ORIGINAL ARTICLE

Frequency of ADRs and their Economic Impact in a Tertiary Care Public Sector Hospital in South India

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Abstract

Background: Adverse drug reactions (ADRs) are significant causes of morbidity and mortality worldwide and also increase the healthcare cost due to hospital admission and extended hospital stay. Many countries spend 15–20% of the hospital budgets to treat drug-related problem. In India, the frequency of ADRs to individual drugs and their economic burdens are rarely evaluated.

Aim: The aim of this article was to study the frequency and pattern of occurrence of ADRs and their economic impact in a hospitalized patient.

Materials and methods: The prospective, observational study was carried out in four wards of the general medicine department. The WHO's definition of an ADR and intensive monitoring method was adopted. The direct cost imposed by ADRs was calculated using the available resources and indirect cost according to the human capital approach. The frequency and pattern of ADRs were evaluated.

Results: A total of 3012 patients were intensively monitored and among them 317 patients were identified with ADRs. Among 317 patients, 8.8% of the patients developed ADRs during the hospital stay, 1.7% patients were admitted to hospital due to ADRs, death due to ADRs was 0.32%, and the overall incidence of ADR was 10.5%. The higher frequency of the ADRs was observed with methotrexate (33.33%), followed by dapsone (23.8%) and antitubercular drugs (ATT) (22.58%). The average cost per patient in the management of ADRs was ₹3367.

Conclusion: Early detection and prevention of ADRs reduce the morbidity, mortality, and healthcare expenditures. The outcome of this study may be used to predict and prevent ADRs, which results in the effective healthcare budget of the hospital.

Keywords: Adverse drug reactions, Economic burden, Public sector hospital.

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Introduction

Adverse drug reactions (ADRs) cause significant morbidity and mortality across the world, they also increase the healthcare cost to the hospitals as well as the patient.[1,2] In modern times, the rational use of medicine and the safety of patients are considered to be important. They are also important for the development of very effective health policy and aid in a better delivery of healthcare.[3] Across the world, several studies have reported ADRs during hospital stay ranging from 1.7% to 32.7%, whereas patient admitted with ADRs were between 2.5% and 21.4%.[4–7] There is a vast difference in disease prevalence, ADR reporting system, drug use pattern and drug management system between developed and developing countries which impacts the frequency of ADRs development and economic burden.[8]

The reported incidence of adverse drug reactions in India ranges from 3.7% to 32.7%. A study from Mysuru reported that 3.7% of hospitalized patients experienced an ADR. In addition to that 0.7% of the hospital admission was due to ADR, followed by 1.8% of them had fatal ADR and the average direct cost involved in treating the ADRs per patient was ₹690 (US$ 15).[4] Another study from Chandigarh reported both direct and indirect cost incurred due to ADRs was ₹319,500.[9] A Pune-based study reported 4.75% overall incidence of ADR. 3.6% of the hospitalized patients had experienced ADRs and ADR related patient admission was 1.72%. The direct cost of treatment per ADR reported was ₹412.79 (US$ 9.30).[10] Another study from Srinagar concluded the overall incidence of ADR was found to be 6.23% and the average direct cost for ADR treatment per patient was US$ 65.[11] The cost for the treatment of the adverse drug reaction varies considerably based on the type of hospitals and various other factors. However in India, very few studies explored the economic burden of ADRs in public sector hospitals. Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), a tertiary care teaching public sector hospital, having 2,150 beds, has been actively involved in pharmacovigilance program since 2005.[12] The currently available insufficient information on the frequency of adverse drug reactions to individual drugs and its economic burden, did not allow us to properly size up the problem and plan action in this regard. Therefore the current study primary aim is to estimate the occurrence rate, pattern adverse drug reactions and secondary aim to measure the economic loss due to adverse drug reactions in a tertiary care public sector hospital.

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Materials and Methods

The prospective observational study was conducted in the four wards of the general medicine department of JIPMER, over a period for one year and adopted the intensive monitoring pharmacovigilance method. The study protocol was reviewed and approved by the JIPMER Scientific Advisory Committee (JSAC) and the Institute Ethics Committee (Human studies reference number: JIP/IEC/SC/2012/2/29) of JIPMER, Puducherry.

Inclusion Criteria

- Patients of either sex who developed ADR during treatment and whoever gets admitted due to ADR.

Exclusion Criteria

- Patient who developed ADR due to intentional or accidental poisoning.
- Patient with drug abuse, intoxication and over dose.
- ADR due to fresh blood or blood products transfusion.
- Patients from outpatient department

Data Collection Procedure

The study investigator and pharmacovigilance associate (PvPI) reviewed the patient's drug treatment charts, clinician and nursing notes of all the patients admitted in general medicine wards during the study period (Monday to Saturday). The review was conducted to screen the case records and the patient was interviewed for the presence of any ADRs. The objective markers of ADRs, e.g., laboratory results were identified from the case notes and hospital information system (HIS). The subjective marker of ADRs like headache, rash and nausea were identified through the patient progress notes, patient interview and finally there was a discussion with the concerned medical team. The ADRs defined according to World Health Organization (WHO)[13] and as per study inclusion, exclusion criteria, after explaining the study purpose and details to each subject, informed written consent was obtained and included in the study.

