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A Pharmacovigilance Study on Causality and Severity Assessment of Adverse Drug Reactions in a Teaching Hospital

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ABSTRACT

Objectives: The main purpose of the study is to assess the causality, severity, preventability of ADRs and factors associated with ADRs in chronic disease patients of tertiary care teaching hospital.

Study setting and Design: A Prospective observational longitudinal study was conducted in a tertiary care teaching hospital at Hyderabad, India, for 3 years.

Materials and Methods: Patients of age group > 18 years were included in the study. All the patients were distributed according to their gender, age, number medications used, disease condition and socioeconomic state. The reported ADRs were analyzed by WHO-UMC causality, Hartwig's Siegel's scale and modified Shumock and Thornton criteria respectively. Statistical analysis used: Descriptive statistical analysis was used.

Results: A total of 691 patients enrolled in the study, in that 391 patients reported with 510 ADRs. Of these 37.0% are in-patients and 62.9% are out-patients. Majority of the patients are female category (58.0%) and 45.8% of ADRs reported from adults (41-60 years). 65.8% patients are non-adherent to medication. Life style habits, economic status and education are found to be predictors for ADRs. WHO-UMC scale showed 42.9% of ADRs probable. Hartwig's and Siegel's severity scales shown 13.1 % ADRs are severe followed by 33.7% moderate ADRs and 40% of ADRs were preventable.

Conclusion: Hence our study advises that there is a need of improvement in ADR reporting from health care professionals. This study also suggests further research in India for the improvement of possible intervention strategies to reduce burden and cost of ADR.

Keywords: *Prospective, ADR reporting, WHO-UMC, Hartwig's Siegel's scale, Shumock and Thornton..*

1. INTRODUCTION

According to WHO Pharmacovigilance (PV) is defined as the science and activities relating to the detection assessment, understanding and prevention of adverse effects or any other drug-related problem. In reaction to the 1962 thalidomide tragedy, WHO launched the Programme for International Drug Monitoring[1].One PvPI's goals include monitoring adverse drug reactions (ADRs) in the Indian population, educating medical professionals about the significance of ADR reporting in India, tracking the benefit-risk profile of medicine, producing independent, evidence-based recommendations regarding medication safety, assisting the CDSCO in developing safety-related regulatory decisions for medicine, sharing findings with all relevant parties, and establishing a national center of excellence that meets international drug safety monitoring standards.[2]. Following the recommendations relevant to each chronic ailment is generally advised. The majority of clinical practice guidelines, however, does not address or adapt their recommendations for older patients with multiple conditions, and polypharmacy will unavoidably result from following all guidelines for all medicines a patient is taking [3]. An estimated 50.8 million persons in India had diabetes in 2010, and by 2030, that figure is predicted to increase to 87 million [4]. According to reports, diabetes is becoming more and more common in India's cities and rural areas[5].When managing diabetes mellitus, a prescriber's understanding of the pharmacokinetics and pharmacodynamics of medications and how they interact with normal aging physiology is essential. The information is necessary to reduce and even prevent the negative

effects of hypoglycemia and the side effects of anti-diabetic medications [6]. It was also discovered that there were an estimated 1 billion hypertensive persons worldwide in 2000, and that number was expected to rise to 1.56 billion by 2025[7]. Adverse drug reactions are common with antihypertensive drugs, which can restrict treatment options and decrease patient compliance, both of which can make it more difficult to control blood pressure. It was thought that the varying frequencies of unpleasant effects for different kinds of antihypertensive drugs were likely related to their varying cessation rates [8, 9]. In order to treat tuberculosis, costly and harmful anti-tubercular medications must be administered for an extended period of time [10, 11]. The Revised National Tuberculosis Control Program (RNTCP) in India follows the internationally recommended directly observed treatments (DOTS) guidelines for treatment TB from August 2007 onward [12]. The female gender, age (very young and very old), multiple medications and the co-morbid medical conditions, socioeconomic status, educational status and lifestyle habits are considered as the important risk factors for ADRs [13].

