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A Prospective Study on Adverse Drug Reactions in Inpatients of General Medicine Department in a Tertiary Care Hospital- A clinical Pharmacist-led Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors KCBR, SH and VM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors GS and PN managed the analyses of the study. Author UK managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The present study was carried out to determine the incidence of Adverse Drug Reactions (ADRs) in general medicine department and to assess and analyze the causality, severity, and preventability of ADRs. A prospective observational study was conducted in the general medicine department for six months. All patients receiving drug therapy are considered and are selected based on the inclusion criteria. Patient demographic details like age, gender, diagnosis, past medical history, concomitant medications, etc., are recorded from the patient data gathering form. The causality assessment is accomplished using Naranjo and WHO scales. The severity is carried out using the

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Modified Hartwig and Siegel scale. The preventability evaluation is accomplished using the Modified Schmock and Thornton scale. The study included 385 patients were between the age group of 18 years and, out of which 34 patients developed adverse drug effects including female and male. Patients between the age group of 40-50 years (18.1%) developed a high incidence of ADRs. The causality was assessed using Naranjo's causality assessment scale, 44.1% reactions were probable; 29.4% reactions were certain, 23.5% reactions were possible and 2.9 % reactions were conditional. When the reactions were assessed most of them were assessed 55.1% were moderate and 61.8% were probably preventable. Appropriate observation of the drug effect is essential to ensure the safety of the patient. This also will have the advantage of reducing the incidence of the ADRs, thus deplete the complications and helps to improve the quality of life of the patients.

Keywords: Adverse drug reaction; causality; severity; preventability; naranjo scale.

1. INTRODUCTION

A drug may be defined as a chemical substance that is used in the treatment, cure, prevention or diagnosis of a disease or used to enhance physical or mental well-being. The WHO defines a drug as "any substance or product that is used or intended to be used to modify or explore the physiological system, or pathological state in the benefit of the recipient. An adverse drug reaction may be defined as "any harmful or unpleasant reaction that may be resulting from an intervention which is related to the use of a medicinal product, which predicts a hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regimen or withdrawal". ADR monitoring is still in the earlies stages in India where reporting is rarely performed. [1].

Underreporting has been the major challenge either in voluntary reporting or spontaneous reporting and it is common even in developed countries with a functional ADR reporting system. This may be due to various reasons like lack of knowledge, increase in the workload etc. A method to deal with this problem is to increase awareness about the advantages of ADR reporting. In the global scenario, the responsibility of ADR reporting is comparatively high and is responsible for considerable morbidity, mortality, prolonged hospitalization and increased cost. [2]

Adverse drug effects have a substantial negative effect on both health ad health care costs. In India government hospitals serves as the main source in creating an appropriate database, since the majority of the population prefers government hospitals. [3]

Adverse drug effects are the fifth leading cause of death and are therefore responsible for the hospitalization all over the world. [4] There are definite risk factors for ADR, which can be classified into four as patient-related, drug-related, disease-related and social-related. [5] Awareness among the health care professional is necessary to win the goals of pharmacovigilance. [6] Predisposing factors of ADR include age, polypharmacy, gender, immune system and pharmacogenetics. ADRs have a substantial effect on the health of the community as well as on health care costs. ADRs are the biggest responsibility of the health care provider and may require supplementary study and drug therapies for the treatment of those adverse reactions caused to the patient. The use of drugs is increasing day by day with the occurrence of new diseases, use of multiple drugs can lead to a variety of adverse drug reactions. It is evident that adverse drug reactions unfavorably affect the patients' quality of life and thus can result in loss of patient's confidence in the health care system which may in turn result in medication adherence. [7] To make the drugs safer, their safety profiles are studied before their commercial release, with further adverse drug reaction monitoring. An important drawback of a clinical trial is that adverse effect that occurs within a limited duration of a study is reported. Consistent and compulsory training of health care professionals on reporting the ADRs is needed, thus attaining appropriate signals. [8]

2. MATERIALS AND METHODS

A prospective observational study was conducted over six months in the General Medicine Department of Justice K.S Hegde Charitable Hospital, Deralakatte, Mangaluru. A suitable data collection form and ADR reporting form was designed to collect and document the data. During the study period, the case sheets of hospitalized patients of the general medicine department were reviewed on daily basis. The

patient who may develop an ADR during the hospital stay and those who are admitted due to an ADR was enrolled in the study. When suspected ADRs are found, they are bought to the notice of the concerned physician and the suitable information involving socio-demographic details of the patient, diagnosis, laboratory test details, details of drugs used during the hospitalization (name of drug, dosage form, frequency, route of administration and duration of treatment), the reaction to the drug and its management was recorded in the patient data collection form and ADR monitoring and reporting form.

