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Monitoring, Reporting and Evaluation of various Adverse Drug Reactions (ADRs) Under Pharmacovigilance Programme of India (PvPI) in a Tertiary Cardiac Care Hospital, Tamil Nadu

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ABSTRACT

Background and Objective: The objective of the study was to monitor, evaluate and analyse various ADRs in a tertiary care hospital and to determine the causality, severity and preventability of reactions.

Methodology: After obtaining approval from Institutional Ethics Committee a prospective observational study was carried out for the period of 12 months (Mar2019-Feb2019). All patients were followed up for ADRs which were evaluated for incidence, frequency, causality, severity, type of ADRs, drug classes, individual drug causing reaction, organ system affected, management and outcome of ADR. Causality was graded according to WHO-UMC scale. Severity according to Modified Hartwig and Siegel scale and preventability based on Modified Schumock and Thornton Scale. Organ System Affected by ADRs were categorized by using IBM Micromedex®.

Results and Discussion: A total of 210 ADRs were reported from 4721 patients during the study period with male (64.2%) predominance over female (35.7%). Most of the reported ADRs were of type A category (87.7%). The class of drug responsible for causing more ADRs was found to be anti-hypertensive (26%) and Diuretics (18%). The most common clinical manifestations of ADRs during the research period was hypokalaemia (11.4%). The most commonly affected organ system was Endocrine metabolic (20%). The suspected ADRs were assessed for their causality, it was revealed that (33.3%) were probable, (64.2%) were possible and (5%) were unlikely. The severity was assessed and observed that (52.8%) were mild, (39%) were moderate and (8%) severe. Preventability of ADR was shown (54.7%) reactions were definitely preventable and (36.1%) reactions were probably preventable and (9%) reactions were not preventable.

Conclusion: Involvement of a pharmacist in patient care can help in prevention and early detection of ADRs, also by detecting new and rare ADRs regulatory decision for the drugs can be made or altered.

Keywords: Adverse drug reaction, Pharmacovigilance, Causality assessment, Severity, Preventability, Spontaneous reporting

INTRODUCTION

Adverse drug reactions (ADRs) are the reaction which causes any unwanted/uncomfortable effects from medication resulting in physical, mental, and functional injuries. The WHO defines an ADR 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 the modification of physiologic function" [1].

An ADR is a type of ADE, whose cause can be directly attributed to a drug and its physiologic properties [8]. A main distinction between ADRs and ADEs is that ADRs occur despite appropriate prescribing and dosing, whereas ADEs may also be associated with inappropriate use of the drug or other confounders that occur during drug therapy but are not necessarily caused by the pharmacology of the drug itself [8].

ADRs experienced by hospitalized patients are associated with increased morbidity and mortality, prolonged hospitalization, and increased medical expense [5,6]. An increase in the

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number of drugs on the market, an aging population, and an upward trend in poly pharmacy are contributing factors to the prevalence of ADRs worldwide [2-8].

ADRs has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts. The actual incidence of ADRs may be even greater because some ADRs may be undetected or unreported [7,9].

Adverse drug reactions should be quickly identified and managed to limit their effects on the patient. For this reason, several studies have suggested that ADRs are a major public health concern [10,11-15].

CLASSIFICATION

The types of adverse reaction can be explained as "more common ADRs" including type A and B reactions; and "less common ADRs" which include type C, D and E reactions.

ADRs are classified into following categories:

- **Type-A:** It is the most common type (up to 70%) - Dose dependent, predictable from the known pharmacology of the drug, severity increases with dose. e.g., hypotension by beta- blockers, hypoglycaemia caused by insulin or oral hypoglycaemic or non-steroidal anti- inflammatory drugs induced gastric ulcers.
- **Type-B:** Rare, idiosyncratic, genetically determined, unpredictable, mechanisms are unknown, Serious, can be fatal; unrelated to the dose, e.g., hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol.
- **Type-C:** Reaction depends upon the chemical nature of the drug or excipient rather than pharmacological properties. Occurs as a result of continuous drug use. May be irreversible, unexpected, unpredictable, e.g., tardive dyskinesia by antipsychotics.
- **Type-D:** These reactions occur because of the physical nature of the drug formulation and/or the method of administration. Delayed occurrence of ADRs, even after the cessation of treatment, e.g., corneal opacities after thioridazine, ophthalmopathy after chloroquine, or pulmonary/peritoneal fibrosis by methyserzide.
- **Type-E:** These reactions are pharmacologically predictable and also known as withdrawal reactions. Occurs typically with the depressant drugs, e.g., hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypotension caused by alpha-blockers (Prazosin) or ACE inhibitors.
- **Type-F:** These reactions occur only in susceptible patients or individuals with genetically determined, inherited metabolic disorder. Results from the ineffective treatment (previously excluded from analysis according to WHO definition), e.g., accelerated hypertension because of inefficient control [16,17-20,50].

CLASSIFICATION OF ADR BASED ON ITS SEVERITY

The severity of a ADR can be categorized into 4 which are mild, moderate, severe and lethal.

1. Mild adverse reactions are those in which no antidote or treatment is required and also hospitalization is not required. Example - constipation caused by opioids.

2. Moderate adverse reaction requires treatment where doses may be modified, but there is no necessity for the therapy to be discontinued. Also, hospitalization may be prolonged for the patient with moderate adverse reaction. Example-venous thrombosis caused by hormonal contraceptive falls under this category.