Economic Burden due to ADRs

The direct cost associated with the management of ADRs (from the beginning of the ADR to end of treatment) was calculated by considering the actual purchasing cost of drugs and medical devices born by the institute. The length of stay extended due to ADRs and laboratory investigations for management of ADRs were discussed with the medical team and then it was included. The extended hospital stay of bed charge per day and patient food cost per day and laboratory investigation charge was calculated according to hospital information type C class charge (bed charge fifty rupees per day, food cost sixty rupees per day and laboratory investigation charge were minimal). Since the hospital was public sector the cost of physician, nursing, administration charge was not taken into account. The indirect costs of ADR treatment were calculated according to the human capital approach 2013 (actual loss to the patient/caretaker) like traveling expenses, daily wages of patient and caretaker (one per patient) and for the miscellaneous expenses, the patients or caretaker were interviewed the actual cost was calculated. However, the intangible cost like pain, sadness and depression of patients due to ADR were not considered in the study.

Data Documentation

The data were included either sex who developed ADR during treatment, whoever gets admitted due to ADRs. Who developed ADR due to intentional or accidental poisoning, drug abuse, intoxication, overdose and ADR due to fresh blood or blood product transfusion was excluded. The identified ADRs were documented in the suspected ADR documentation form provided by the Indian Pharmacopoeia Commission (IPC). The name and quantity of drug prescribed for ADR management, number of hospital stay days extended for ADR management and indirect cost interviewed from patient or caretaker were documented, separately designed data collection proforma.

Constitution of the Independent Clinical Panel

The documented ADRs were assessed by a panel of experts consisted of two clinical pharmacologists, one clinician, a research scholar and one pharmacovigilance associate. The panel evaluated the causality,[14,15] severity,[16] types of reactions[17] and seriousness[18] of ADR using the appropriate scale. The reactions associated with the system involved were coded using World Health Organization Adverse Drug Reaction Terminology (WHO-ART). Drugs associated with ADRs were classified using WHO-Anatomical Therapeutical Classification (WHO-ATC). When there is a disagreement between members of the clinical panel, a consensus has arrived after discussion. The opinion of treating clinicians was also considered in arriving at a consensus. Information required for the assessment of ADR was obtained from standard drug information resources.

Evaluation of Results

All the identified ADRs were evaluated to identify the pattern the concerning patient demographic characteristics, reaction characteristics, medication usage of adverse drug reaction. The data was analyzed to determine the incidence, type of reaction, causality, severity, the seriousness of reaction, organ system affected, drugs implicated ADRs, risk factors for the development of ADRs, the cost associated with the treatment of ADRs. The frequency of ADRs to individual drugs calculated according to Hurwitz et al.,[19] number of patients developed ADR for particular drug/total number of a patient exposed for particular drug $\times$ 100.

Statistical Analysis

All the data analyzed descriptively using Graph Pad Instat Version 3.0 and SPSS version 19.0 (IBM PASW Statistics; 19.0). The distribution of all the categorical data related to the patient characteristics such as gender, type of drug use, organ affected, etc., was presented on the frequencies and percentage. The logistic regression analysis was used to find out the association of risk factors for the development of ADRs like gender, diagnosis, age group, number of drug intake, number of hospital stays. All statistical analysis was carried out for two-tailed significance and $p < 0.05$ were considered as statistically significant.

Results

General Demographic Characteristic of the Study Population

A total of 3,012 patients were intensively monitored during the study period. Among them, 317 patients identified 382 ADRs. Amidst 317 patients, 265 (8.8%) patients developed ADRs during the hospital stay, 52 (1.7%) patients admitted to hospital due to ADRs and death

Table 1: Demographic characteristics of study population

Characteristics	*Patients without ADR*	*Patients with ADR*	*Total number of study patients*
No. of patients *n* (%)	2,695 (89.48)	317 (10.52)	3,012 (100)
Gender			
Male *n* (%)	1,777 (90.5)	187 (9.5)	1,964 (65.2)
Female *n* (%)	918 (87.6)	130 (12.4)	1,048 (34.8)
Age (years)			
Median (IQR)	45 (30–58)	48 (32–59)	45 (30–58)
Range	1–92	8–85	1–92
Age categories			
1–18 years, *n* (%)	200 (94.4)	12 (5.6)	212 (7)
19–60 years, *n* (%)	1,874 (89.2)	228 (10.8)	2,102 (69.8)
>60 years, *n* (%)	621 (88.9)	77 (11.1)	698 (23.2)
No. of diagnosis			
1, *n* (%)	1,144 (94.4)	68 (5.6)	1,212 (40.2)
≥2, *n* (%)	1,551 (86.2)	249 (13.8)	1,800 (59.8)
No. of drugs taken			
Median (IQR)	6 (5–8)	7 (5–8)	6 (5–8)
Range	1–17	1–21	1–21
Cumulative no. of drugs	17,645	2,162	19,807
Hospital stay (days)			
Median (IQR)	6 (3–9)	9 (6–13)	6 (4–9)
Range	1–42	2–63	1–63
Cumulative days of stay	18,495	3,468	21,963