At the end of the study, the patient data collection form and ADR reporting form are used to analyze the causality, severity and preventability of the reaction using respective scales. The ADRs were subjected to causality assessment using the WHO probability scale (definite, probable, possible, unclassifiable, unlikely, conditional) and Naranjo's scale (definite, probable, possible, unlikely). The severity level is assessed using the Hartwig's severity assessment scale (mild, moderate, severe) and further the ADRs were assessed for Preventability using Modified Schumock and Thornton's Criteria (definitely preventable, probably preventable, not preventable)

2.1 Statistical Analysis

Qualitative characteristics like patient medication history, comorbidities, diagnosis, drugs were reported using frequency/ percentage. Categorical data like age, causality, probability, severity and preventability were expressed as a percentage and corresponding frequency. Data obtained was entered in Microsoft Excel® spreadsheet and analyzed by using SPSS version 16.0.

3. RESULTS

3.1 Demographic Details of the Patient

3.1.1 Age-wise distribution of the patients with incidence of ADR

The patients enrolled in this study comes under the age group 18-90 years. The incidence of ADR was high in patients belonging to the age group 41-50 years while compared to other age groups. Table 1 shows the age-wise distribution of patients with the incidence of ADRs.

3.1.2 Gender wise distribution of the patients with the incidence of ADR

Among the 385 patients enrolled 139 were females and 246 were males. The maximum number of ADRs were found in females (9.4%) while compared to males (8.5%). The details are represented in Table 2.

3.2 Comorbidities Among Patients

During the study, 351 diseases were present from 385 cases. The most common diseases were found to be hypertension (27.2%), followed by diabetes mellitus (18.9%), urinary tract infections (5.97%), hepatitis (5.71%), lower respiratory tract infections (4.41%). The details of the distribution of diseases in these patients with or without ADRs are given in Table 3.

Table 1. Age wise distribution of the patients with the incidence of ADR

Age group (years)	Total number of patients (n = 385)	Number of patients with ADRs (n = 34)
18-30	80 (20.7%)	7 (8.8%)
31-40	64 (16.6%)	6 (9.4%)
41-50	70 (18.1%)	10 (14.3%)
51-60	61 (15.8%)	7 (11.5%)
61-70	66 (17.1%)	1 (1.5%)
71-80	39 (10.1%)	3 (7.7%)
81-90	5 (1.2%)	-

Table 2. Gender wise distribution of the patients with the incidence of ADR

Gender	Total number of patients (n = 385)	Number of patients with ADRs (n = 34)
Male	246 (63.8%)	21 (8.5%)
Female	139 (36.1%)	13 (9.4%)

Table 3. Comorbidities among patients

Diseases	With ADRs (n = 34)	Without ADRs (n = 286)
Hypothyroidism	-	5 (1.7%)
Ischemic heart disease	1 (2.9%)	15 (5.2%)
Type II DM	5 (14.7%)	68 (23.8%)
Hypertension	9 (26.5%)	96 (33.6%)
Chronic liver disease	-	22 (7.7%)
Epilepsy	-	1 (0.35%)
Peptic ulcer	-	4 (1.4%)
Chronic obstructive pulmonary disease	1 (2.9%)	31 (10.8%)
Tuberculosis	3 (8.8%)	10 (3.5%)
Seizure	2 (5.9%)	7 (2.4%)
Viral hepatitis	1 (2.9%)	21 (7.0%)
Cerebral venous thrombosis	1 (2.9%)	-
Auto immune haemolytic anaemia	1 (2.9%)	-
Depressive disorder	1 (2.9%)	3 (1.05%)
Haemoptysis	1 (2.9%)	-
Congestive cardiac failure	1 (2.9%)	1 (0.35%)
Rheumatoid arthritis	-	1 (0.35%)
Hyperthyroidism	-	1 (0.35%)

3.3 Drugs Responsible For ADRS

The class of drugs which commonly caused ADRs were antibiotic (26.2%), corticosteroids (11.7%), antihypertensive (11.6%), antipsychotics (11.6%), anticoagulants (11.6%), followed by antiemetic (5.8%) and antitubercular drugs (5.8%). The details of drugs causing ADRs are given in Table 4.

