ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 11, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

EVALUATION OF CUTANEOUS ADVERSE DRUG REACTIONS IN A TERTIARY CARE HOSPITAL IN SOUTHERN INDIA: A RETROSPECTIVE ANALYSIS

ANKITA PANIGRAHY[1], ASIYA BEGUM[2], USHARANI PINGALI[1], MEKALA PADMAJA[1], AMAL SAJEEV[3]

[1]Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. [2]Department of Dermatology and Venereology, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. [3]PVPI Associate, Adverse Drug Reaction Monitoring Centre, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India.
*Corresponding author: Usharani Pingali; Email: ushapingali@yahoo.com

Received: 02 August 2024, Revised and Accepted: 15 September 2024

ABSTRACT

Objective: This study was undertaken to understand the demographic profile, common causative drugs, and the presentations of cutaneous adverse drug reactions (CADR) among the patients of our hospital.

Methods: This is a retrospective analytical study. All CADR reported to our adverse drug reaction monitoring center from dermatology outpatient department (OPD), other OPDs, intensive care units, and inpatient wards of our hospital from September 2022 to March 2024 was collected from VIGIFLOW (software used by the pharmacovigilance program of India). The data was then analyzed.

Results: A total of 272 CADR were reported over the study period. The median age of presentation was 41 years (Interquartile range=23). Overall 44 (16.18%) serious and 228 (83.82%) non-serious CADR were reported. Erythematous maculopapular rash was the most common clinical presentation (63%). Bullous exfoliative drug eruptions and Stevens Johnson's syndrome were some of the serious CADR. The most common suspected medications were antibiotics (42.15%) followed by non-steroidal anti-inflammatory drugs (8.92%). In 76% of the cases, the suspected medication was withdrawn. The outcome was reported as "Recovering" in 52% of the cases. On causality assessment, 251 (92%) CADR were classified as "Possible."

Conclusion: A CADR is a common yet preventable health problem. As seen from our study, most of the suspected medications were withdrawn and subsequently the patients were recovering from the CADR. Hence, early diagnosis, identification, and withdrawal of the implicating drugs help in timely recovery and prevention of complications, which in turn help in decreasing the burden on our healthcare system.

Keywords: Drug eruptions, Maculopapular rash, Beta-lactams, Non-steroidal anti-inflammatory drugs.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i11.52291. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

As per the World Health Organization definition, an adverse drug reaction (ADR) is defined as "A response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function" [1].

In clinical practice, cutaneous ADRs (CADR) are very commonly seen as a presenting complaint in up to 5% of both outpatients and inpatients in a hospital setting [2]. Yet, there is a high degree of underreporting for CADR leading to a lack of comprehensive knowledge regarding their incidence, and severity across different population groups in our country. The CADR may range from mild-to-severe or life-threatening, posing a significant burden on patients, healthcare settings, and society at large. Furthermore, the costs incurred due to CADR such as for hospitalization, treatment modalities, and loss of wages, may many times exceed the cost of medications [3].

Whenever a drug is released into the market, it has been tested in <1% of the world's population during clinical trials, giving us only a limited knowledge of suspected ADRs [4]. Hence, the CADR that is reported from the patients after taking the drugs with passage of time is very crucial for pharmacovigilance.

The predisposing factors for ADRs are many. Genetic makeup of an individual, previous history of any drug allergy especially cutaneous manifestations, and any associated hepatic or renal impairment or autoimmune disease states pose a higher risk for the development of CADR.

Maculopapular rash, urticaria, and fixed drug eruptions (FDEs) are among the most common CADR. Besides them, many patients do present to the emergency room with serious CADR such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia, and systemic symptoms. The incidence of these wide spectra of CADR increases with polypharmacy, as many times drug-drug interactions too contribute to CADR.

It has also been shown by previous researchers that the clinical presentation of CADR and the drug(s) causing them have a geographic variation in our country [2,3]. Hence, this study was undertaken to understand the demographic profile, common causative drugs, and the presentation of CADR among the patients of our hospital.