Individuals who have diabetes are more likely to experience several major health issues. Serious conditions affecting the heart, blood vessels, eyes, kidneys, nerves, and teeth can result from persistently elevated blood glucose levels. Individuals who have diabetes are also more susceptible to infections [14]. According to reports, 70% of diabetes patients worldwide also have hypertension, and diabetic individuals are twice as likely to acquire hypertension as euglycemic people [15]. Patients with type 2 diabetes have been found to have a significant prevalence of DRPs [16].

2. MATERIALS AND METHODS

ADRs in chronic conditions were evaluated for causality, severity, and preventability. The study also assessed the frequency of adverse drug reactions (ADRs) linked to patients' socioeconomic level, occupation, medication adherence, and educational attainment.

Our institution is an approved ADR monitoring center (AMC) under the "Indian Pharmacovigilance Program." Physicians, clinical pharmacy interns, postgraduate medical students, and surrounding teaching hospitals provide suspected adverse drug reactions (ADRs) to the AMC. For the worldwide monitoring of ADRs, we send information to the WHO's "VigiFlow software," which is supplied by the Indian Pharmacopoeia Commission in Ghaziabad, India.

Study Design

Prospective observational longitudinal study with active pharmacovigilance reporting system.

Study Period

The study was conducted over a period of 2 years from May 2022 to April 2024

Ethics committee approval

The study protocol was reviewed and approved by Institutional Human Ethical Committee of Shadnagat Super Speciality Hospital authority prior to the commencement of study.

Study criteria

Inclusion Criteria

Patients of age from 18 years and both genders

Both inpatients and outpatient

Patients with any chronic disease and co-morbid medical condition

Exclusion Criteria

Children’s and pregnant women.

Patients receiving medicines other than allopathic

Patients who experienced adverse event to vaccines, blood and /or blood products.

Adverse event to poisoning/ drug abuse and dependence

Source of Data

For both inpatients and outpatients, patient case sheets containing the clinicians' admission notes, prior discharge summaries that were available with the patient, reference notes from other clinicians, and conversations with the patient or their caregivers at the time of inclusion were taken into consideration as sources of past medical and medication history. Important sources of knowledge about current medical conditions included the notes made by clinicians and conversations with interns and medical postgraduate (PG) students. Nursing notes from the patient's daily drug consumption during the hospital stay were examined. OPD cards, prescription and pharmacy invoices, or the patient's or caregiver's empty medicine strip were used to verify the outpatient's drug use.

Assessment of ADR reports

Organ Systems Affected due to ADRs

International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Medications Implicated in ADRs

Drugs that implicated in adverse reaction were coded using the WHO Anatomical,

Therapeutic and Chemical (ATC) classification

Statistical Analysis

Data analysis was done using descriptive statistics. Tables and charts were used to illustrate each statistic, which was expressed as a percentage. Age, gender, quantity of medicines used, drug class, medication adherence, habits, economic position, education, and occupation were the categories utilized to separate the data.

3. RESULTS & DISCUSSION

1. Study Population

691 patients met the study criteria were included in the study. Of which 37.0% (n=256) were inpatients and 62.9% (n=435) were outpatients.

2. Characteristics of the Study Population

Out of 691 study patients, 41.9% (n=290) and 58.0% (n=401) were male and female respectively. Majority of the patients were in the age group of 40-60 (45.8%). 46% of patients using drugs between 1-2 drugs. 65.8% of patients are non adherent to their medication. 34.5% of patients are both alcoholic and smokers. 50.6% patients are not educated. 28.6% Unemployed followed by 20.1% patients are formers and 34% of patients are economically lower in class.