3.4 Clinical Patterns of ADRS

The most commonly caused ADR was constipation (32.3%) followed by pedal edema (17.6%), rashes (14.7%), dizziness (14.7%), vomiting (14.7%) and cough (14.7%). The different types of ADRs are mentioned in Table 5.

3.5 Suspected Drugs with ADRS

The commonly used drugs responsible for ADRs were Constipation (32.3%) followed by pedal edema (17.6%). The suspected drugs along with ADRs are given in Table 6.

3.6 Assessment of ADRS

3.6.1 Naranjo's causality assessment of ADRs

The Naranjo's causality scale shows that the majority of the ADRs were probable 22 (64.7%), considering that 8 (23.5%) reactions were possible and 4 (11.80%) reactions were definite. The assessment of ADR by Naranjo's scale is illustrated in Fig. 1.

3.6.2 WHO probability

According to WHO causality assessment, it was found that the majority of reactions were probable 15 (44.1%), while 10 (29.4%) reactions were certain, 8 (23.5%) reactions were possible and 1 (2.9%) reaction was conditional. The below Table shows the ADRs assessed by WHO causality scale and is sketched in Fig. 2.

3.6.3 Severity assessment of ADRs

Hartwig severity scale was used to assess the severity of the suspected ADRs, which was found that 15 (44.1%) reactions were mild, whereas 19 (55.9%) reactions were moderate. The outline of the severity levels is given in Table 7.

3.6.4 Preventability of ADR

To assess the preventability of suspected ADR, Modified Schumock and Thornton Criteria was used. Among which 21 (61.8%) reactions were probably preventable compared to 13 (38.2%) reaction which are definitely preventable. The details concerning the preventability assessment of ADRs is illustrated in Fig. 3.

Table 4. Drugs responsible for ADRS

Drug Class	Drug Name	ATC Code	Frequency
Antibiotics	Amikacin	D06AX12	1 (2.9%)
	Amoxicillin + Clavulanic acid	J01CR02	4 (11.7%)
	Ceftriaxone	J01DD04	1 (2.9%)
	Sulfamethoxazole + Trimethoprim	J01EE01	3 (8.8%)
	Vancomycin	J01XA01	1 (2.9%)
	Azithromycin	JA1FA01	1 (2.9%)
	Doxycycline	J01AA02	1 (2.9%)
	Cefixime	J01DD08	-
Anti-Diabetic	Insulin	A10AD01	2 (5.8%)
	Glibenclamide	A10BB01	-
	Metformin	A10BA02	-
	Glimepiride+Metformin	A10BB12 + A10BA02	-
	Glimepiride	A10BB12	-
	Glipizide	A10BB07	-
Anti-Hypertensive	Losartan	C09CA01	-
	Telmisartan	C09CA07	1 (2.9%)
	Olmesartan	C09CA08	-
	Amlodipine	C08CA01	1 (2.9%)
	Cilnidipine	C08CA14	2 (5.8%)
Xanthine Oxidase Inhibitors	Febuxostat	M04AA03	1 (2.9%)
	Allopurinol	M04AA01	-
Anti-Psychotics	Desvenlafaxine	N06AX23	2 (5.8%)
	Lorazepam	N05BA06	2 (5.8%)
	Olanzapine	N05AH03	-
	Lithium	N05AN01	-
Analgesics	Acetaminophen+Tramadol	N02AJ13	1 (2.9%)
Anti-Coagulants	Warfarin	B01AA03	2 (5.8%)
	Heparin	C05BA53	2 (5.8%)
Corticosteroids	Dexamethasone	C05AA05	1 (2.9%)
	Prednisolone	S02BA03	3 (8.8%)
Anti-Emetics	Ondansetron	A04AA01	2 (5.8%)
Electrolyte Replenisher	Potassium Chloride	A12BA51	1 (2.9%)
Anti- Tubercular Drugs	Isoniazid+Rifampicin	J04AC01+J04AM05	2 (5.8%)
	Pyrazinamide+Ethambutol	J04AK01+J04AK02	-