METHODS

This retrospective study was conducted after approval from the Institutional Ethics Committee (EC/Nizam's Institute of Medical Sciences [NIMS]/3406/2024). Data of all CADR from dermatology outpatient department (OPD), other OPDs, intensive care units, and inpatient wards of our hospital that was reported to our ADR monitoring center (AMC – established under the Pharmacovigilance Programme of India [PvPI]) was collected. CADR from the period of September 2022–March 2024 was extracted from VIGIFLOW which is the software used by PvPI.

The following details were noted for each CADR: Gender, type of cutaneous reaction, suspected drug or drugs, route of drug administration, action taken with respect to the drug (drug withdrawn or dose increased or dose reduced or dose not changed), outcome of the

reaction (patient recovered/recovering/not recovered/fatal/recovered with sequelae) and seriousness of the reaction (non-serious or serious).

Analysis of the data was carried out in the ADR monitoring center of our tertiary care teaching hospital in Southern India. Causality assessment was reported in each case as per the World Health Organization Uppsala Monitoring Centre (WHO-UMC) criteria based on the details of each ADR, drug details. The CADR were categorized into "certain," "probable," "possible," "unlikely," "conditional/unclassified" and "unaccessible" based on the temporal relationship between drug intake, the onset of reaction, underlying pathology, whether de-challenge (improvement after stopping of drug) or rechallenge (recurrence or exacerbation of reaction after re-exposure) was done.

Statistical analysis

Data was entered and analyzed using a Microsoft excel sheet. The quantitative variable i.e age is summarized as median with Interquartile range [IQR], and categorical data are expressed using frequency and percentage.

RESULTS

A total of 272 CADR were reported during the study period. Many of the patients with CADR were female (52%). The age and gender-wise distribution is shown in Table 1. The median age of presentation was 41 years with an IQR of 23 years.

Overall, erythematous maculopapular rash was the most common clinical presentation (63%) followed by urticaria (08%). The wide spectrum of reported CADR is depicted in Fig. 1.

Table 1: Age and sex-wise distribution of patients presenting with cutaneous adverse drug reaction (n=272)

Variables	n (%)
Age (years)	
0–20	25 (9.19)
21–40	105 (38.60)
41–60	96 (35.29)
>60	46 (16.91)
Sex	
Female	141 (52)
Male	131 (48)

Regarding the suspected medications, a total of 325 drugs were reported as suspected for the CADR. Antimicrobials (42.15%) followed by non-steroidal anti-inflammatory drugs (NSAIDs) (8.92%) were the most common drugs causing CADR (Fig. 2).

Among the antimicrobials, beta lactams, that is, cephalosporins (mainly Cefoperazone+Sulbactam, Ceftriaxone, Cefixime), carbapenems and penicillins, were implicated in causing the CADR in a total of 82 cases (Fig. 3).

Most of the CADR caused by NSAIDs were non-serious and included reactions such as FDEs caused by piroxicam, paracetamol, naproxen, etc. Contrast agents used for diagnostic tests in our hospital caused CADR in seven cases all of which were non-serious and six among them recovered on symptomatic management, while one was recovering. Miscellaneous drugs included CADR due to normal saline infusion, montelukast, erebroprotein hydrolysate, calcium carbonate, etc.

In our study, out of the 272 CADR, 44 (16.18%) serious and 228 (83.82%) non-serious CADR were reported. Of the serious CADR, 20 cases of drug rashes, eight bullous exfoliative drug eruptions, three cases of SJS (Fig. 4), two anaphylactic reactions, one TEN, and other reactions were reported. The suspected medications causing causing serious CADR are depicted in Table 2. However, there was no death reported in any patient.

In most of the cases (n=272), the suspected medications were administered orally (64%) followed by the intravenous route (32%). Four CADR were due to topical applications of chlorhexidine, minoxidil, and a hair dye and two CADR were due to subcutaneous administration of enoxaparin (Fig. 5). Most of the CADR occurred within 1–7 days post-drug administration, while in some cases the reactions were reported a few months after initiation of therapy, especially with antiepileptic drugs.