ADR, adverse drug reaction; IQR, inter quartile range

Table 2: System organ class (SOC) affected due to ADRs

System organ class (WHO-ART SOC code)	*n (%), [95 CI]*
Skin and appendages disorders (0100)	76 (19.9), [16–24]
Gastrointestinal system disorders (0600)	58 (15.19), [12–19]
Central and peripheral nervous system disorders (0410)	40 (10.47), [7–13]
Body as whole general disorders (1810)	33 (8.64), [5–11]
Metabolic and nutritional disorders (0800)	32 (8.38), [6–11]
Urinary system disorders (1300)	28 (7.33), [4–9]
Liver and biliary disorders (0700)	21 (5.5), [3–8]
Platelet bleeding and clotting disorders (1230)	15 (3.93), [2–7]
Heart rate and rhythm disorders (1030)	13 (3.40), [1–6]
Red blood cell disorders (1210)	13 (3.40), [1–6]
White cell and reticuloendothelial system disorders (1220)	12 (3.15), [1–5]
Respiratory system disorders (1100)	11 (2.88), [1–6]
Cardiovascular disorders general (1010)	5 (1.31), [1–4]
Endocrine disorders (0900)	5 (1.31), [1–4]
Psychiatric disorders (0500)	5 (1.31), [1–4]
Musculoskeletal system disorders (1200)	4 (1.04), [1–4]
Vision disorders (0431)	4 (1.04), [1–4]
Reproductive disorders male (1410)	2 (0.52), [0.7–2]
Reproductive disorders female (1420)	2 (0. 52), [0.7–2]
Application site disorders (1820)	2 (0.52), [0.7–2]
Neoplasm (1700)	1 (0.26), [0.3–1.5]

WHO-ART SOC, World Health Organization Adverse Drug Reaction Terminology System Organ Class

due to ADRs was 1 (0.32%). The death was due to warfarin-induced intracranial bleed. The overall incidence of the ADR was found to be 10.5% and the average number of ADRs in a patient was 1.2, among the patients who suffered from ADR. The demographic details of the study population are presented in Table 1.

Characteristics and Assessment of Adverse Drug Reactions

Classification of ADRs

The types of ADR were classified according to Wills and Brown classification. In our study type A reactions have accounted for 72% (*n* = 275) of ADRs and followed by type H reaction was 19.6% (*n* = 75), type U reaction was 8.2% (*n* = 31) and type C reaction 0.2% (*n* = 1).

Seriousness of ADRs

Among the 382 ADRs, the serious ADRs were found to be 54.2% (*n* = 207) and non-serious were 45.8% (*n* = 175). Among the serious ADRs, life-threatening ADRs were 8.4% (*n* = 32), hospitalization initial were 15.2% (*n* = 58), hospital prolongation were 27% (*n* = 103), required intervention to prevent permanent impairment or damage were 3.4% (*n* = 13) and death was 0.32% (*n* = 1).

Causality Assessment of ADRs

According to WHO-probability scale, the majority 56.54% (*n* = 216) of the ADRs were possible followed by 29.32% (*n* = 112) were probable, 12.04% (*n* = 46) were certain, 1.05% (*n* = 4) were unlikely and 1.05% (*n* = 4) were unclassifiable in relation to the suspected drugs. Using Naranjo's algorithm 66% (*n* = 252) were defined as probable, 29.3%. (*n* = 112) were possible and 4.7% (*n* = 18) were definite.

Severity of ADRs

The severity of majority 67.8% (*n* = 259) of ADRs were moderate (level 3, level 4a and 4b) followed by mild 23.6% (*n* = 90) (level 1 and 2) and severe 8.6% (*n* = 33) (level 5 and 7).

System Organ Class (SOC) Affected due to ADRs

The most commonly affected system organ class were skin and appendage disorder [*n* = 76 (19.9%)] followed by gastrointestinal disorder [*n* = 58 (15.8%)] and neurology disorder [*n* = 40 (10.47%)]. Rash and vomiting (each *n* = 19) were the most commonly identified ADRs followed by giddiness and hepatocellular damage (each *n* = 18). The details of the system organ class affected by the ADRs and commonly reported ADRs are presented in Table 2.

