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A RETROSPECTIVE INVESTIGATION OF ADVERSE DRUG REACTIONS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

Introduction: An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy. To evaluate the probability of true ADRs from suspected ADRs, Naranjo *et al*. has proposed a tool and has been widely used as Naranjo Algorithm. The main aims of this study are to assess the pattern of ADRs, causality, offending drugs, monitoring and documenting suspected ADR(s) and to prevent the occurrence. **Methodology:** A retrospective study was carried over a period of 6 months. The reactions were categorized based on patient demographics and ADR characteristics (the type of ADR, causality, severity, system affected, outcome and management). Data were demonstrated in the form of frequency and tables. **Results:** Causality assessment of suspected ADRs using Naranjo's scale showed that 16.66% of them were probable and 83.33 % categorized as possible. The severity of reactions was reported as 46.66% each in case of mild and moderate. 6.66% considered as severe. **Conclusion:** This study concluded that the reporting of ADRs is fairly good in this hospital. Although the ADRs in the present study were serious and preventable. Monitoring and management of such ADRs through therapeutic interventions beneficial for patient care.

Keywords: Adverse drug reaction, Causality, Naranjo scale, Monitoring, Severity

INTRODUCTION:

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy. ADRs are a major cause of morbidity and place a substantial burden on limited healthcare resources. Multiple factors influence ADR susceptibility, including multiple drug therapy, disease severity, age, and the type and number of drugs prescribed **[1]**. It is universally accepted that ‘‘No drug absolutely free from side effects”. From the literature it is observed that 5% of all hospital admissions were related to drug-induced problems and 10–20% of hospitalized patients are developing ADRs, it is estimated that ADRs are the fourth to the sixth leading cause of death **[2]**.

According to the WHO, ‘‘Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problem, particularly long-term and short-term adverse effects of medicines”. Pharmacovigilance aims at making the best use of medicines with the help of high-quality data gathered through a reporting system. Good pharmacovigilance helps in the minimization or prevention of ADRs through early detection and effective communication, which ultimately help each patient to receive optimum therapy. It can generate evidence that will inspire public confidence and trust in drugs **[3, 4]**.

Traditionally, ADRs have been classified into two types, Type A reactions – sometimes referred to as augmented reactions – which are ‘dose-dependent’ and predictable on the basis of the pharmacology of the drug and Type B reactions – bizarre reactions – which are idiosyncratic and not predictable on the basis of the pharmacology **[5]**.

All healthcare professionals and others including consumers may report a suspected adverse drug reaction. Pharmaceutical companies may send report on adverse drug reaction for their product directly to the NCC-PvPI. The health and safety of Indian population is a matter of national concern. Occurrence of ADR constitutes a significant economic burden on the patient and the government. As a prudent and vigilant healthcare professional (HCPs), it is the responsibility of HCPs to report adverse drug reactions associated with use of medicines to safeguard the health of patients. India has a vast population that exhibits genetic and ethnic variability, there also exists a vast variation in disease prevalence. The data so

generated will help to make vital policy decisions regarding safe use of medicines in Indian population. In order to foster the culture of reporting, PvPI encourages reporting of all types of suspected ADRs- irrespective of whether they are known or unknown, serious or nonserious, frequent or rare and regardless of an established causal relationship to PvPI. Although Pharmacovigilance is primarily concerned with pharmaceutical medicines and vaccines, adverse reactions associated with drugs used in traditional medicine (e.g., herbal remedies), medical devices, contrast media and other pharmaceuticals are also monitored. Special areas of interest include outcomes associated with the drug use during pregnancy, lactation period, and in paediatric and geriatric populations. In addition, reporting of lack of efficacy of medicines and suspected pharmaceutical defects are also recommended to report. Reporting of ADRs encountered with overdose, abuse, off-label use, misuse or occupational exposure is not currently included in the purview of PvPI **[6, 7]**.

All healthcare professionals (clinicians, dentists, pharmacists, nurses, etc.) can report adverse drug reactions using the 'Suspected Adverse Drug Reaction Reporting Form'. Pharmaceutical companies can use this form to send their Individual Case Safety Reports (ICSRs) **[8, 9]**.