Classification of Disease condition according to ICD-10 Version: 2016

Out of 691 patients 41.6% patients having endocrine, nutritional and metabolic diseases (E00-E90), followed by 18.6% certain infectious and parasitic diseases (A00-B99). The disease condition details are given in Table -1

Table-1: Classification of disease condition according to ICD-10

ICD10 Chapter	Disease Condition	ICD-10 Code	Total (n=691)	Incidence (%)
I	Certain infectious and parasitic diseases	(A00-B99)	129	18.6
II	Neoplasams	(C00-D48)	1	0.1
III	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	(D50-D89)	18	2.6
IV	Endocrine, nutritional and metabolic diseases	(E00-E90)	288	41.6
V	Mental and behavioural disorders	(F00-F99)	7	1.0
VI	Diseases of the nervous system	(G00-G99)	29	4.1
VII	Diseases of the eye and adnexa	(H00-H59)	2	0.2
VIII	Diseases of the ear and mastoid process	(H60-H95)	2	0.2
IX	Diseases of the circulatory system	(I00-I99)	44	6.3
X	Diseases of the respiratory system	(J00-J99)	22	3.1
XI	Diseases of the digestive system	(K00-K93)	23	3.3
XIII	Diseases of the musculoskeletal system and connective tissue	(M00-M99)	18	2.6
XIV	Diseases of the genitourinary system	(N00-N99)	10	1.4

XV	Pregnancy, childbirth and the puerperium	(O00-O99)	15	2.1
XVIII	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	(R00-R99)	75	10.8
Chapter XIX	Injury, poisoning and certain other consequences of external causes	(S00-T98)	1	0.1
Chapter XXI	Factors influencing health status and contact with health services	(Z00-Z99)	7	1.0

Medication Non-Adherence

Out of 691 patients 455 (65.8%) are non-adherent to their medication to due to following factors. In that 39.3% of patients are not following their medications due to drug related factors. The details of medication non-adherence are given in Table-2

Table-2. The reasons for medication non- adherence

Factors affecting Medication adherence	**Number (%) (n=455)**
Drug Related Factors	179 (39.3)
Patient Related Factors	128 (28.1)
Disease Related Factors	97 (21.3)
Health System Related Factors	51 (11.2)

Fig 1: Factors influencing drug adherence.

Adverse Drug Reaction

Out of 691 patients enrolled in the study 391 patients reported with 510 ADRs during the study period. The incidence of ADRs details are given in Table-3

Table-3 Incidence of ADRs based on patient characteristics

Number of patients (n=691)	Number of patients with ADR (n=391)	Incidence	Number of ADRs (n=510)	Percentage of ADRs(%)
Category				
Inpatients 256	106	41.4	143	28.0
Out patients 435	285	65.5	367	71.9
Gender				
Male 290	190	65.5	239	46.8
Female 401	201	50.1	271	53.1
Age (years)				
Young Adults 89	31	34.8	48	9.4
Adults 317	187	58.9	258	50.5
Elderly (> 61) 285	173	60.7	204	40.0
Number of Medications				
1-2 318	218	68.5	261	51.1
3-4 258	108	41.8	159	31.1
>5 115	65	56.5	90	17.6
Medication Adherence				
Adherence 236	113	47.8	169	33.1
Non Adherence 455	278	61.0	341	66.8
Disease condition ICD-10				
(A00-B99) 129	107	82.9	176	34.5
(C00-D48) 1	1	100	1	0.1

(D50-D89) 18	9	50	13	2.5
(E00-E90) 288	145	50.3	152	29.8
(F00-F99) 7	4	57.1	6	1.1
(G00-G99) 29	17	58.6	24	4.7
(H00-H59) 2	1	50	1	0.1
(H60-H95) 2	1	50	1	0.1
(I00-I99) 44	23	52.2	26	5.0
(J00-J99) 22	16	72.7	21	4.1
(K00-K93) 23	11	47.8	13	2.5
(M00-M99) 18	6	33.3	9	1.7
(N00-N99) 10	4	40	7	1.3
(O00-O99) 15	8	53.3	12	2.3
(R00-R99) 75	34	45.3	42	8.2
(S00-T98) 1	1	100	1	0.1
(Z00-Z99) 7	3	42.8	5	0.9

Department-wise distribution of ADRs

Maximum number of ADRs were reported from the department of general medicine (69.5%), similar with the study done [17,18] followed by Pulmonology (15.8%), OBG (5.8%) and DVL (2.5%). The department wise details are given in Table.4