Anatomical and Therapeutic Class (ATC) of Medication Implicated in ADRs

Anatomical class of medication frequently implicated in the ADRs were anti-infective system (J) (*n* = 116, 30.37%) followed by alimentary tract and metabolism (A) (*n* = 81, 21.2%). Among the anti-infective systems, anti-bacterial (J01) (*n* = 72, 18.85%) and antimycobacterial (J04) (*n* = 29, 7.59%) were the common drugs causing ADRs. Anatomical and therapeutical classes of medication implicated in ADRs are presented in Table 3.

Table 3: Anatomical and therapeutic class of medication implicated in ADRs

Anatomical class [code] (number of ADRs, %)	*Therapeutic class [code]*	*Number of ADRs (%)*
Anti-infective systemic use [J] (116, 30.37)	Antibacterial for systemic use [J01]	72 (18.85)
	Antimycobacterials [J04]	29 (7.59)
	Antiviral for systemic use [J05]	11 (2.88)
	Antimycotics for systemic use [J02]	4 (1.05)
Alimentary tract and metabolism [A] (81, 21. 20)	Anti-diarrheals, intestinal/anti-inflammatory/anti-infective agents [A07]	44 (11.52)
	Drugs used in diabetes [A10]	29 (7.59)
	Drugs for acid-related disorders [A07]	5 (1.31)
	Anabolic agents for systemic use [A14]	2 (0.52)
	Antiemetics and antinauseants [A04]	1 (0.26)
Cardiovascular system [C] (56, 14.66)	Calcium channel blockers [C08]	15 (3.93)
	Beta-blocking agents [C07]	11 (2.88)
	Cardiac therapy glycoside [C01]	8 (2.09)
	Diuretics [C03]	8 (2.09)
	Agents acting on the renin angiotensin system [C09]	7 (1.83)
	Antihypertensive [C02]	4 (1.05)
	Lipid-modifying agents [C10]	3 (0.79)
Nervous system [N] (39, 10.21)	Antiepileptic [N03]	23 (6.03)
	Other analgesics [N01]	7 (1.83)
	Analgesic [N02]	5 (1.31)
	Antiparkinson drugs [N04]	2 (0.52)
	Psycholeptics [N05]	2 (0.52)
Antineoplastic and immune modulating agents [L] (35, 9.17)	Antineoplastic agents [L01]	23 (6.03)
	Imuunosuppresants [L04]	12 (3.14)
Blood and blood-forming organs [B] (30, 7.86)	Antithrombotic agents [B01]	27 (7.07)
	Blood substitute preparation [B05]	3 (0.79)
Musculoskeletal system [M] (9, 2.35)	Anti-inflammatory and anti-rheumatic products [M01]	6 (1.57)
	Anti-gout preparations [M04]	2 (0.52)
	Drugs for treatment of bone diseases [M05]	1 (0.26)
Dermatological [D] (8, 2.09)	Anti-acne preparations [D10]	8 (2.09)
Antiparasitic products, insecticides and repellents [P] (6, 1.57)	Antiprotozoals [P01]	6 (1.57)
Respiratory system [R] (1, 0.26)	Drugs for obstructive airway diseases [R03]	1 (0.26)
Systemic hormonal preparations, excluding sex hormones and insulins [H] (1, 0.26)	Corticosteroids for systemic use [H02]	1 (0.26)

ADRs, adverse drug reactions

Frequency of ADRs for Individual Drugs and their Incidence

The higher incidence of the adverse drug reactions was observed with methotrexate (33.33%), followed by dapsone (23.8%) and antitubercular drugs (ATT) (22.58%). The incidence of ADRs of cyclophosphamide and vancomycin observed in our study were 21.05% and 18.42%, respectively. The top five drugs causing the higher number ADRs were ATT (25), ceftriaxone (22), vancomycin (21), phenytoin (17), and prednisolone (16) (Table 4).

Risk Factors for the Occurrence of Adverse Drug Reactions

Multivariate regression analysis revealed that factors like gender, presence of comorbid medical conditions, polypharmacy and length of hospital stay were the risk factors for the development of adverse drug reaction.

Economic Burden Imposed by Adverse Drug Reactions

During the study period, 382 ADRs were identified. Of the total ADRs, 293 (76.7%) ADRs from 248 patients cost incurred in the management of ADRs. Amidst 293 ADRs, 209 ADRs have increased the length of stay (LOS) with 172 patients. The extended hospital stay was accounted for 1,002 bed days and the median increase in the length of stay was 5.8 days. The total economic loss from 248 patients of ADR was found to be ₹835,133, which includes total direct cost ₹296,093 (includes drug cost, food cost, bed charge and lab charges only) and total indirect cost ₹539,040 [includes traveling expenses, daily wages of patient and caretaker (one per patient) and miscellaneous expenses]. Considering the direct and indirect cost imposed by ADR per patient was ₹3,367 (₹835,133/248). The severity-based costs imposed by ADRs were shown in Table 5.