Recognition of ADRs and Causality assessment play an important role in better management of the adverse reactions. Different tools are developed to categories ADRs that help to confirm the probability of ADRs. To evaluate the probability of true ADRs from suspected ADRs, Naranjo *et al*. has proposed a tool and has been widely used as Naranjo Algorithm **[10]**.

Pharmacists are a vital link between the patient and the health system before and during the course of drug therapy. Pharmacists are uniquely qualified to provide valuable information on drug products, can play an important role in monitoring adverse events, and help design and implement system improvements related to ADRs in their health systems. Programs should focus on surveillance, complete documentation within medical records, reporting to and review by an interdisciplinary committee, and education to achieve an overall goal of reducing the risk and severity of ADRs within an organization. All pharmacists should understand their role in recognizing, evaluating, reporting, and educating both patients and providers on ADRs **[6]**.

This is a retrospective study, conducted at a tertiary care hospital for a period of six

months. The main aims of this study is to assess the pattern of ADRs, causality, offending drugs, monitoring and documenting suspected ADR(s) and to prevent the occurrence. Each reported ADR was assessed for its causality by using Naranjo's scale. Study strongly suggests there is a greater need for streamlining of hospital-based ADR reporting as well as monitoring system to create awareness, and promote more accurate reporting of ADR(s) among healthcare professionals. The present study was carried out to evaluate the probability of true ADRs from suspected ADRs by using Naranjo Algorithm and to improve the scientific basis of causality assessment before it is sent to National Pharmacovigilance Centre.

MATERIALS AND METHODS:

A retrospective study was carried over a period of 6 months from December 2021 to June 2022 in Sagar hospitals, Banashankari at Bengaluru, India. The ADRs reported from various departments of the hospital to the ADR reporting unit. Mode of reporting and documentation of ADRs in the unit is discussed elsewhere in the text. ADRs notified between study period (6 months) were selected and evaluated for the purpose of our study. Additional details on the ADRs were collected for evaluation purpose from the respective case records wherever required.

Ethics and consent:

This study was conducted after obtaining the ethical approval from the ethical committee of the hospital and with consent from individual patients.

Study site:

A 1000 bedded tertiary care teaching hospital providing both in-patient and out patients services. The hospital specialties are general medicine, surgery, OBG, pediatrics, orthopedics, ENT, Pulmonology, Nephrology and neurology. Sagar hospital also provide best facility for intern's students from different departments like Pharmacy, Nursing and Radiology.

Study criteria:

Inclusion criteria:

1. Both male and female patients
2. Both OP and IP patients
3. Patients on age group above 18 years

Exclusion Criteria:

1. Patient below age of 18years
2. Pregnant females.
3. Incomplete patient records
4. Reactions due to over dose/ under dose

Functioning of the ADR reporting system:

Clinical meetings with all HCPs were conducted regarding the importance of monitoring and reporting of ADRs**.** At the time of admission, all the patients were assessed for the previous allergies, ADRs, and

past medical history and were noted in the case sheets. The symptoms/signs observed through the clinical review process were assessed for their relation with the drug(s). If the reaction is not related to the underlying disease and/or its complication or if the possible causal relation is more with the drug than other possible causes, then it will be suspected as an ADR and was confirmed with the support of literature. Such ADRs reported in institutional suspected ADR reporting form and ADR notification form were analyzed for their completeness, credibility, and correctness. Suspected ADRs were, reported and documented in PvPI suspected ADR reporting form.

Data were carefully evaluated based on the following essential elements by analyzing patient and reaction characteristics: patient initials, gender, date of reaction (onset), description of the reaction or problem, suspected medication(s), indications for use, concomitant medical products including self-medication and herbal remedies, de-challenge, re-challenge and outcomes. After initial notification of a suspected ADR, additional details were collected concerning previous allergies, concomitant medications, co-morbidities, ADR management and outcome, and other details necessary for evaluation through direct interview with the reporter and patients, and/or evaluation of patient medical records. These suspected ADRs were then reported to PvPI ADR monitoring centers (AMCs); at Rajiv Gandhi Institute of chest disease.

Evaluation of data*:* The reactions were categorized based on patient demographics and ADR characteristics (the type of ADR, causality, severity, system affected, outcome and management).