Table 5. Different types of ADRS

ADRs	ICD Code	Frequency (n = 34)
Gastritis	K29.70	1 (2.9%)
Constipation	K59.00	11 (32.3%)
Thrombocytopenia	D69.6	3 (8.8%)
Dizziness	R42	5 (14.7%)
Hepatitis	B19	2 (5.8%)
Vomiting	R11.10	5 (14.7%)
Hypoglycemia	E16.2	2 (5.8%)
Pedal Edema	R60.9	6 (17.6%)
Cough	R05	1 (2.9%)
Rashes	R21	5 (14.7%)
Uveitis	H20.00	1 (2.9%)
Itching	L29.9	1 (2.9%)

Nausea	R11.0	1 (2.9%)
Weakness	R53.1	1 (2.9%)
Abdominal Pain	R10.9	1 (2.9%)
Erythema	L53.9	1 (2.9%)
Headache	R51	1 (2.9%)
Insomnia	G47.00	1 (2.9%)
Diabetes Mellitus	E11.9	1 (2.9%)

Table 6. Suspected drugs with ADRS

Drug	Pattern of ADR	Frequency (n = 34)
Insulin	Hypoglycemia	2 (5.8%)
Telmisartan	Cough	1 (2.9%)
Amlodipine	Pedal edema	1 (2.9%)
Cilnidipine	Pedal edema	2 (5.8%)
Amikacin	Hepatitis	1 (2.9%)
Amoxicillin + Clavulanic acid	Constipation	4 (11.7%)
Ceftriaxone	Rashes	1 (2.9%)
Sulfamethoxazole+Trimethoprim	Uveitis	1 (2.9%)
	itching	1 (2.9%)
	periorbital edema	1 (2.9%)
Vancomycin	Vomiting	1 (2.9%)
Azithromycin	Nausea and vomiting	1 (2.9%)
Doxycycline	Constipation	1 (2.9%)
Febuxostat	Rashes	1 (2.9%)
Desvenlafaxine	Nausea and vomiting	2 (5.8%)
Lorazepam	Constipation	1 (2.9%)
	Dizziness	1 (2.9%)
Acetaminophen + Tramadol	Constipation	1 (2.9%)
Warfarin	Pedal edema	2 (5.8%)
Heparin	Thrombocytopenia	2 (5.8%)
Dexamethasone	Rashes	1 (2.9%)
Prednisolone	Insomnia	1 (2.9%)
	Gastritis	1 (2.9%)
	Headache	1 (2.9%)
Ondansetron	Constipation	2 (5.8%)
Potassium Chloride	Erythema	1 (2.9%)
Isoniazid + Rifampicin	Vomiting	2 (5.8%)