Discussion

Participant's Description

Adverse drug reactions are a serious health concern for society. The mortality and morbidity associated with hospital admissions and during hospitalization related to adverse drug reactions result in economic burden to the country.[20] Based on the "Health at a Glance 2017" from the organization of economic cooperation and development (OECD) report stated that India's, spending on health care is very less compared to the developed countries,[21] so it is very important to utilize the money very effectively. Identifying and preventing the ADRs by effective monitoring of the patients is very important in any healthcare setting. Most of the advanced countries have good infrastructure for adverse drug reaction reporting systems at the national level. Adverse drug reaction reporting programs on an institutional basis can provide valuable information about potential problems in drug usage in that institution. So we have taken up a study to evaluate the incidence and pattern of ADRs, its economic impact in our hospital setting.

In our study, a total of 3,012 patients were intensively monitored for ADRs in the general medicine ward. Three hundred and eighty two ADRs from 317 patients were considered for final analysis. In our study, 1.7% of patients were admitted to hospital due to ADRs which is less when compared to the other published reports from South India which reports 3.4% and 14%.[22,23] Most of the study reported that 2.9–6.7% of all hospital admissions are due to ADR which is higher compared to our study findings.[24,25] This difference could be attributed to different sample sizes, study setting, methods of monitoring and different study designs. However in

Table 4: Frequency of ADRs for individual drugs and their incidence

Individual drugs [ATC code]	*Number of patients exposed to drugs*	*Number of patients developed ADRs*	*Incidence (%)*	*Total number of ADRs (%) (n = 382)*
Methotrexate [L04AX03]	12	4	33.33	9 (2.36)
Dapsone [D10AX05]	21	5	23.80	6 (1.57)
Rifampicin, pyrazinamide, ethambutol and isoniazid, [J04AM06]	93	21	22.58	25 (6.6)
Cyclophosphamide [L01AA01]	19	4	21.05	4 (1.04)
Vancomycin [A07AA09]	114	21	18.42	21 (5.5)
Carbamazepine [N03AF01]	28	5	17.85	6 (1.57)
Zidovudine [J05AF01]	28	5	17.85	6 (1.57)
Cytarabine [L01BC01]	35	6	17.14	6 (1.57)
Amphotericin B [J02AA01]	18	3	16.66	3 (0.79)
Asparaginase [L01XX02]	18	3	16.66	4 (1.04)
Vinblatsine [L01CA01]	12	2	16.66	3 (0.79)
Antithymocyte immunoglobulin [L04AA04]	7	1	14.29	1 (0.26)
Pertuzumab [L01XC13]	7	1	14.29	1 (0.26)
Phenytoin [N03AB02]	99	13	13.13	17 (4.46)
Allopurinol [M04AA01]	18	2	11.11	2 (0.52)
Linezolid [J01XX08]	18	2	11.11	2 (0.52)
Olanzapine [N05AH03]	9	1	11.11	1 (0.26)
Streptokinase [B01AD01]	27	3	11.11	4 (1.04)
Ciclosporin [L04AD01]	19	2	10.53	2 (0.52)
Warfarin [B01AA03]	92	9	9.78	11 (2.88)
Ceftazidime [J01DD02]	32	3	9.38	3 (0.79)
Ciprofloxacin [J01MA02]	54	5	9.26	5 (1.31)
Streptomycin combinations [A07AA54]	33	3	9.10	4 (1.04)
Aciclovir	55	5	9.10	5 (1.31)
Rifampicin, pyrazinamide and isoniazid [J04AM05]	22	2	9.10	2 (0.52)
Spironolactone [C03DA01]	33	3	9.10	3 (0.79)
Sulfasalazine [A07EC01]	11	1	9.10	1 (0.26)
Digoxin [C01AA05]	62	5	8.06	6 (1.57)
Piperacillin and beta-lactamase inhibitor [J01CR05]	62	5	8.06	6 (1.57)
Glibenclamide [A10BB01]	41	3	7.32	3 (0.79)
Insulin mixtard [A10AD01]	124	9	7.26	9 (2.36)
Cefixime [J01DD08]	14	1	7.14	1 (0.26)
Doxorubicin [L01DB01]	14	1	7.14	1 (0.26)
Oxaliplatin [L01XA03]	14	1	7.14	2 (0.52)
Pioglitazone [A10BG03]	14	1	7.14	1 (0.26)
Prazosin [C02CA0]	14	1	7.14	3 (0.79)
Zoledronic acid [M05BA08]	14	1	7.14	1 (0.26)
Prednisolone [A07EA01]	184	13	7.07	16 (4.2)
Amlodipine [C08CA01]	195	13	6.66	15 (3.93)
Insulin insulatard [A10AE01]	31	2	6.45	5 (1.31)
Artesunate [P01BE03]	17	1	5.88	2 (0.52)
Ofloxacin [J01MA01]	34	2	5.88	2 (0.52)
Insulin actrapid [A10AB01]	35	2	5.71	2 (0.52)
Daunorubicin [L01DB02]	18	1	5.55	1 (0.26)
Stanozolol [A14AA02]	18	1	5.55	2 (0.52)
Diclofenac [M01AB05]	94	5	5.32	6 (1.57)
Acenocoumarol [B01AA07]	38	2	5.26	3 (0.79)
Amoxicillin and beta-lactamase inhibitors [J01CR02]	38	2	5.26	2 (0.52)