3. Severe ADR, is potentially life threatening. It is recommended to discontinue the drug therapy and special treatment is required. Example-angioedema caused by enalapril.

4. Lethal ADR that may bring about death either directly or indirectly. Example- Hemorrhage due to anticoagulants [21,22-25].

OBJECTIVE

The aim of the study is to identify the occurrence, types, and management of ADRs, as well as to analyse the causal relationship, severity, and preventability of ADRs in tertiary care super- speciality hospital in Chennai, Tamil Nadu**.**

METHODOLOGY

The prospective observational study was carried out in Frontier Lifeline Hospital, Chennai. The study was enrolled after the clearance/approval from the Institutional Ethics Committee of Frontier Lifeline Hospital, Chennai [26-28].

STUDY DURATION

The study was carried out for the period of 12 months (Mar 2019-Feb2020).

INCLUSION CRITERIA

- Patient of either sex and any age group
- Patient admitted to hospital due to suspected ADR
- Hospitalise patient who developed ADRs
- ADR caused by contrast media

EXCLUSION CRITERIA

- Patient treated on out-patient department (OPD) basis
- ADR caused by medication error or adverse event
- Patient with drug abuse and medication non compliance
- Patient who developed ADR during the transfusion of blood or blood products and vaccines/medical device

METHODS

Two Pharmacovigilance associates from the regional ADR Monitoring Centre (AMC) were invited to sensitize all our health care professionals on Pharmacovigilance Programme of India, ADR and importance of reporting the same. The clinical pharmacist used to take part in the ward rounds along with physicians, and actively monitor for any ADRs including laboratory investigations if indicated clinically. On intimation of suspected ADRs by the physician or suspicion by clinical pharmacist, the ADR Reporting form was filled up and reported to Pharmacovigilance Programme of India via regional AMC within 24 hrs of time frame, the case was followed up for further details, All the data were kept confidential in respect of the national laws. Patient case notes/files and suspected ADR notification forms were used as main sources of data collection. All the documented ADRs were analyzed for incidence, types of ADRs, drug classes, and individual drug causing reaction, organ system affected, predisposing factors, management and outcome of ADRs. Organ system affected by ADRs were categorized using IBM Micromedex®, Causality assessment was done using WHO-UMC scale, Severity was assessed using modified Hartwig and Siegel, and while preventability was assessed using modified Schumock and Thornton scale [29-34].

To strengthen the awareness of the ADR reporting system posters were displayed. As a reminder, clinical pharmacist highlighted the importance of ADRs reporting system to the nurses during the weekly in- service nursing education class.

RESULTS

A total of 4,721 patient were admitted during the study period, among them 210 ADR was observed. Of 2,340 angiograms done, 15 developed ADR by Radioactive Contrast Media during the research period [35-38].

GENDER DISTRIBUTION

ADRs were detected from patient with a predominance of male gender (64.2%) over females (35.7%) as depicted in **Table 1 and Figure 1.**

Table 1. Gender wise distribution of adrs**.**

Gender	No of patient with ADRs	Percentage
Male	135	64.2%
Female	75	35.7%

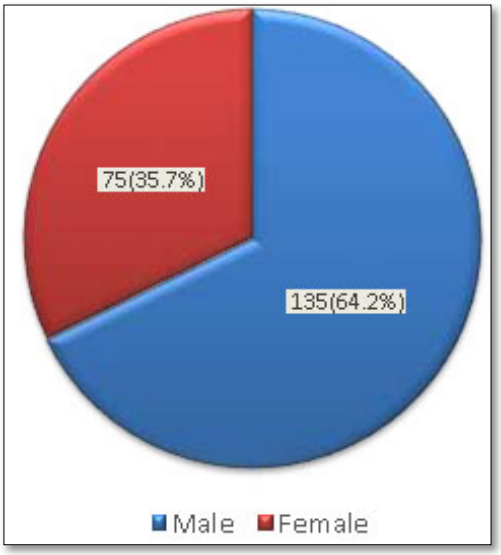

Figure 1. Gender wise distribution of ADRs.

AGE DISTRIBUTION

ADRs were frequently encountered in geriatric patients in the age group of 60-79 years old as shown in **Table 2, Figure 2.**

Table 2. Age wise distribution of ADRs**.**

Age	No of Patient with ADRs	Percentage
≤ 40	10	4.7%
40- 59	61	29%
60-79	118	56.1%
80 and above	21	10%