Table-4: Department wise distribution of ADRs

Department	**No. of ADRS (n=510)**	**Incidence (%)**
General Medicine	356	69.8
Pulmonology	78	15.2

Obstetrics and gynaecology	30	5.8
DVL (dermatology, vernerology, leprology)	16	3.1
Orthopaedics	9	1.7
Psychiatry	9	1.7
Other*	12	2.3

(* casualty, ENT, neurology & surgery**)**

II. **Organ system affected by ADRs.**

In our study gastrointestinal system accounts for 26.2% ADRs and Skin disorders accounts for 26%, having similar reports from the study [19, 20]. The details of organ system affected are given in Table-5

Table.5: Distribution of ADRs based on system organ class affected

System organ class (WHOART SOC code)	**Number of (ADRs (n=510)**	**Incidence (%)**
Body as a whole - general disorders (1810)	59	11.5
Cardiovascular disorders (1010)	7	1.3
Central & peripheral nervous system disorders 0410	44	8.6
Gastro-intestinal system disorders (0600)	134	26.2
Hearing and vestibular disorders 0432	01	0.1
Heart rate and rhythm disorders 1030	4	0.7
Liver and biliary system disorders	10	1.9
Metabolic and nutritional disorders 0800	62	12.1
Musculo-skeletal system disorders 0200	12	2.3
Platelet, bleeding & clotting disorders 1230	07	1.3
Psychiatric disorders 0500	12	2.3
Red blood cell disorders (1210)	04	0.7
Respiratory system disorders 1100	09	1.7
Skin and appendages disorders (0100)	133	26.0
Urinary system disorders 1300	08	1.5
Special senses other, disorders 0433	01	0.1
Vision disorders 0431	01	0.1
White cell disorders 1220	02	0.3

c. Types of medication implicated in ADRs

Antimicrobial agents accounts for 35.4% (n=181), which is in accordance with the result of studies [21, 22] and antidiabetic drugs accounts for 17.6% (n=90) followed by analgesic and anti-inflammatory drugs (9.6%, n= 49) of ADRs. The details of types of medication are given in Figure

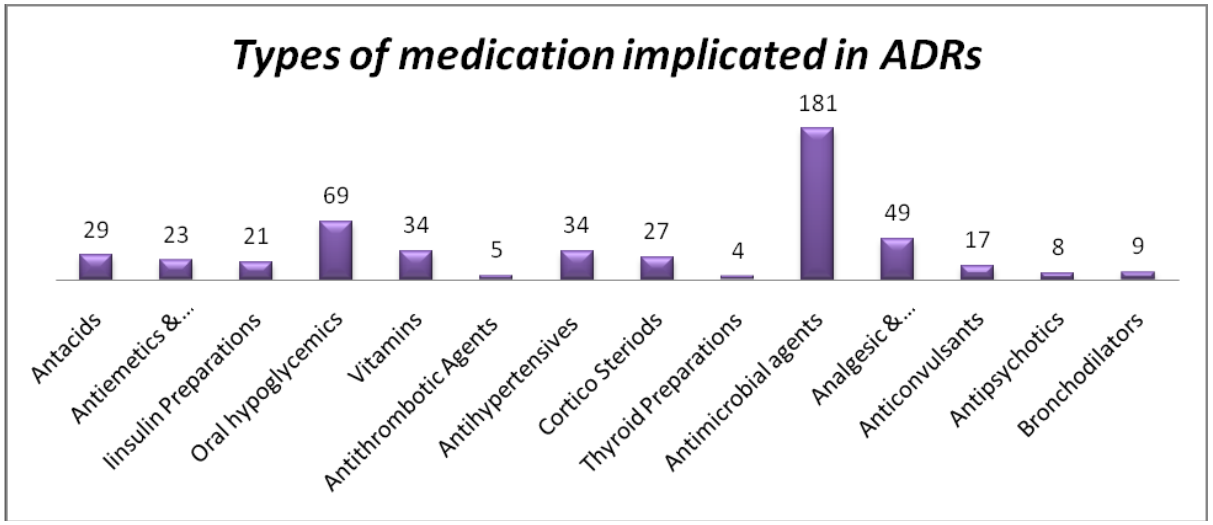

Fig:2 Type of medication implicated in ADRs.