Contd…

Contd…

Individual drugs [ATC code]	*Number of patients exposed to drugs*	*Number of patients developed ADRs*	*Incidence (%)*	*Total number of ADRs (%) (n = 382)*
Meropenem [J01DH02]	62	3	4.83	5 (1.31)
Sulfamethoxazole and trimethoprim [J01EE01]	84	4	4.76	7 (1.84)
Lithium [N05AN01]	22	1	4.55	1 (0.26)
Atenolol and nifedipine [C07FB03]	46	2	4.35	2 (0.52)
Isosorbide mononitrate [C01DA14]	46	2	4.35	2 (0.52)
Valproic acid [N03AG01]	46	2	4.35	3 (0.79)
Vincristine [L01CA02]	23	1	4.35	1 (0.26)
Ceftriaxone [J01DD04]	439	19	4.33	22 (5.74)
Enoxaparin [B01AB05]	142	6	4.23	6 (1.57)
Topiramate [N03AX11]	25	1	4	1 ((0.26)
Levodopa [N04BA01]	53	2	3.77	2 (0.52)
Chloroquine [P01BA01]	27	1	3.70	1 (0.26)
Atenolol [C07AB03]	84	3	3.57	5 (1.31)
Loperamide [A07DA03]	28	1	3.57	2 (0.52)
Cefoperazone and beta-lactamase inhibitors [J01DD62]	58	2	3.45	3 (0.79)
Metoprolol [C07AB02]	60	2	3.33	3 (0.79)
Enalapril [C09AA02]	183	6	3.28	7 (1.84)
Dexamethasone [D07AB19]	68	2	2.94	2 (0.52)
Methyldopa [C02AB01]	34	1	2.94	1 (0.26)
Metformin [A10BA02]	243	7	2.88	7 (1.84)
Roxithromycin [J01FA06]	36	1	2.78	1 (0.26)
Tinidazole [P01AB02]	36	1	2.78	2 (0.52)
Triamterene [C03DB02]	36	1	2.78	1 (0.26)
Benzyl penicillin [J01CE01]	38	1	2.63	1 (0.26)
Voriconazole [J02AC03]	38	1	2.63	1 (0.26)
Morphine [N02AA01]	39	1	2.56	1 (0.26)
Methylprednisolone [H02AB04]	41	1	2.44	1 (0.26)
Nitrofurantoin [J01XE01]	46	1	2.17	1 (0.26)
Cloxacillin [J01CF02]	48	1	2.08	2 (0.52)
Hydroxychloroquine [P01BA02]	48	1	2.08	1 (0.26)
Ciprofloxacin and metronidazole [J01RA10]	49	1	2.04	1 (0.26)
Nebivolol [C07AB12]	54	1	1.85	1 (0.26)
Hydrochlorothiazide [C03AA03]	56	1	1.79	1 (0.26)
Electrolytes [B05BB01]	61	1	1.64	2 (0.52)
Ondansetron [A04AA01]	62	1	1.61	1 (0.26)
Amikacin [J01GB06]	127	2	1.57	2 (0.52)
Glipizide [A10BB07]	64	1	1.56	2 (0.52)
Potassium chloride [B05XA01]	78	1	1.28	1 (0.26)
Tramadol [N02AX02]	246	3	1.22	4 (1.04)
Paracetamol [N02BE01]	444	5	1.13	7 (1.84)
Amoxicillin [J01CA04]	89	1	1.12	1 (0.26)
Cefotoxime [J01DD01]	89	1	1.12	1 (0.26)
Azithromycin [J01FA10]	250	2	0.8	3 (0.79)
Salbutamol [R03AC02]	163	1	0.61	1 (0.26)
Atorvastatin [C10AA05]	328	2	0.61	2 (0.52)
Furosemide [C03CA01]	510	3	0.59	3 (0.79)
Ranitidine [A02BA02]	363	2	0.55	3 (0.79)
Aspirin [N02BA01]	33	2	0.49	3 (0.79)
Famotidine [A02BA03]	383	1	0.26	2 (0.52)

ATC, anatomical therapeutical class code; ADRs, adverse drug reactions

Table 5: Severity-based cost imposed by ADRs

		Direct cost		*Indirect cost*	
Severity level of ADRs	*Total number of adverse drug reactions*	*Number of ADRs cost incurred*	*Average cost (total cost) (₹)*	*Number of ADRs cost incurred*	*Average cost (total cost) (₹)*
Mild	90	8	171.5 (1,372)	–	–
Moderate	259	252	898 (226,299)	174	2,410 (419,440)
Severe	33	33	2,073 (68,422)	33	3,624 (119,600)

Direct cost: excludes of doctors, nursing, pharmacist dispensing and administration fee; Indirect cost: excludes intangible cost; ₹: Indian rupee; ADRs, adverse drug reactions

the present study, 8.8% of patients developed ADRs during the hospitalization which is high compared to the other South Indian studies, which reported 3.7% of patients developed ADRs during hospitalization.[4,22] This study findings emphasize the need for critical monitoring of ADRs so that it can be prevented.