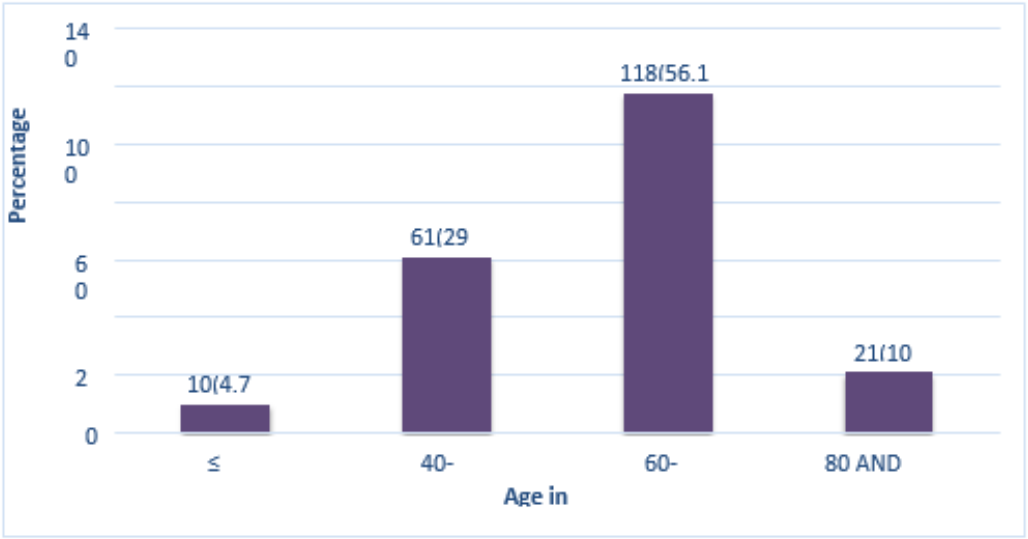

Figure 2. Age wise distribution of ADRs.

The primary objectives of this study are to assess the incidence of medication errors, to evaluate percentage of error prone abbreviations, to assess the incidence of adverse drug reactions.

DISTRIBUTION OF ADRS

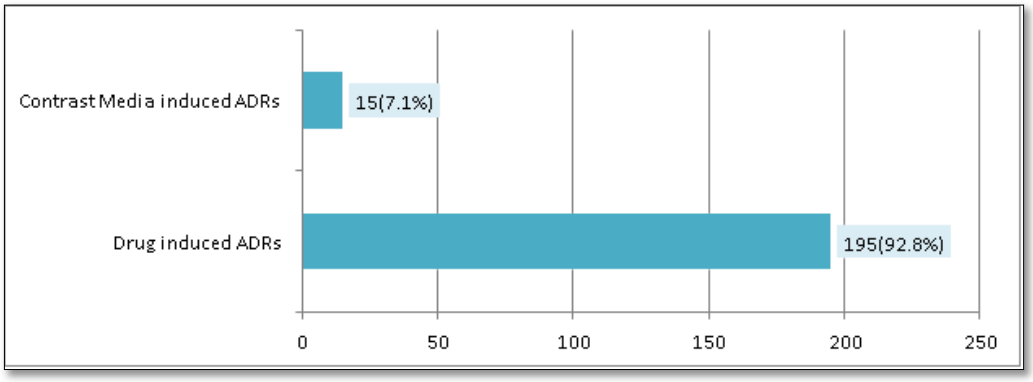

Figure 3: Distribution of ADRs.

Drug Utilization Pattern

Table 3, Figure 4 indicates that majority of ADRs was encountered by antihypertensive drugs (26%) followed by diuretics (18%), anticoagulants (17%), antibiotics (8.5%), contrast media (15%) [39-45].

Table 3. Drug Utilization Pattern.

Drug Classification	No of patient with ADRs	Percentage
Anti-hypertensive	55	26.1%
Diuretics	38	18%
Anti-coagulants	36	17.1%
Antibiotics	18	8.5%
Anti-arrhythmic	7	3.3%
Anti-epidemic	6	2.8%
Antiplatelet	6	2.8%
Antianginal	5	2.3%
Corticosteroids	4	1.9%
Others	23	10.9%
Contrast media	15	7.1%

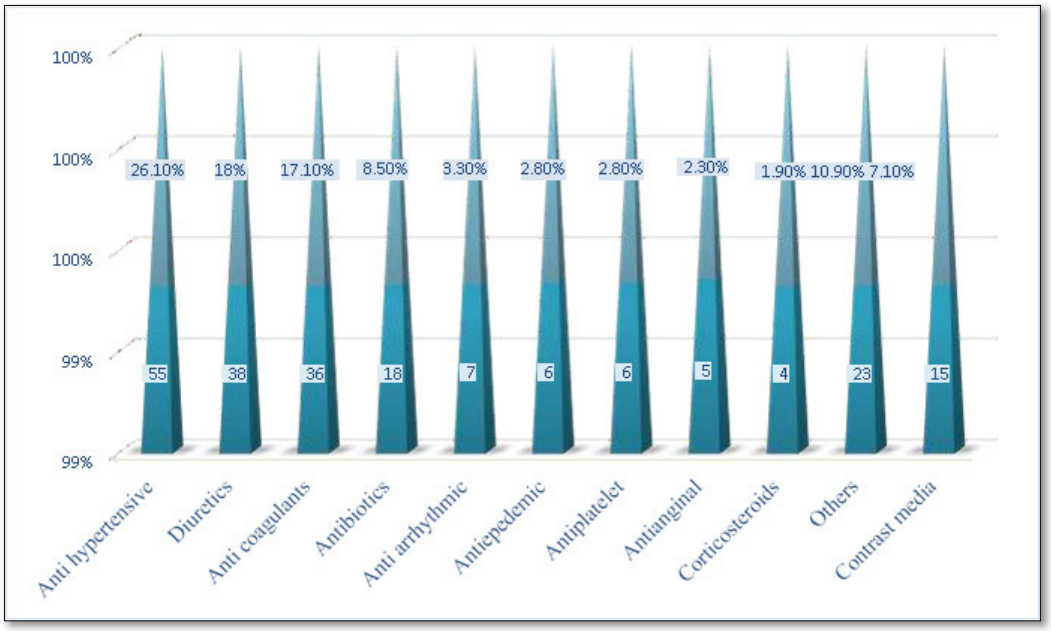

Figure 4. Drug Utilization Pattern.