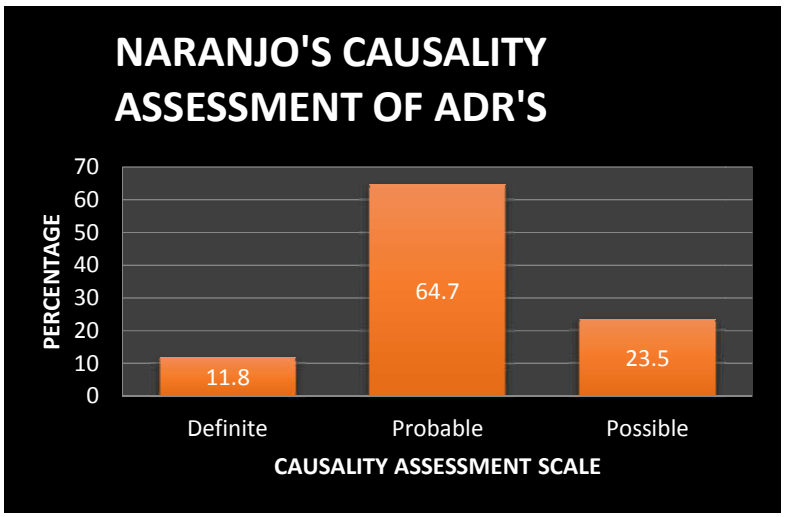

Fig. 1. Naranjo's causality assessment of ADRs

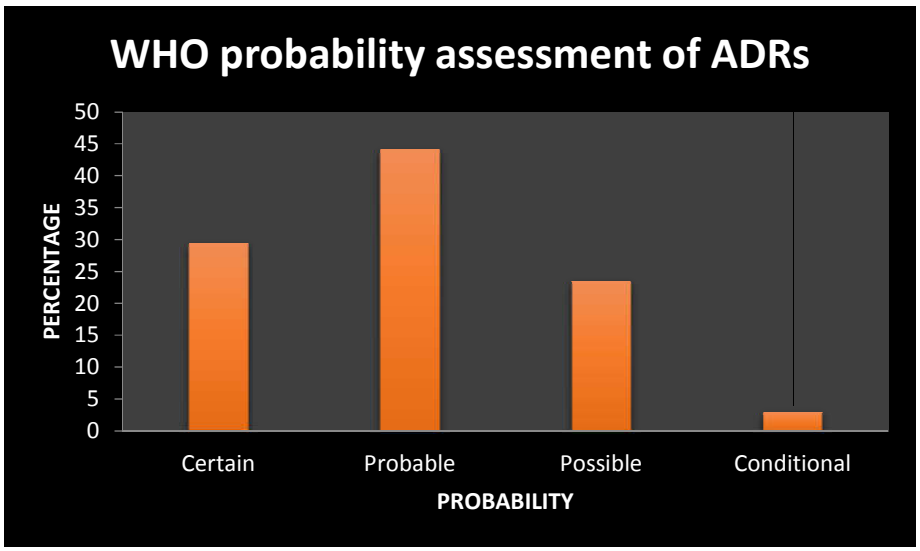

Fig. 2. WHO probability scale assessment of ADRs

Table 7. Severity assessment of ADRs

Severity		Number of ADRs (n = 34)	Percentage
MILD	LEVEL 1	-	-
	LEVEL 2	15	44.1%
MODERATE	LEVEL 3	14	41.2%
	LEVEL 4	5	14.7%
SEVERE	LEVEL 5	-	-
	LEVEL 6	-	-

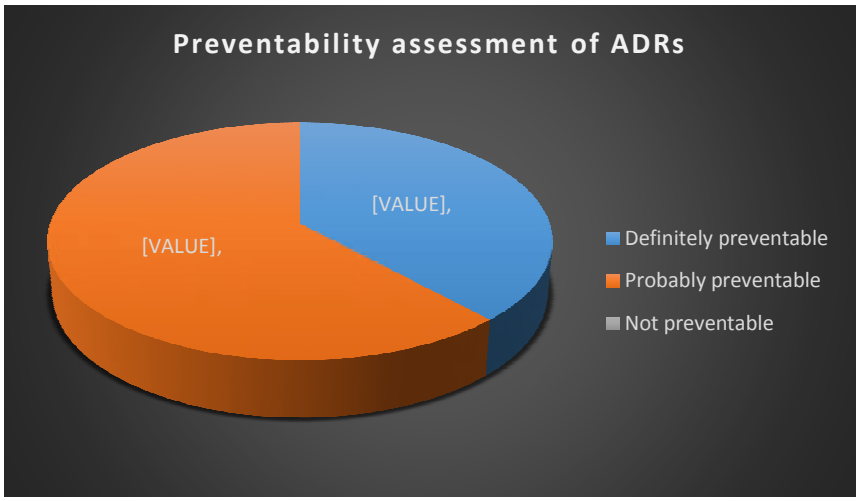

Fig. 3. Preventability assessment of ADRs

3.7 Management Of ADRS

From the 34 identified ADRs, management of these ADRs was done through withdrawal of the drug in 17 (47.2%) cases. There was no change in 11 (30.5%) cases of suspected drugs and 6 (16.6%) cases the dose was altered. The details on the management of ADR are schematically represented in Fig. 4.

3.8 Treatment Of ADRS

There was no need for treatment in 16 (47.05%) cases while there was a need for specific treatment in 12 (35.2%) cases and in 6 (17.6%) patients there was the need for symptomatic treatment. The treatment of ADRs is schematically given in Fig. 5.