Incidence of Adverse Drug Reactions

The overall incidence of ADRs was 10.5% which is consistent with the findings from Arulmani et al.[22] and Peter et al.[26] They reported incidence of 9.8% and 10.42%. However, studies from Mysuru and Gujarat reported the incidence rate of a hospitalized patient as 4.4%, 2.4%.[4,27] This could be attributed to under-reporting of ADRs whereas in our study intensive monitoring was done which resulted in more numbers of ADR observed.

In this study, the occurrence of ADRs was more in females when compared to the male group which was similar to that of other studies.[4,22] Some studies have reported male patients have more ADRs than females.[24,28] and this difference can be due to more male patients getting admitted and monitored in the hospital. In our study, the higher incidence of ADRs reported in females compared to men. This may be due to female patients have lower body weight and more body fat than men and the lower concentration of hepatic enzymes.[29] So rational dose titration may lead to the minimization of ADRs in females. Among the patients who experienced ADRs 78.5% of patients have more than two comorbid conditions. As the multiple diseases need various drugs for the treatment it leads to polypharmacy. The more the number of drugs prescribed, the higher is the probability of the occurrence of ADRs. The frequencies of ADR were higher in elderly patients (11.1%) and followed by 19–59 years (10.8%). Our findings were consistent with the studies reported from UK[2] and India.[23] which showed that geriatrics patients experience ADRs more compared to other age groups. In the present study, 70% of the patients admitted were in the age group of 19–59 years followed by 23% of them were geriatrics patients. This is in agreement with reported from Ramesh et al.[4] which noticed that 67% of the patients were adults and nearly 30% were geriatrics patients.

Assessment of Adverse Drug Reactions

In our study type A reactions accounted for 72% of ADRs and followed by a type H reaction of 19.6%. These findings were in agreement with other study reports from South India whereas type A reactions were commonly observed.[30] Another South Indian study found a predominance of type B reactions, which is contradictory to our study findings.[31] Arulmani et al. have reported type H reactions were most commonly observed which contradictors our findings.[22] Type A reactions are mostly drug related and preventable. Type B reactions were pharmacologically predictable and type H reactions are unpredictable and unpreventable. In our study type A reactions were mostly observed which can be prevented from their known pharmacology and its intended effects so it was potentially avoidable. Critical monitoring of drug usage in patients can help in preventing type A reactions.

In our study 54.2% of ADRs were serious and among them, 8.4% was life-threatening followed by ADRs causing hospital prolongation and admission were 27% and 15.2%, respectively. Study findings from Gujarat reported that life-threatening ADRs were 8.3% which is similar to our study findings. In addition to that 42.1% of ADRs leads to initial or prolongation of hospitalization which is also in agreement with our findings. Our study revealed that only 3.4% ADRs required intervention to prevent permanent damage which is contradictory to study reported from Gujarat which reveals 43% of ADRs required intervention to prevent permanent damage.[32] This may be due to higher antitubercular and antiretroviral drugs prescribed in their study which resulted in higher immunologically mediated hypersensitivity reactions. The study reported from Italy revealed 28% of ADRs were serious which is less compared to our study findings and further 26% of ADRs lead to hospitalization which is also less compared to our study.[33] This attributed difference may be due to the study was conducted in children's whereas in our study all age groups of patients admitted in general medicine wards were monitored. In the current study, 54% were serious ADRs, so it is prudent to vigilantly monitor and follow-up the patients for early identification and prevention of serious ADRs. These findings suggest that the prescriber should remain vigilant and also educate the patient about the possible side effects of drugs.

Causality assessment of ADRs as per WHO scale reveals the majority of the ADRs, belong to possible (56.54%) followed by probable (29.32%) and certain (12%). Using Naranjo's algorithm 66% of ADRs were classified as probable followed by 29.3% of them as possible and 4.7% of them were definite. Our study findings were in agreement with an Arulmani et al.[22] which reported that as per Naranjo scale 62% of ADRs were probable and 31% of them were possible. Another study from Telangana[30] about the causality assessment as per Naranjo's scale reveals 58% of ADRs were probable which is slightly less than our findings and followed by 30% were possible which is higher than our study findings.