In 76% of the patients, the suspected drug was withdrawn while the dose was not changed in 14% of the cases (Fig. 6). Symptomatic treatment was given in all the cases as per the standard clinical treatment practice of the clinicians.

A total of 33% of patients had recovered from the CADR, while 52% of patients were recovering from the reactions. The outcome was unknown in 10% of the cases as the patients were lost to follow-up and in 3% of the cases the patients had not recovered from the reactions.

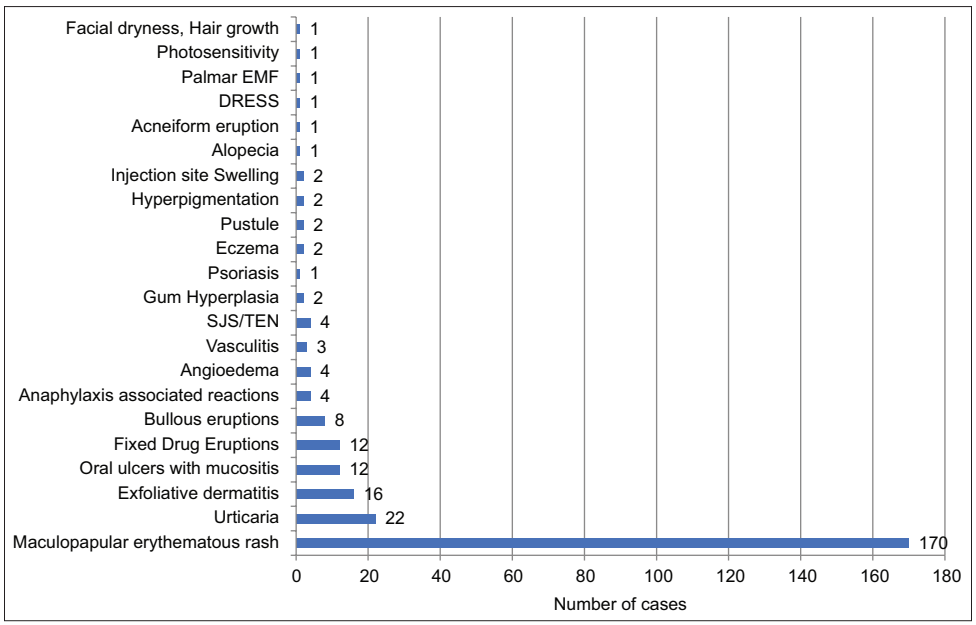

Fig. 1: Clinical presentations of different cutaneous adverse drug reaction (n=272)

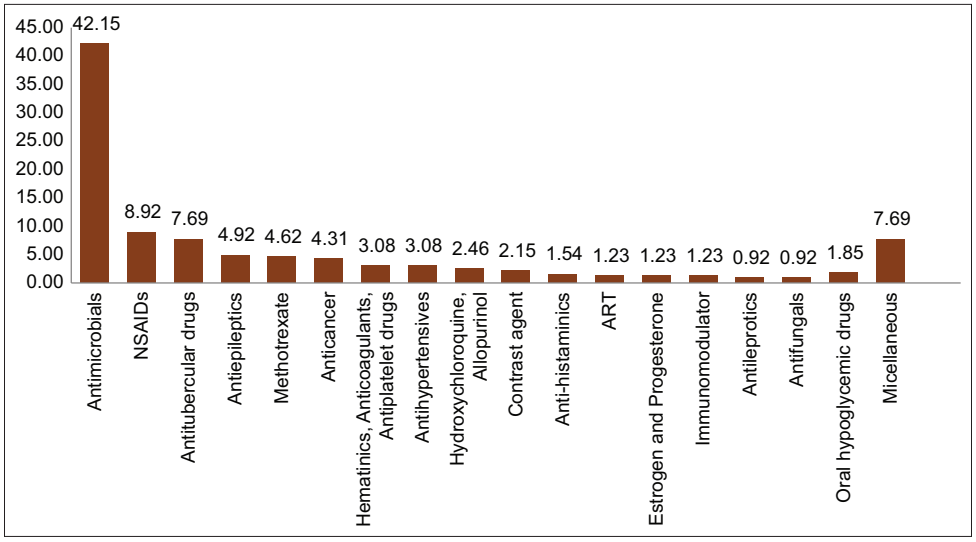

Fig. 2: Suspected medications of cutaneous adverse drug reaction (n=325)