Patient demographics: The patient's age and gender were considered in the evaluation. In accordance with reference article patients were divided into 2 categories, adults and elderly.

ADR Characteristics: Based on the information in the reported ADRs form, categorization was done using Naranjo's ADR Probability scale. This probability scale evaluates the causality of ADRs and categorize them as definite, probable, possible and doubtful

Management and outcomes: Patients outcomes were reported as death, fully recovered, recovering, or unknown. The management strategies used for the ADRs were categorized as drug withdrawal, dose reduction, additional treatment for the ADR, or no change in regimen with no additional treatment.

Data Analysis:

Total number of 30 reported cases of ADRs were evaluated. Along with thorough drug history, records of preliminary information, detailed history regarding presenting symptoms, intensity and duration was reviewed and considered. The data was entered in excel sheet using and data were demonstrated in the form of frequency and tables. Data were finally represented in percentage.

RESULT:

Table 1: Distribution based on demographics

Parameter	No. of ADR (n=30)	Percentage (%)
GENDER		
Male	14	46.6
Female	16	53.3
AGE GROUPS		
18-39	1	3.33
40-65	23	73.3
Above 65	07	23.3

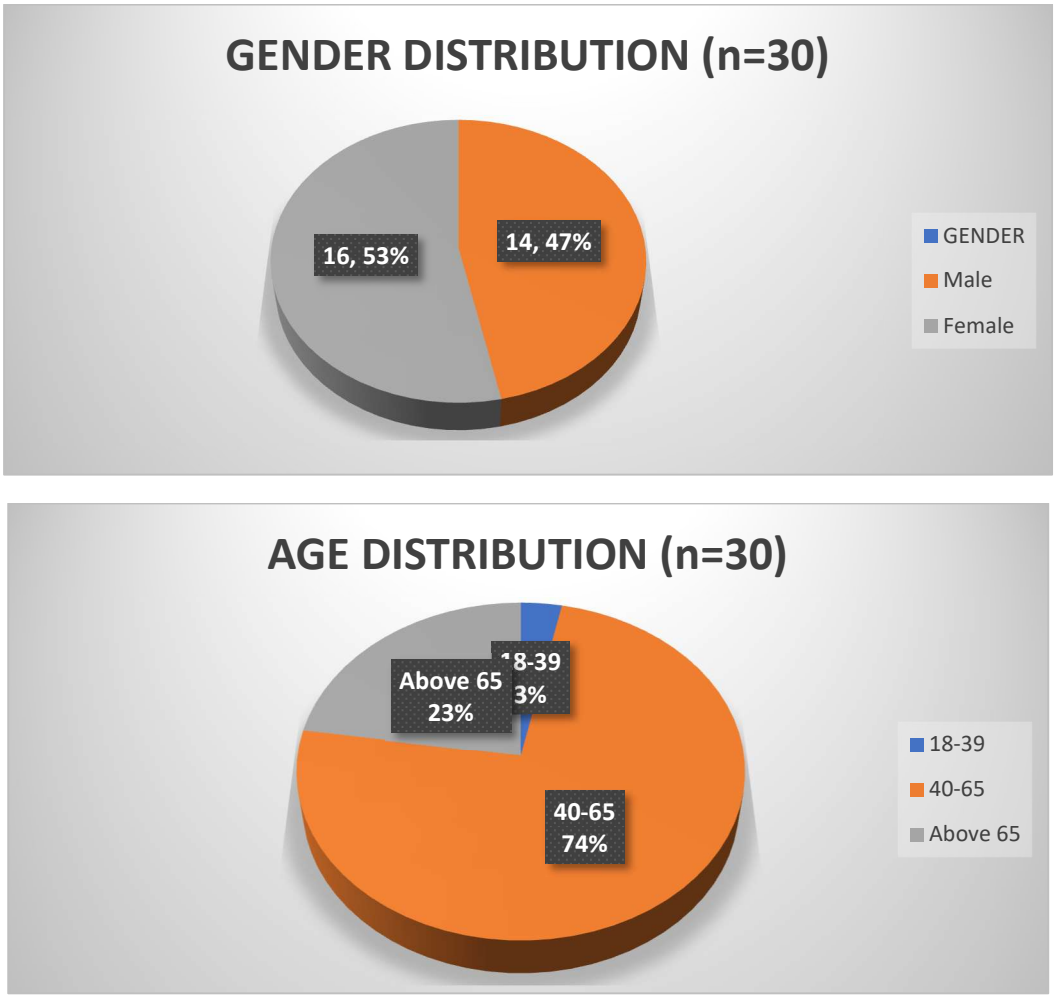

Figure 1: Distribution based on demographics

Table 2: List of drug class suspected ADRs

Drug class	No. of ADR (n=30)	Percentage %
Human albumin	1	3.33
Mucolytic agents	1	3.33
Acetylcholinesterase	2	6.66
Hemostatics	2	6.66
Contrast media	5	16.66
Antibiotics	19	63.33

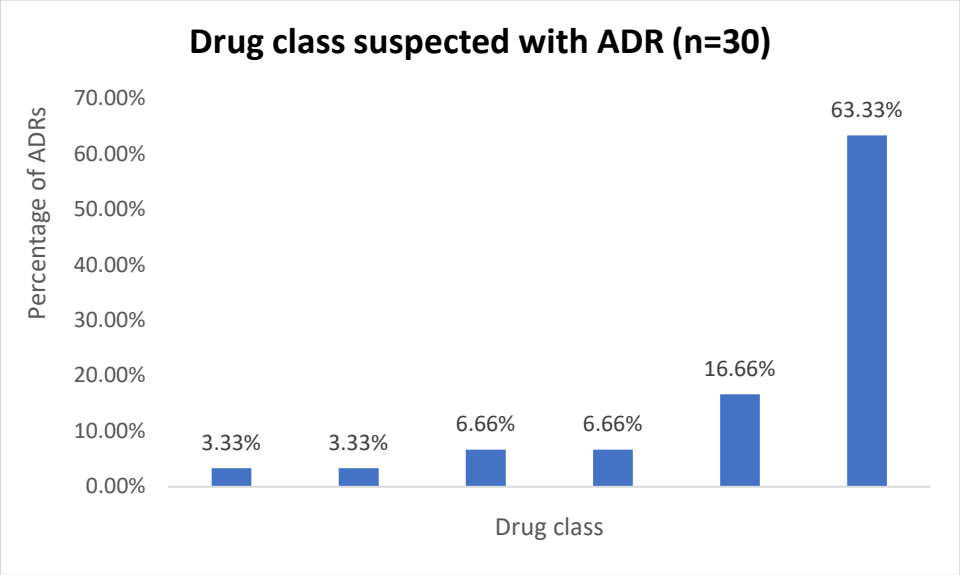

Figure 2: List of drug class suspected ADRs

Table 3: Distribution of Adverse Drug Reaction

Sl. No	Description of ADR	Suspected Products	No. of ADRs (n=30)
1.	Hypersensitivity		26 (86.66%)
	Itching	Aminoglycosides and Fluroquinolones	2
	Itching and rashes	Contrast media, Mucolytic agents Fluroquinolones Beta lactam antibiotics Human albumin	18
	Chills and rashes	Contrast media	3
	Erythema	Cephalosporins	1
	Blisters	Hemostatics	2
2.	Respiratory system		1 (3.33%)
	Breathlessness	Acetylcholinesterase inhibitors	1
3.	Gastrointestinal disturbances		1 (3.33%)
	Diarrhea and loose motion	Amoxiclav	1
4.	Musculoskeletal		1 (3.33%)
	Arthralgia	Penicillin	1
5.	CVS		1 (3.33%)
	Bradycardia	Acetylcholinesterase	1

Table 4: Causality and severity assessment of ADRs

Description of ADR	Severity assessment of ADR			Causality assessment of ADR	
	Mild	Moderate	Severe	Possible	Probable
Hypersensitivity					
Itching	1 (3.33%)	1 (3.33%)		2 (6.66%)	
Itching and rashes	10 (33.33%)	8 (26.66)		18 (60%)	