In our study as per severity, 68% of ADRs were moderate followed by mild 24% and only 8% of ADRs were found to be severe. Study findings of severity assessment using the Hartwig and Siegel scale from Telangana also revealed that most of the ADRs were moderate and only 8% of them were severe. These findings were comparable to our study results.[30] Our study findings the majority of ADRs were moderate in severity in accordance with other studies.[4]

Most Commonly Affected Organ Systems due to ADRs and Medication-implicated ADRs

The most commonly affected system organ classes were skin and appendage disorder (19.9%) followed by gastrointestinal disorder (15.8%)] and neurology disorders (10.47%). The results were comparable with the study reported from the USA which revealed that the system most badly affected was the gastrointestinal system and dermatological.[34] Our study findings also consistent with studies reported from south India which reveals gastrointestinal, dermatological and nervous system were predominantly involved reported organ class of system involved in adverse drug reactions.[22,24] Rash and vomiting was the most commonly identified ADRs followed by giddiness and hepatocellular damage. Our study findings were in agreement with Manipal-based study which reported dermatology was the most commonly affected organ system with skin rash as the most frequently reported reaction.[35] In the present study anti-infective system followed by the alimentary tract and metabolism, cardiovascular system was commonly involved. Among the therapeutic class of drugs, antibacterial followed by anti-inflammatory and anti-diabetics therapeutic classes of drugs were commonly implicated in ADRs. Our finding is consistent with the studies reported by Suh et al.[36] and Prosser et al.[34] They have reported anti-infective and anti-inflammatory drugs were predominantly involved in the development of ADRs. So antibiotics usage should be monitored and an antibiotic sensitivity test should be done in suspected resistance cases to prevent the antibiotic resistance.

Risk Factors for the Occurrence of Adverse Drug Reactions

The median number of drugs prescribed per ADR developed patient was 6.5 which was consistent with the study reported from France and Spain.[28,37] The median hospital stay per ADR developed patient was 6 days which was consistent with findings from other studies.[38] Studies reported from the USA and England had 3 median days per patient which is less compared to our study.[39] Predisposing factors were assessed for the risk of ADRs based on various factors like age, gender, no of drugs, length of hospital stay, etc. Multivariate regression analysis identified female gender, presence of comorbid medical conditions, polypharmacy and length of stay as the risk factor for the development of adverse drug reaction. Length of stay and polypharmacy were strong indicators for the risk of adverse drug reactions. Those who take more than two drugs have a higher risk of ADR and more than or equal to 6 drugs have 2.5 times more likely to experience ADRs as compared to patients taking 1–2 drugs. Similarly, patients who stay more than or equal to 5 days stay in hospital have 4.95 times more risk for the development of ADRs. So it's important to have medication review and focused monitoring to avoid unnecessary drugs.

Economic Burden Imposed by Adverse Drug Reactions

The results revealed that total economic loss from 248 patients with ADR was ₹835,133 and the cost imposed (total direct and indirect cost) by ADR per patient was ₹3,367. The direct cost for the treatment per ADR was ₹1,010. Our study results were comparable to study findings of economic assessment of ADRs in a private hospital which revealed the average direct cost per patient hospitalized with an ADR was ₹4,945. The north-Indian study revealed the total direct cost (₹56,620) and indirect cost (₹262,880) for the total cost for treatment of ADRs was ₹319,500.[9] These differences may be due to study setting and other factors such as public sector hospital and private hospital. Another study from Pune[10] reported the average cost incurred due to ADR related hospitalization was found to be ₹578.55 and ADR cost occurred in hospitalized inpatient was ₹441.86. We didn't assess separately cost of ADRs in hospitalized patient and ADRs related hospitalization. This was one of the limitations of our study. In our study total, direct cost was ₹296,093 includes drug cost, food cost, bed charge and lab charge only. The total indirect cost was ₹539,040 includes traveling expenses, daily wages of patient and caretaker and miscellaneous expenses. Most of the studies in India only reported direct costs for the treatment of the ADRs.[4,7,10,22] We have assessed both the direct and indirect cost associated with ADRs. The direct cost of ADRs was about the management of ADRs. Assessing the indirect cost was also very important as it reveals the economic burden of ADRs. The average direct cost incurred in each mild, moderate and severe reactions were ₹171.5, ₹898, ₹2,073, respectively which was higher than the study reported by Arulmani et al.[22] This difference may depend upon the nature of the hospital, the year of study the conducted and other factors. Our findings suggest that vigilant monitoring of ADRs and prevention of ADRs was the need of the hour. Establishment of standardized operating approaches and voluntary reporting of suspected ADR's by all healthcare professionals working in the hospital can result in better monitoring and prevention of adverse drug reactions. Computerized prescribing may lead to a reduction in ADRs and if possible it can be implemented.

Conclusion

The study concludes the overall incidence of ADRs in general medicine was found to be 10.5%. The incidence of ADRs during hospital stay was 8.8%, patients admitted due to ADRs and deaths due to ADRs were 1.7% and 0.32%, respectively. The average cost per patient in the management of ADRs was ₹3,367. The outcome of this study may useful to predict and prevention of ADRs early, therefore reduces the treatment cost of general medicine wards which results in the effective healthcare budget of the hospital.

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