is essential to confirm the drug aetiology and also it is compulsory for the economic studies like this. A study conducted by Rajeshreddy SGSV et al. [7] stated that about 54% of ADRs were probably related and 46% ADRs were possibly related. Asawari R et al. [27] study reported that 43.36% were of Possible.

The seriousness and the severity of the reaction are directly related to the cost burden, also necessary for risk assessment, which is an important parameter to be considered in the ADR management. We found that the majority (35.37%) of the ADRs were not serious and 31.22% were serious reactions which required intervention to prevent permanent damage or prolonged hospitalization. We found that most of the ADRs (51.31%) were mild in nature, and only 9.17% of ADRs were of severe. Very few studies were found in relation to the seriousness of the ADRs, R J Lihite et al. [11] and N Moore et al. [21] have stated little about the serious ADRs.

Preventability assessment is also an important process in the analysis of the ADRs as it gives information about the possibilities of avoiding the ADRs occurrences in the patients. In this study, almost around 91.5% of the ADRs were of Preventable and 8.52% ADRs were of Non-Preventable. The reason for this high incidence of preventable ADRs in our study site is lack of time for the healthcare professionals in collecting complete past medication history and health illiteracy of the patients and their caretakers and limited treatment options for the prescribers. AnumSaqib et al. [5] concluded that majority i.e. 90% of the ADEs were preventable and Sivasankaran P et al. [2] stated that 75% of the reported ADRs were preventable.

Through the categorization of drugs involved in the ADRs, we found that antibiotics were majorly (16.81%) involved followed by Antipsychotics (14.87%). The reason for more antibiotic-related ADRs is high prescription rate either in prophylactic or as curative therapy. Studies conducted by Qing-ping et al. [22], Anum Saqib et al. [5], Chan ALF et al. [31] and Lobo et al. [4] concluded that the majority of ADRs were Antibiotics and Analgesics induced.

We have categorized all the reported ADRs according to the SOC and found that the around 60 % of the ADRs were affected the 3 systems

viz., CNS, Skin and GI Systems, studies conducted by Lucca JM et al. [6], Rajeshreddy SGSV et al. [7] and Peter Ehizokhale et al. [9] have concluded the similar results. De Almeida SM et al. [14] study reported respiratory and skin related ADRs were more when compared to other systems.

All the identified ADRs are needed to be managed appropriately and the treatment outcomes were to be assessed continuously, in this study majority of the ADRs i.e. 59.83% were treated with the addition of drugs, in 56.11% of ADRs the causative drug was removed. In 21.83% of the patients, the dose was reduced. Dose reduction, drug withdrawal and replacement with the other similar drug may not increase the medication cost much but the addition of another drug or drugs will bring extra burden to the payer. Response to the treatment was measured by assessing the reaction recovery status and found that, most of the patients (59%) shown a positive response to the treatment, and this information is lacking in the predominant number of cases (30.35%) which may be due to sudden discharge of patients against the medical advice and in 46 outpatients who developed ADR follow up information is not available due to their unavailability and 1 fatal reaction (0.22%) was observed in this study. In our study site, ADRs were well managed and we have not observed any recurrences in the study patients.

We have estimated the cost burden on both patients and health care centre and found that a total of INR 989164.5 was spent by both the hospital and the patients, of which 77 % amount was spent by the hospital which includes the consultation, investigation, and medication charges and the remaining amount was spent by the patients from their pocket, which includes investigation, medication charges and income lost due to the ADRs.

Indirect cost burden (INR 206463.7) occupies around 21% and remaining was direct Cost burden (INR 782700.8), which is divided into various types of charges which includes hospital charges (88%), medication cost (7%) and investigation charges (5%). We further estimated the cost burden on the patient and the hospital (as study site is a Govt.) and found 97% was spent by the hospital and only 3% was spent by the patients. This indicates that government had spent INR 761433.15 for managing ADRs, of this amount; a considerable spent could be

prevented as 91.5% of the ADRs were of Preventable. Out of total cost INR 989164.5 spent for treating ADRs, 79% is direct cost and remaining 21% is indirect cost. Qing-ping et al. [22] categorized and estimated the direct and the indirect cost burden and found to be 74% and 26% respectively.

The occurrence of ADR resulted in the loss of patient's or their caretaker's working hours and resulted in the loss of their income in that particular period. In our study, a total of 644 working days were lost by both the inpatients and outpatients, resulted in a loss of INR 206463.70. The total Indirect cost in both IP and OP patients was INR 199090.00/- and INR 7373.70 respectively. A study conducted by Adusumilli PK et al., [19] also shows similar results.

The increase in the hospitalization is directly linked to the increase in the cost of the treatment. These study results are similar to the study conducted by Nicholas Moore et al.,[21]. This study site is a government general hospital and all the medical facilities were free services, but unavailability of all the investigational procedures, ambiguous values in the reports in some cases, physicians suggested for private diagnosis for the patients who are affordable. We have not considered the amount spent on the food, and some nonmonetary losses like emotional stress, pain, and discomfort.

Several studies (Perrone V. [29], Lucca JM et al. [6], Chen Wu et al. [10], K.J. Patel et al. [3], N Moore et al. [21], Chan ALF et al. [31] and Janet Sultana et al. [32]) have been conducted in various countries on the economic burden of the ADRs with different methodologies and demonstrated various aspects of like type of care, severity, class of drugs etc., and all authors have insisted the need of a safety monitoring committee to manage these issues and minimize the cost burden.

The results show that the occurrence of ADRs has a great impact on the economic burden of both hospital and patients. Since this study considered the government supply cost/prices in all the aspects like medicines and investigations the burden on the patients is less, the total cost burden calculated with this study may rise by at least 50 %, if patients consult private health care centres other than the government. And the total cost has to be spent by the patients, unless they

have any insurance coverage or third party payment.

## 5. CONCLUSION

This study result warns the health care professionals and the patients to concentrate on the ADR monitoring and its management. This study may also help in knowing the hidden treatment cost because of drug use. We suggest the hospital authority to establish a safety monitoring committee with multidiscipline members leads by a clinical pharmacist to decrease the unnecessary cost burdens due to the ADR. We also suggest further research needed for the identification of possibilities in preventing ADR occurrence and to develop possible intervention policies to minimize the costs and discomforts due to drug use.

## 6. LIMITATIONS

This research was conducted in a government hospital and the cost burden may not be comparable with the private hospital care.

## CONSENT

An informed consent was obtained from all the patients after explaining about the study before collecting the information from them.

## ETHICAL APPROVAL

This study was initiated after getting ethical approval from the Institutional Ethical Committee of Rajiv Gandhi Institute of Medical Sciences, Kadapa, Andhra Pradesh, India.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.



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