d. Type of Reporters

All the ADRs reported spontaneously, in that majority of the ADRs (28.8%) were reported by PG/ Pharm.D Interns, followed by physicians (22.7) and nurses (18.8%). Highest reporting from Pharm.D interns, because active participation in daily ward rounds and performing bedside patient counselling and patient to patient interaction. Surprisingly patients are also involved in reporting of the ADRs showing that improvement in awareness of drug usage and related problems. The details of reporters are given in Figure.3

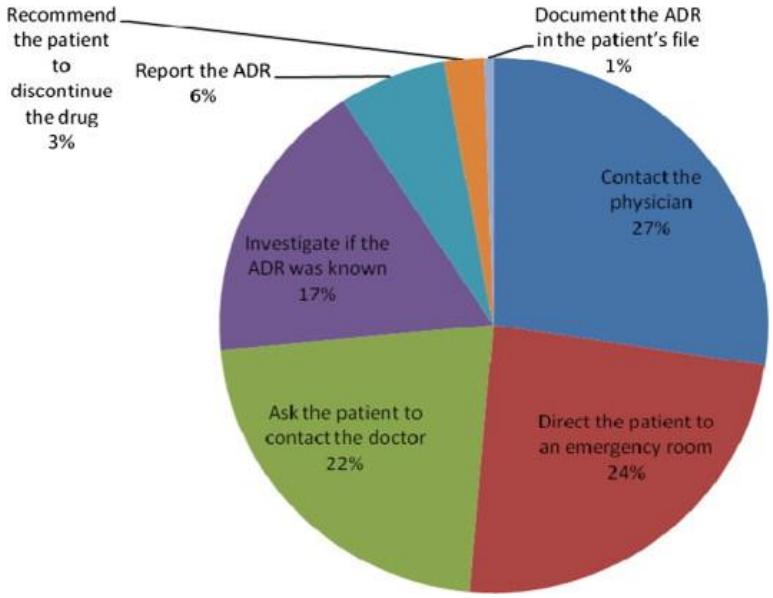

Fig.3: Type of reporters

e. Predictability of the ADRs

A total of 76.6% (n=391) of the adverse drug reactions were predictable, related with the study [23] and 23.3% (n= 119) of the adverse drug reactions were not predictable. The details of predictability of the ADRs are given in Figure.4