ROUTE OF DRUG ADMINISTRATION

Most of the ADRs was commonly encountered in oral route of drug administration as depicted in **Table 4, Figure 5** [46-48].

Table 4. Route of drug administration.

Routes of Administration	No of patient with ADR	Percentage
ORAL	144	68.5%
IV	52	24.7%
IA	13	6.1%
SC	1	0.4%

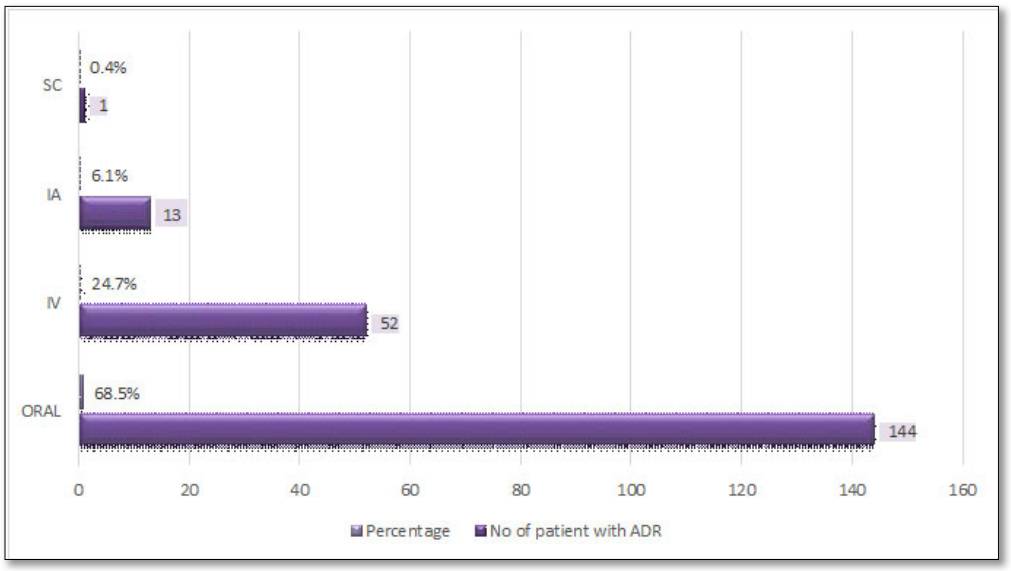

Figure 5. Route of drug administration.

TYPES OF ADR

Type A reaction (87.7%) accounted for majority of report compared to type B (6.6) and type F (6.1) as shown in **Table 5, Figure 6** [49].

Table 5. Types of ADR.

Type of ADR	No of patient with ADRs	Percentage
Type A	183	87.7%
Type B	14	6.6%
Type C	0	0
Type D	0	0
Type E	0	0
Type F	13	6.1%

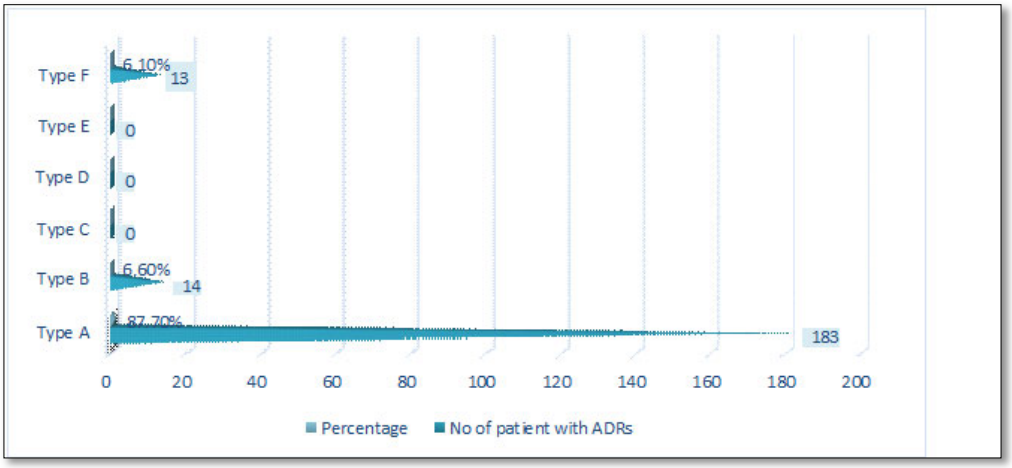

Figure 6. Types of ADR.

CLINICAL MANIFESTATION

The most common clinical manifestations of ADRs during the study was hypokalaemia (11.4%) followed by breathlessness (7.6%), hematuria (7.1%) pedal edema (6.1%) and others shown in **Table 6** [50-52].

Table 6. Clinical Manifestation of ADRs.