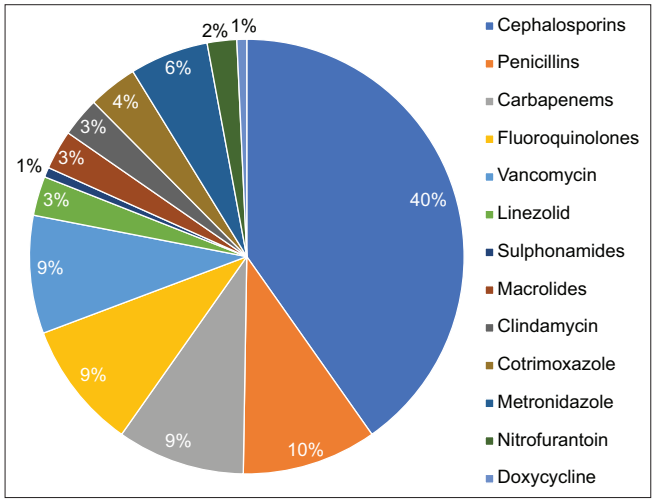

Fig 3: Antimicrobials causing cutaneous adverse drug reaction (n=136)

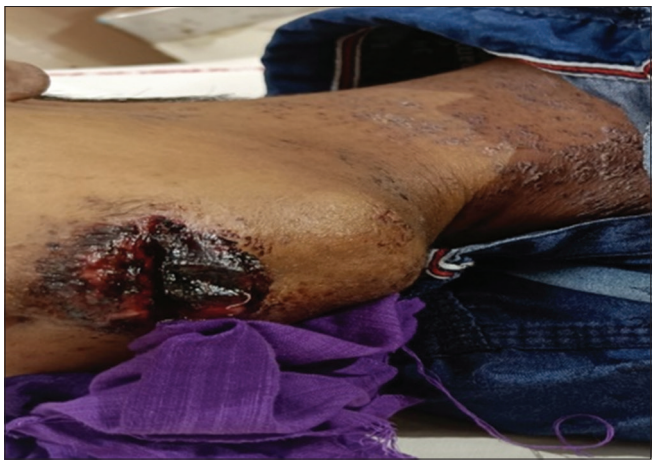

Fig. 4: A case of Stevens-Johnson syndrome with beta-lactams

On causality assessment, only 22 (8%) CADR were found to be probable while 250 CADR were recorded as possible (92%) as per WHO-UMC criteria. The CADRs that were classified as probable are depicted in Table 3 with their outcomes.