3.9 Outcome of Management of ADRS

This study shows that 26 (76.4%) of reactions were recovered while in 8 (23.5%) cases, the symptoms were continued. The details concerning the outcome are depicted below in Fig. 6.

3.10 Dechallenge of ADRS

Definite improvement was shown in 11 (61.1%) cases and there was no dechallenge in 13 (36.1%) and 2 (5.55%) were unknown. The details are given below in Fig. 7.

3.11 Rechallenge of ADRS

There was no rechallenge in 28 (82.3%) cases. There was recurrence of symptoms in 3 (8.82%) cases and 3 (8.8%) cases were unknown. Rechallenge of ADRs are shown in Fig. 8.

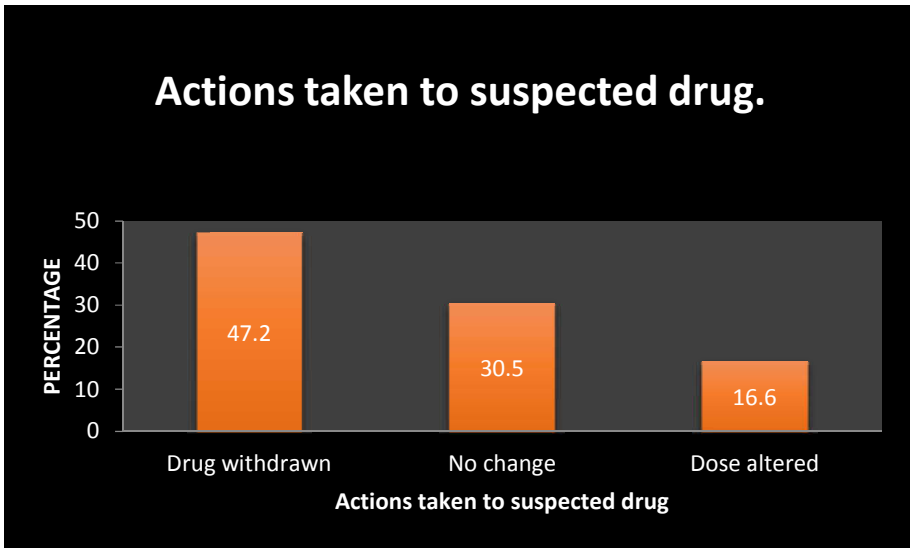

Fig. 4. Actions taken to suspected drug

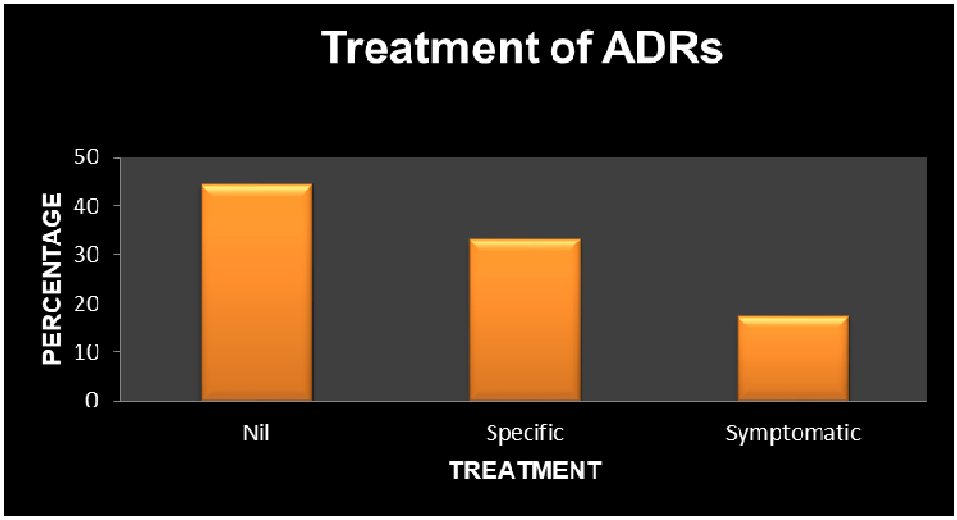

Fig. 5. Treatment of ADRs

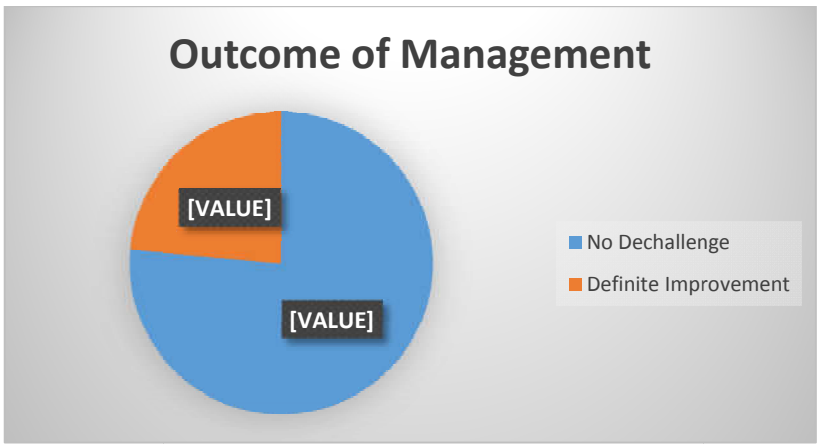