Clinical Manifestation	No of patient with ADRs	Percentage
Abdominal pain	1	0.4%
Alopecia	2	0.9%
Angioedema	1	0.4%
AV block	1	0.4%
Black stools	4	1.9%
Bloody stools	1	0.4%
Bradycardia	3	1.4%
Blood sputum	2	0.9%
Breathlessness	16	7.6%
Burning sensation	1	0.4%
Chest pain	4	1.9%
Constipation	2	0.9%
Severe Cough	3	1.4%
Cough and Breathlessness	1	0.4%
Diarrhoea	8	3.8%
Ecchymotic rash	3	1.4%
Edema	1	0.4%
Elevated liver Enzyme	3	1.4%
Facial palsy	1	0.4%
Gastritis	3	1.4%
Giddiness	9	4.2%
Gum bleeding	4	1.9%
Gynecomastia	1	0.4%
Severe headache	2	0.9%
Heart block	1	0.4%
Hematuria	15	7.1%
Hyperglycemia	2	0.9%
Hyperkalemia	9	4.2%

Hypokalemia	24	11.4%
Hyponatremia	1	0.4%
Hypotension	5	2.3%
Itching	9	4.2%
Left thigh Haematoma	1	0.4%
Leukopenia	1	0.4%
GI bleeding	1	0.4%
Maculopapular Erythematous	1	0.4%
Muscle cramp	2	0.9%
Myelosuppression	1	0.4%
Nasal bleeding	2	0.9%
Nausea and Vomiting	1	0.4%
Double vision	1	0.4%
Oral candidiasis	1	0.4%
Palpitation	3	1.4%
Pedal edema	13	6.1%
Rashes	2	0.9%
Pulmonary edema	2	0.9%
Rectal bleeding	1	0.4%
Rigors and chills	1	0.4%
Severe Vomiting	7	3.3%
Sinus bradycardia	1	0.45%
Swelling	3	1.4%
Symptomatic Bradycardia	1	0.45%
Syncope	4	1.9%
Thrombocytopenia	3	1.4%
Vertigo falsy Syndrome	1	0.4%
Wheezing	1	0.4%
Fever	3	1.4%
Hypertension	1	0.4%
Nephropathy	8	3.8%

WHO CAUSALITY ASSESSMENT SCALE

Causality assessment was done using WHO-UMC scale. The assessment showed that out of 210 ADRs, (33.3%) were probable, (64.2 %) were possible, (5%) were unlikely as shown in **Table 7, Figure 7**.

Table 7. WHO Causality assessment scale.

WHO UMC scale	No of patient with ADR	Percentage
Certain	0	0
Probable	70	33%
Possible	135	64%
Unlikely	5	2%
Unclassified	0	0
Unclassifiable	0	0

SEVERITY ASSESSMENT BY MODIFIED HARTWIG AND SIEGAL SCALE

According to the modified Hartwig and Siegel scale most of the ADRs reported in the study were mild (52.8%) in nature followed by (39%) were moderate and (8%) were severe as depicted in **Table 8, Figure 8.**

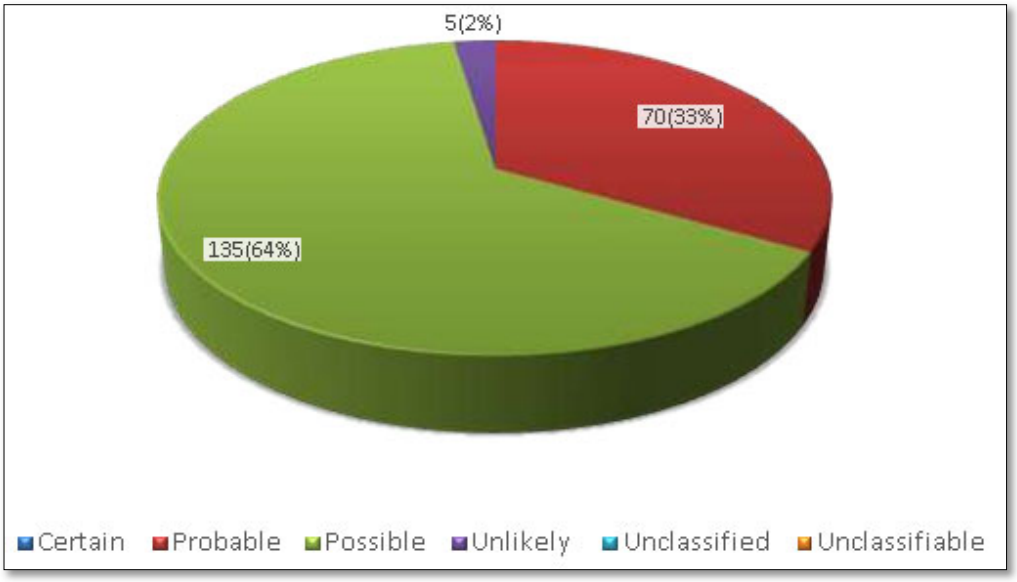

Figure 7. WHO Causality assessment scale.

Table 8. Severity assessment by modified Hartwig and Siegal scale.