Chills and rashes	2 (6.66%)	1 (3.33%)		3 (10%)	
Erythema		1 (3.33%)			1 (3.33%)
Blisters	1 (3.33%)	1 (3.33%)			2 (3.33%)
Respiratory system					
Breathlessness			1 (3.33%)		1 (3.33%)
Gastrointestinal disturbances					
Diarrhea and loose motion		1 (3.33%)		1 (3.33%)	
Musculoskeletal					
Arthralgia		1 (3.33%)		1(3.33%)	
CVS					
Bradycardia			1 (3.33%)		1 (3.33%)
TOTAL	14(46.66%)	14(46.66%)	2(6.66%)	25 (83.33%)	5 (16.66%)

Table 5: Distribution of ADR based on outcomes and management

Parameter	No. of ADR	%
Outcomes of ADR		
Fatal	0	0
Recovering	20	66.66
Unknown	0	0
Continuing	0	0
Recovered	8	40
Not-recovered	2	6.66
ADR management		
Addition of another drug	11	36.66
Dechallenge	2	6.66
Drug withdrew only	4	13.33
No change	7	23.33
Dose reduced	4	13.33
No information	2	6.66

Table 6: List of drugs used for ADR managements

SL.NO	Description of ADR	Drugs for ADR Management
1.	Hypersensitivity	
	Itching	Inj Avil & Inj Hydrocortisone 100mg
	Itching and rashes	Oral Prednisone 0.1% - Mometasone furoate onitment Inj Hydrocortisone 100mg IV & Inj Pheniramine maleate 1 amp IV Inj Hydrocortisone 100mg IV Inj Avil (Pheniramine Maleate)
	Chills and rashes	Inj Efcorlin 100mg IV stat, Inj Avil 1 amp IV Stat
	Erythema	Agent discontinued
	Blisters	Agent discontinued
2.	Respiratory system	
	Breathlessness	Inj Avil 1 ampule IV stat, Inj H Cort 200mg IV stat, Nebulization with duolin and budecort, IVF NS bolus started, Oxygen
3.	Gastrointestinal disturbances	
	Diarrhea and loose motion	T Metrogyl 400mg
4.	Musculoskeletal	
	Arthralgia	Tab Omnacortil 40mg OD- 3days and 20mg OD 3days
5.	CVS	
	Bradycardia	Atropine IV

Implementation of ADR reporting and monitoring system in the hospital was successfully done by displaying the posters, through oral campaign, and formal speeches related to importance of reporting ADRs, by the clinical pharmacist. There were 30 ADRs reported, during study period of six months.

Those ADR suspected patients, either visited the hospital with already developed ADRs, or developed ADR during their stay in the hospital. The results of the age categorization revealed that the patients between 40 - 65 years age group experienced maximum ADRs which were about 73.3%, followed by 23.3% in age above 65 years old and 3.33% in 18-30 years age group. Patients who experienced ADR during the study period 16 (53.3%) were female and 14(46.6%) were female.

Causality assessment of suspected ADRs using Naranjo's scale showed that 16.66% of them were probable and 83.33 % categorized as possible. The severity of reactions was reported as 46.66% each in case of mild and moderate. 6.66% considered as severe. No fatal cases were reported. Dechallange was done in 2 (6.66%) and the affected patients were not subjected to rechallenge. Most of the of the ADRs were recovered by addition of symptomatic treatment. Outcomes of the ADRs were, 66.66% of the patients were on recovering condition, 40% people recovered completely and 6.66% case statistics say not recovered but adverse event is mild in causality.

DISCUSSION:

Our data suggest that Naranjo scale is the most consistent for causal imputation of hospital ADR. The advantage of this tool is the quality of the report; it has been used as standard scale in causality studies. Despite its simplicity and wide applicability, the Naranjo Adverse Drug Reactions Probability Scale (NADRPS) is yet to be systematically evaluate for the causality assessment **[18]**.

For the remaining algorithms, we noted a weak agreement between the judges on ADR causality. Studies have shown a great variability in the results of imputation of ADR using different algorithms. Furthermore, they have significant limitations that reduce the accuracy and reliability of the assessment of the probability of ADR. Considering Naranjo *et al*. (1981) algorithm, data from previous study showed slight agreement between the judges **[15]**, because it was developed and validated for the assessment of ADRs that occur during randomized clinical trials. Other authors suggest the use of this tool for the imputation of ADR **[15]** due to its rapid implementation.