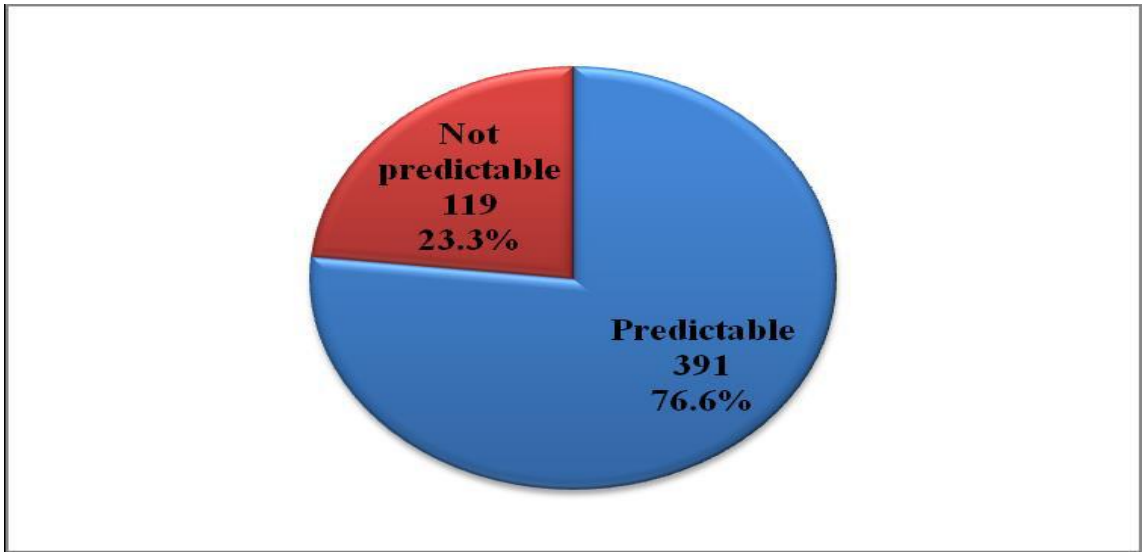

Fig.4: Predictability of the ADRs

Approximately three-fourth of reported ADRs was predictable. This result perhaps may due to the reason that majority of the reactions were exacerbation of pharmacological actions of the drugs that act on various organs and associated receptor site.

f. Causality assessment of reported ADRs

Majority of the ADRs belonged to 'probable' in their casual relationship, as assessed

by WHO probability Scale [n=219 (42.9%)], similar with study [17].The causality categories of reported ADRs are presented in Figure.5

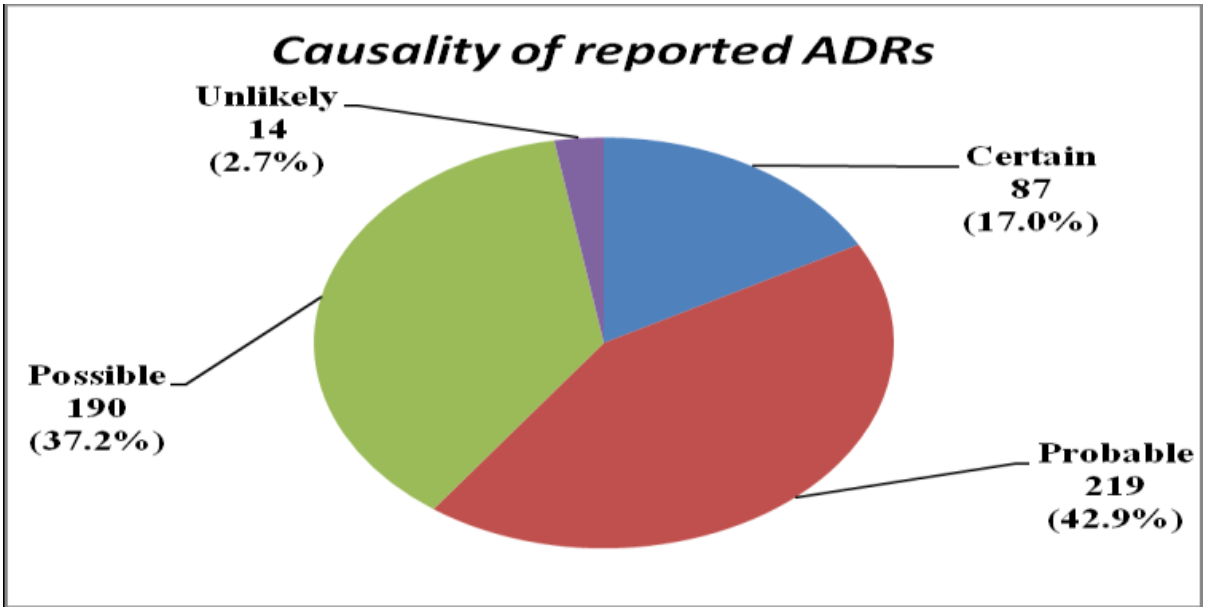

Fig.5: WHO-UMC Causality categories of reported ADRs

The WHO UMC proposed causality assessment is generally accepted method and most widely used method for causality assessment in clinical practice as they offered a simple methodology. Majority of the ADRs were assigned 'Probable' casual association between the adverse drug event and suspected drug.

g. Severity assessment of ADRs

Most of the reported ADRs were of 'Mild' in their severity and hence did not require withdrawal of the suspected drug especially when the benefits outweighed the risk. This finding coincide with [24, 25] the details of severity of ADRs are given in Figure.6