Condition	No of patient with ADRs	Percentage
Mild	111	52.8%
Moderate	82	39%
Severe	17	8%

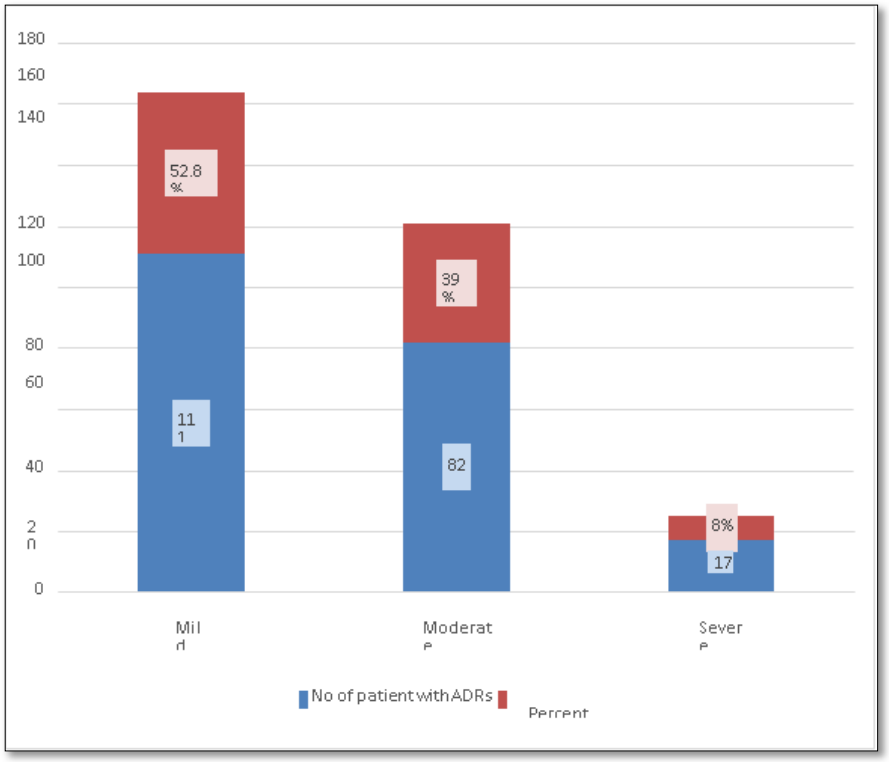

Figure 8. Severity assessment by modified Hartwig and Siegal scale.

Preventability Assessment by Modified Schumock and Thornton Scale

Preventability assessment using modified Schumock and Thornton revealed that 115 (54.7%) ADRs were definitely preventable, 76 (36%) ADRs were probably preventable, 19 (9%) were not preventable as shown in **Table 9, Figure 9**.

Table 9. Preventability Assessment by Modified Schumock and Thornton scale.

Condition	No of patient with ADR	Percentage
Definitely Preventable	115	54.7%
Probably Preventable	76	36%
Not preventable	19	9%

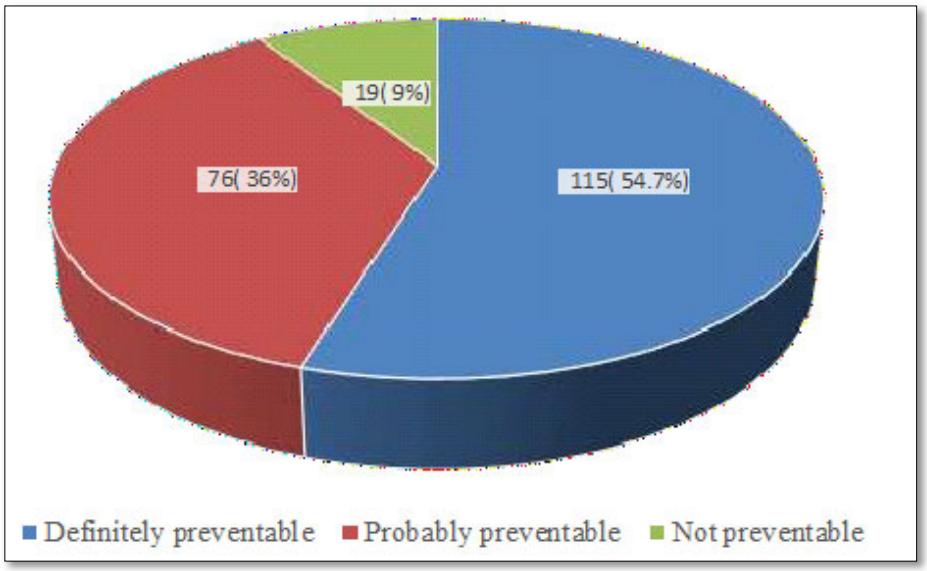

Figure 9. Preventability Assessment by Modified Schumock and Thornton scale.

ORGAN SYSTEM AFFECTED DUE TO ADRS

In our study we observed that several Organ systems was affected due to ADRs and among them most affected organ system was endocrine metabolic (20) as shown in **Table 10, Figure 10**.