Fig. 6. Outcome of management of ADR

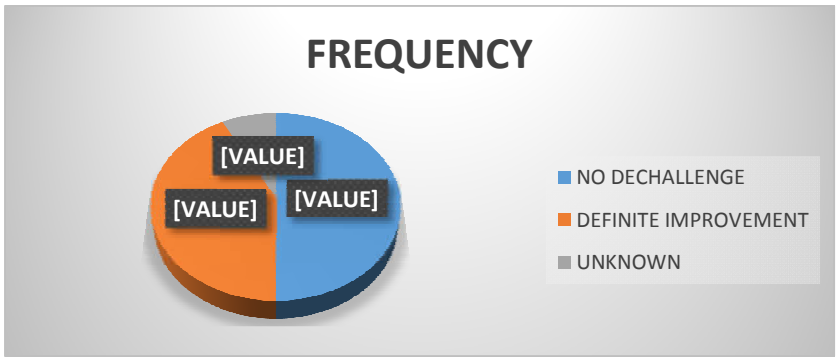

Fig. 7. Dechallenge of ADRs

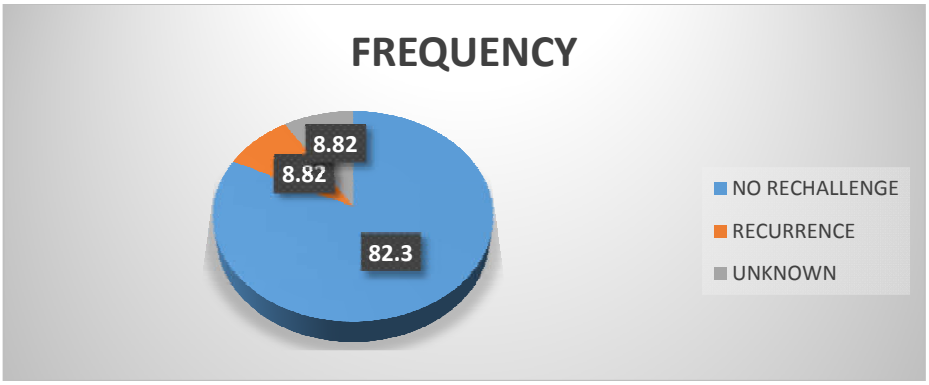

Fig. 8. Rechallenge of ADRs

4. DISCUSSION

Adverse drug reaction is any noxious and unwanted problems that occur at a dose which that is used in patients for prophylaxis. According to the studies conducted, most of the ADRs were attributed from the department of general medicine. The major challenge in spontaneous reporting of ADR is underreporting might be as a result of an increase in workload, of opinion that reporting will not lead to any improvement and lack of knowledge. The details attained from the study will be favorable for the physician and other health care providers in choosing and restricting the use of suspected drugs.