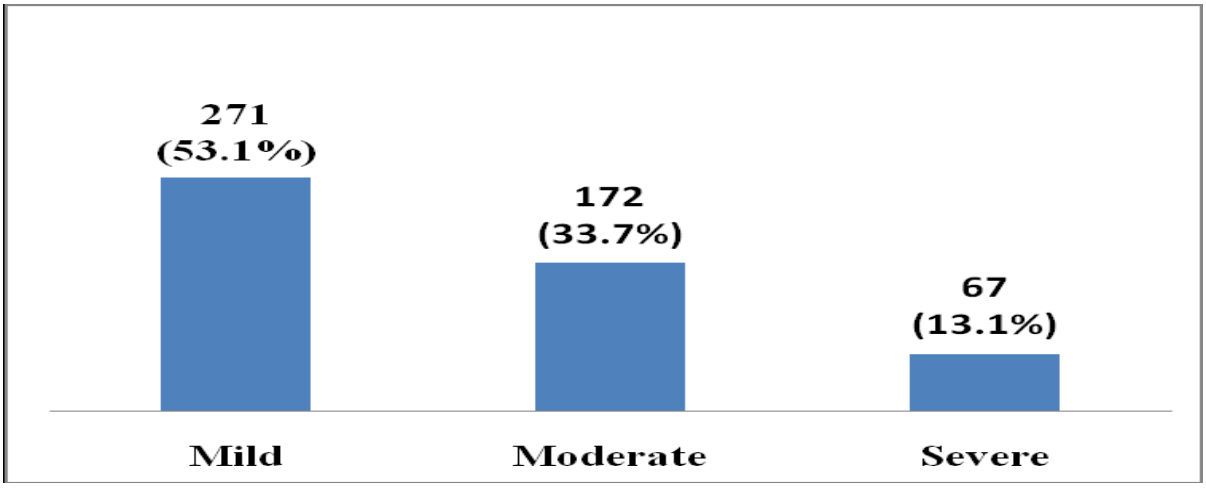

Fig.6: Severity of ADRs

h. Preventability of the ADRs

Of the 510 reported ADRs, 269 (52.7%) were classified as probable preventable, which is variance with the study done [24].The details of the preventability of ADRs are presented in Figure.7

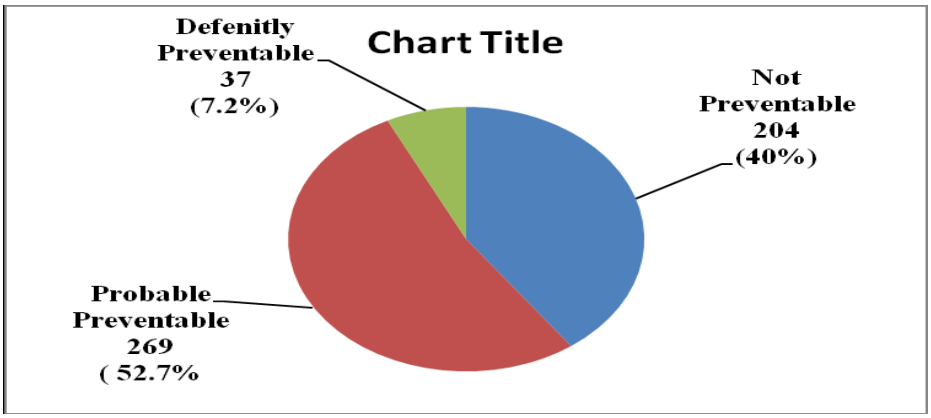

Fig .7: Preventability of ADRs

4. CONCLUSION

According to our research, the reports from the students were useful and contained information that was pertinent to clinical settings. By identifying novel, severe, and uncommon drug responses, ADR monitoring via spontaneous reporting systems contributes to patient safety. ADR reporting should be introduced to Pharm.D. Interns and postgraduate medical students during their clinical teaching placement as they prepare to become future health care professionals. The current study focuses on the adverse drug reaction profile of antibiotics, cardiovascular, antidiabetic, and tubercular agents. It is crucial to observe the doctors who provide the most often prescribed medications in hospitals. Effective pharmacovigilance implementation would therefore lead to more stringent vigilance in the use of these medications and their safety evaluation, which would eventually improve patient care.

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