Table 10. Organ system affected due to ADRs

Organ system affected due to ADR	No of patient with ADRs	Percentage
Endocrine metabolic	42	20%
Hematologic	37	17.6%
Cardiovascular	32	15.2%
GI system	21	10%
Respiratory	20	9.5%
Dermatologic- hypersensitivity	16	7.6%
Neurologic	12	5.7%
Renal	8	3.8%
Hepatic	3	1.4%
Others	19	9%

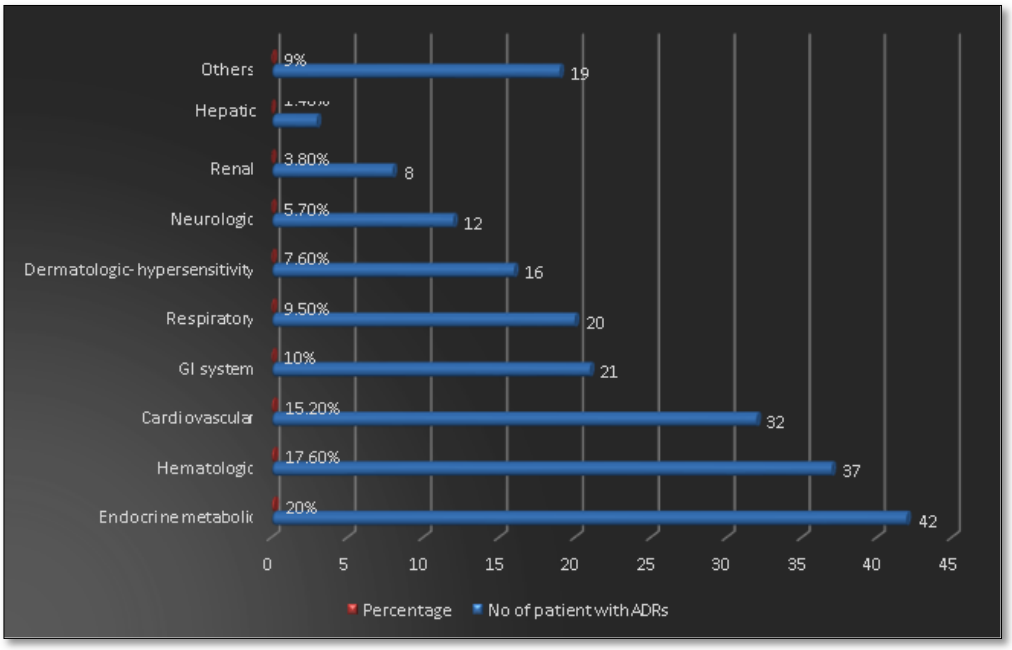

Figure 10. Organ system affected due to ADRs.

MANAGEMENT OF ADRS

As a part of management in 87 cases the drug was withdrawn, no changes were done in 16 cases, dose altered in 28 cases and symptomatic treatment was provided in 38 cases as shown in **Table 11, Figure 11.**

Table 11. Management of ADRs.

Management of ADRs	No of patient with ADRs	Percentage
Dose altered	28	13.3%
Drug withdrawn	87	41.2%
Drug withhold	41	19.5%
No change	16	7.6%
Symptomatic Treatment	38	18%

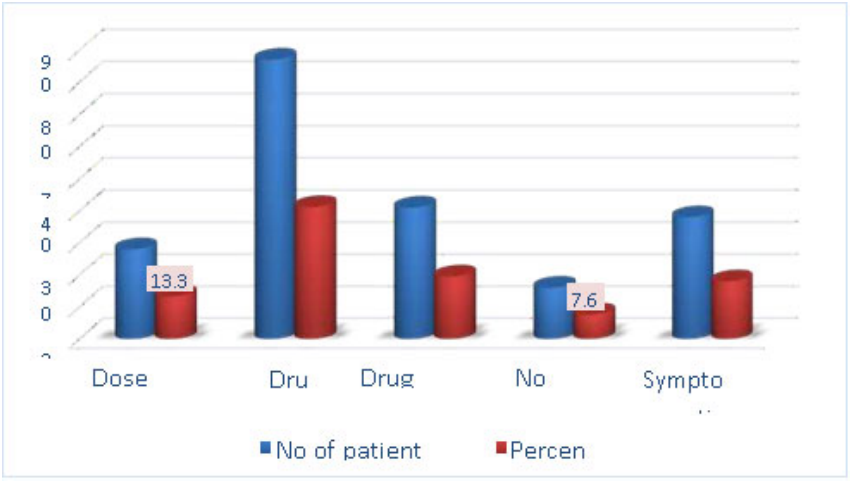

Figure 11. Management of ADRs.

OUTCOME OF ADRS

Adverse drug reaction encountered were treated and the final outcome was measured. About 205 ADRs were recovered and 5 are not known as depicted in **Table 12, Figure 12.**

Table 12. Outcome of ADRs.