In this study the incidence of ADRs was found to be 8.8% and related reports were noted in the

study conducted by Akhideno PE et al. [9] reported an incidence of 6.5%. The patients under the age group of 40-50 years were found to be more susceptible to ADRs (14.3%). 6.8% of patients with ADR were detected in the age group of 3040 years. Because of the large number of study subject compared to other study it showed a more number of ADRs compared to other study. The patients between the age group of 18-30 years showed 8.8% reactions. In the age group of 50-60 years the ADR detected was 11.5%. This study was similar to a study carried out by et al. Morales-Rios O [10] However, in the study conducted by Niwani PO et al. [11] it was observed that patients aged above 65 years had higher occurrence of ADRs (69.6%). The incidence of ADRs observed in females and males was similar in this study. This result is similar to that of the study conducted by Venkatasubbiah M et al., Adhikari A et al. [12,13] Whereas, in the study conducted by Amrita P et al. [14] exhibited that there is a higher occurrence of ADR in male compared to female.

In this study antibiotics (26.2%), corticosteroids (11.7%) and antihypertensive agents (11.6%) were the common classes of drugs that cause ADR. According to the study conducted by Morales-Rios O et al., Alayed N et al. [10,15] shows similar results that antibiotic is the common class of drugs that causes ADR. However, the study conducted by Venkatasubbaiah M et al. [12] shows the result that anticonvulsants are the most common class of drugs that causes ADR followed by antidiabetics and antiulcer agents. Constipation (32.3%) was the most commonly observed ADR found in this study followed by pedal edema (17.6%) equivalent to the study carried out by Watson S et al. [16] whereas, the study conducted by Lihite RJ et al. [17] shows the result that acne (18.03%) was the most commonly observed ADR.

Suspected ADRs were assessed using Naranjo's Causality Assessment Scale. It shows that out of 34 ADRs, 22 (64.7%) of the reactions were Probable,in 8 (23.5%) of the reactions the causality was possible and in 4 (11.8%) of the reactions, the causality was definite. Similar results were observed in the study conducted by Watson S et al. [16] WHO Probability Scale presented that, in 15 (44.1%) of the reactions, the causality was probable, that in 10 (29.4%) of the reactions, the causality was certain and in 8 (23.5%) of the reactions, the causality was possible. This result is similar to that of the reports of the study conducted by Khalil H et al. [18]

The severity of these assumed ADRs were also assessed for its severity. The majority of the reactions were found to be moderate- Level 3 (41.2%) and Level 4 (14.7%) followed by mild (44.1%) This result is similar to that of the study conducted Morales-Rios O et al., Ray Lees NM et al. [10,19] which shows that most of the reactions were mild followed by moderate. The suspected ADRs were assessed by Modified Schmock and Thornton Preventability Scale which shows that most of the identified reactions 21 (61.8%) were Probably Preventable and 13 (38.2%) were Probably Preventable. These results were in accordance with the study conducted by Kumar A et al., [20] which indicates that most of the cases are Probably Preventable followed by Definitely Preventable.

Management of most of the ADRs was done by the withdrawal of the drug, which was exhibited in 47.2% of cases. There was no change of suspected drugs in 30.5% of cases. Doses were altered in 16.6% of cases. The reports are equivalent to that of the study conducted by Guner MD et al., [21] in which 68.18% of patients had improved their condition. The outcome of management of ADRs exhibit that 75% of reactions were recovered followed by 25% of cases in which symptoms were continued. This result is similar to that of the results depicted in the study conducted by Venkatasubbiah M et al., [12] where 36.22% of cases were recovered.It was a timeline study so the sample size restriction was the main limitation of this study.

CONCLUSION

This investigation let to the conclusion that the adverse drug reactions were similar in male and female patients. The common class of drugs that are responsible for ADRs were antibiotics followed by corticosteroids and anti-hypertensive. Causality was assessed using Naranjo's Causality assessment scale which showed that most of the cases were probable. The severity was assessed using Hartwig Severity Scale which gave result that most of the reactions were mild. WHO Probability Scale was used to assess the probability of the reaction which showed that most of them are probable. In most the cases drug withdrawal caused recovery of the patient. Hence, no treatment was needed to manage the ADRs. To minimize the incidence and prevent further complications and occurrence, proper

monitoring of adverse reactions is required. Spontaneous reporting of ADR will help to improve the patient's safety and health and also it may help the physician to avoid those drugs which cause fatal reactions. Hence, importance should be given in spontaneous reporting of ADR, to ensure the safety of the patient.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The study was approved by Institutional Ethics Committee (Ref. No: NGSMIPS/IEC/18/2019-20)

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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