During the period of 6 months, 30 cases of ADRs were reported from different

departments of hospitals. Our study showed female predominance over males in ADRs which is similar to the study done by VS Meda *et al*. **[14]** Highest numbers of ADRs were seen in the patient age between 40- 65 years which is 73.33%, followed by 3.33 % in case of 18-39 years. The previous study showed higher percentage of ADRs in age group between 21 to 40 years **[12]**. However, our study showed 23.33 % ADRs in age group above 65 years explained in **Table 1 and Figure 1**.

Most frequently reported drug reactions were for the class of antimicrobials in 19 (63.33%) cases followed by mucolytic agents in 1(3.33%), contrast media 5(16.66%), human albumin 1(3.33%), hemostatic 2(6.66%) and acetylcholinesterase 2(6.66%) cases explained in **Table 2**. The antimicrobials suspected for ADR cases were aminoglycosides, fluroquinolones and beta lactams (penicillin, cephalosporins and amoxiclav) etc. **[13]**

In **Table 3**, it explains about the distribution of adverse drug reactions. Most frequently reported ADR is hypersensitivity reaction, reported for n=26(86.66%) patients which includes itching, itching and rashes, chills and rashes, erythema and blisters. Further, n=1 (3.33%) ADR from each system, includes respiratory system (breathlessness), Gastrointestinal system (diarrhea and loose motion), musculoskeletal (Arthralgia) and Cardiovascular system (Bradycardia). Studies conducted by Bigby *et al*. shows similar results, antibiotics as the most frequent cause of adverse skin reactions or hypersensitivity reactions reported **[16]**.

On evaluation of the severity of ADRs by Naranjo scale it was evident that most of the dermatological ADRs reported in the study, majority were of moderate severity. **Table 3** explains the causality and severity assessment of ADRs. Severity assessment was done as mild, moderate and severe, majority of the ADRs were moderate followed mild. In case of hypersensitivity reactions, n=14 ADRs were mild, n=12 was moderate. Respiratory system and cardiovascular system, each reported n=1 ADRs classified under severe category. On the other hand, gastrointestinal and musculoskeletal system, each reported n=1 ADRs categorized under moderate. It was seen that majority of ADRs belong “possible” n=25 (83.33%) followed by “probable” n=5 (16.66 %). No ADRs were certain, doubtful and definite. This could be due to small sample size. Detailed description was given in **Table 4**.

The ADR outcomes were distributed under following parameters like fatal, recovering, unknown, continuing, recovered and not recovered. Majority of the ADRs was

recovering (n=20), recovered (n=8) and not recovered is (n=2). ADRs were managed by addition of symptomatic treatment in case of n=20 followed by dechallange n=2, drug withdrawal n=2 and dose reduction n=4. Among n=30, no information was available for (n=2) were explained in detail at **Table 5**.

Table 6 explains the list of drugs used for management of ADRs. Hypersensitivity reactions were managed by drug like hydrocortisone, prednisone, pheniramine maleate and corticosteroid ointments etc., for managing the symptoms of event in respiratory system, oxygen support was given followed by nebulization and steroids. Gastrointestinal disturbances were managed by T. Metronidazole. Adverse Events present in musculoskeletal was managed with tablet omnacortil. In some cases, the suspected agents were discontinued for managing the adverse events.

LIMITATIONS:

The numbers of reported ADR were small in number. Since this study is retrospective, inadequate patient's information might have influenced the causality assessment of some ADRs.

CONCLUSION:

During study period of 6 month, we analyzed female predominance over male gender in ADR cases. Age group between 40-65 years were at high risk. Most frequently reported drug reactions were for the class of antimicrobials in 19 (63.33%). Mostly reported ADR is hypersensitivity reaction. Severity assessment was done as mild, moderate and severe, majority of the ADRs were moderate followed mild. Although the ADRs in the present study were serious and preventable, monitoring and management of such ADRs through therapeutic interventions would be beneficial in better patient care. During this study period, we have encouraged all the HCPs in the monitoring and reporting of ADRs. It is evident that pharmacovigilance systems are needed to facilitate ADR follow-ups by health professionals directly involved in patient care. Pharm. D graduates can visit all the departments and encourages HCPs by conducting awareness and/ training programs on ADR reporting. This study concluded that the reporting of ADRs is fairly good in this hospital.

CONFLICT OF INTEREST

No conflict of interest

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