Outcome	No of patient with ADRS	Percentage
Recovered	205	97.6%
Unknown	5	2.3%

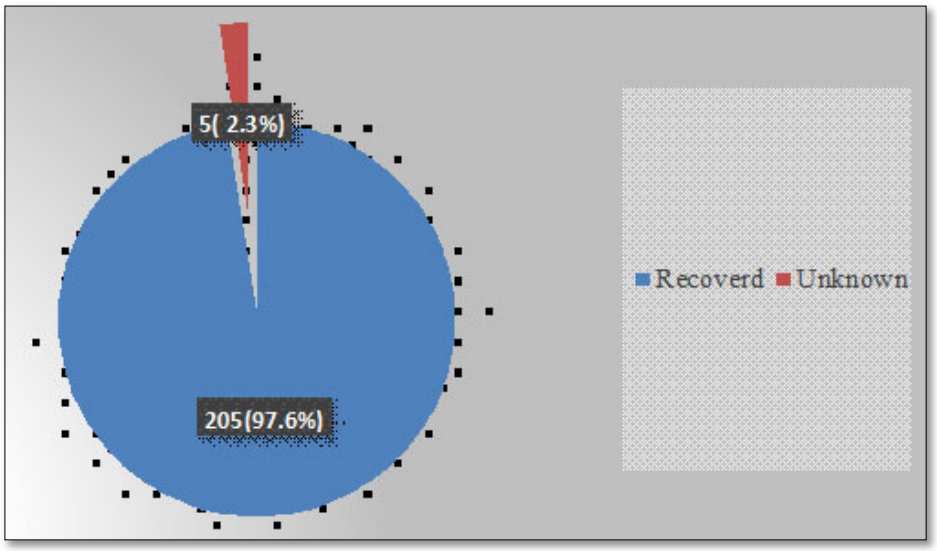

Figure 12. Outcome of ADRs.

HOSPITAL STAY DUE TO ADRS

Table 13, Figure 13 indicates that among 210 reported ADRs 134 cases, were stayed less than 2 days followed by 63 cases, duration of stay was between 3 to 5 days and 13 cases, were stayed more than 6 days.

Table 13. Hospital stay due to ADRs.

No of days	No of patient with ADRs	Percentage
< 2 days	134	63%
3 to 5 days	63	30%
> 6 days	13	6%

DISCUSSION

A total of 4,721 patients were admitted during the study period, among them 210 ADRs were detected from patient with a predominance of male gender (64.2%) over females (35.7%). Majority of patients in the study was also males [53,54]. **Raujo lobo, *et al*.**, have found the incidence of ADRs is unrelated to gender which supports our studies that ADRs did not differ significantly between men and women [54]. ADRs were frequently encountered in geriatric patients in the age group of 60-79 years as shown in **Table 1**. This group of patient has a very high risk of developing ADR due to age-related changes in pharmacokinetics and pharmacodynamics, increasing burden of comorbidity, polypharmacy, inappropriate prescribing and suboptimal monitoring of drugs. Which is in accordance with the study of **Beijer, *et al*.**, and **Priyadharshini, *et al*** [37,55]. In our study majority of ADR

was encountered by antihypertensive drugs (26%) followed by diuretics (38%), anticoagulants (17%), antibiotics (8.5%), contrast media (15%). This study was accordance with **Godbharle SB, *et al*** and **Mjorndal *et al*** [56]. In the study performed by **Mjorndal *et al***., in a clinic of internal medicine at a Swedish university hospital, cardiovascular drugs were the most common class of drugs involved in the induction of ADRs. Thus, selection of appropriate medicines for patients, enhancing patient adherence with the therapy by selecting medicines of lesser ADR profile, reducing unnecessary economic burden to the patients due to unwanted effects of the therapy could prevent the patient from life threatening complication and hospitalization associated with medication.

In our study majority of ADR was developed by oral administration 144(68.52%). Type A reaction (87.7%) accounted for majority of report compared to type B (6.6) and type F (6.1) which constitute approximately 80% of adverse drug reactions these ADRs are potentially avoidable and often predict-able, which is mainly due to consequence of the drug's primary pharmacological effect. The most common clinical manifestations of ADRs during the study period was hypokalemia (11.4%) followed by breathlessness (7.6%), hematuria (7.14%), pedal edema (6.19%).

In our study observed that several Organ systems was affected by medication and among them majority was endocrine metabolic (20) followed by hematology (17), cardiovascular (15), GI system (10) and others. As a part of management in 87 cases the drug was withdrawn, no changes were done in 16 cases, dose altered in 28 cases and symptomatic treatment was provided in 38 cases. Adverse drug reactions encountered were treated and the final outcome was measured. About 205 ADRs were recovered and 5 are not known. 134 cases duration of stay was less than 2 days followed by 63 cases stayed between 3 to 5 days and 13 cases stayed more than 6 days.

In order to intensify the validity of the study, causality assessment was done using **WHO-UMC scale**. The assessment showed that out of 210 ADRs, (33.3%) were probable, (64.2 %) were possible, (5%) were possible. These findings are similar to the study carried out by **Javedh Shareef *et al*** and **Keezhipadathil J *et al*** [1,53].

On the evaluation of the severity of ADRs by the **Hartwig and Siegel severity assessment scale**, it was evident that most of the ADRs reported in the study were mild (52.8%) in nature followed by (39%) were moderate and (8%) were severe. No lethal outcomes were observed or produced during the study period and these findings are similar to the previous studies done by **Arulmani *et al***., and **Shrivastava *et al*** [50,51].

Assessment of the preventability of the ADRs using modified Schumock and Thornton scale revealed that 115 (54.7%) ADRs were definitely preventable. This study is accordance with **Keezhipadathil J *et al*** [1].

CONCLUSION

The present prospective observational study showed that monitoring and reporting of ADRs plays a vital role in medical events. This study shows many factors like age, gender, drug class and drugs with ADR. By implementing the ADR reporting and monitoring system, the pharmacist can easily identify and quantify the risks associated with the use of drugs which promotes drugs safety and better patient care, among health care professionals. Involvement of pharmacist in patient care can also help to detect new and rare ADRs. Monitoring and reporting of ADRs among healthcare professionals should be encouraged as well as creating awareness of ADR reporting among patients can improve quality of life and prevent hospitalization.

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