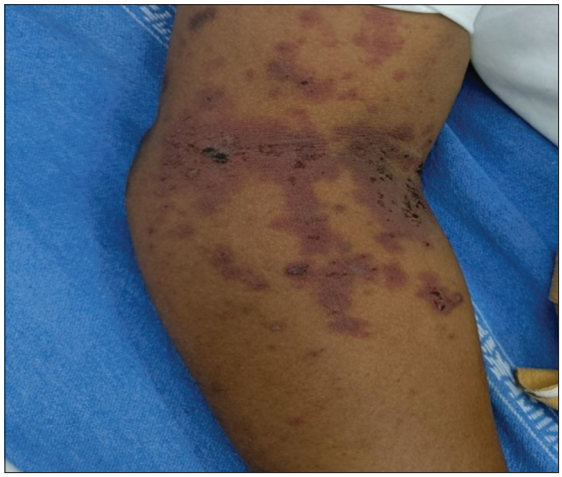

Fig. 5: A case of cutaneous vasculitic reaction with enoxaparin

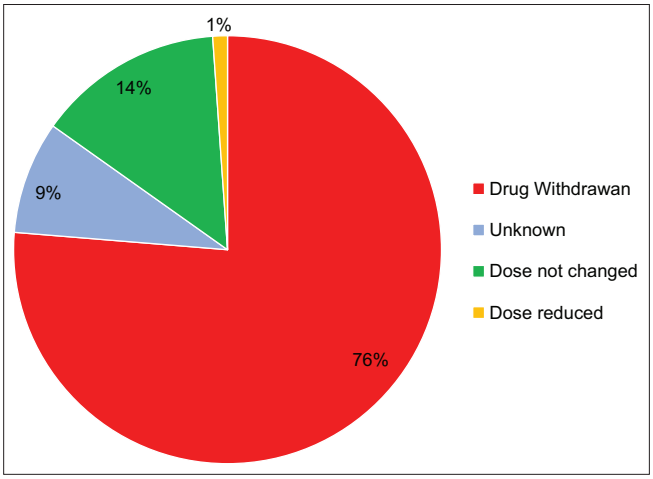

Fig. 6: Action taken with respect to the suspected drug causing cutaneous adverse drug reaction

DISCUSSION

Our study has shown that the incidence of CADR increases with age with the median age of presentation being 41 years. This corroborates with studies by Kumar *et al.*, Patel *et al.*, where majority of the CADR were

Table 2: Serious cutaneous adverse drug reaction (n=44) and their suspected medications

Clinical presentation	Number of CADR	Percentage	Suspected medications
Drug rash Maculopapular Erythematous rash	20	45.45	
Purpuric rash	16	36.37	Beta-lactam antibiotics, ATT drugs, levetiracetam, tramadol
Pruritic rash	1	2.27	Cotrimoxazole
	3	6.82	Cefoperazone+sulbactam, metronidazole Leflunomide, meropenem, vancomycin, phenytoin
Bullous exfoliative lesions	8	18.18	Antitubercular drugs, cefpodoxime+clavulinic acid, misoprostol+mifepristone, piperacillin+tazobactam, levofloxacin, hydroxychloroquine, meropenem, linezolid, cefixime
Stevens Johnsen's syndrome	3	6.82	Cotrimoxazole, aceclofenac, paracetamol, thiocolchicoside, faropenem, levofloxacin, torsemide
Lip angioedema	2	4.55	Enalapril, aspirin, amlodipine, vancomycin
Fixed drug eruptions	2	4.55	Cefixime, ceftriaxone
Anaphylaxis	2	4.55	Ceftriaxone
Mucositis	1	2.27	Capecitabine
Lip ulceration, dry lips, bleeding	1	2.27	Meropenem, clindamycin
Pruritis	1	2.27	Phenytoin
Toxic epidermal necrolysis	1	2.27	Cefixime, azithromycin, chloroquine
Gingival hyperplasia	1	2.27	Phenytoin
Fever, chills, urticaria	1	2.27	Danazol, ormeloxifene
Skin pigmentation	1	2.27	Ferric carboxymaltose

CADR: Cutaneous adverse drug reaction, ATT: Anti-tubercular therapy

Table 3: Probable Cutaneous adverse drug reaction and their suspected medications (n=22)

Clinical presentation	Number of CADR	Percentage	Suspected medications	Outcome
Drug rash	10	45.45		
Maculopapular erythematous rash	6		Cefoperazone+sulbactam, decitabine	Recovered,
Purpuric rash	1		Tramadol, cotrimoxazole, Contrast agent, leflunomide	Recovering
Pruritic rash	3		Cefoperazone+sulbactam Contrast agent, hair dye	
Anaphylactic reactions	4	18.18	Ceftriaxone, irinotecan, hydrocortisone	Recovered
Pruritis	3	13.63	Montelukast, contrast agent	Recovered
Cutaneous blebs with itching	2	9.1	Contrast agent	Recovered
DRESS	1	4.5	Metronidazole	Recovered
Lip swelling	1	4.5	Vancomycin	Recovered
Toxic epidermal necrolysis	1	4.5	Cefixime, azithromycin, chloroquine	Unknown

DRESS: Drug reaction with eosinophilia and systemic symptoms

in the age group of 40–60 years [5,6]. It has been shown by the same researchers that both pediatric and geriatric patients are more prone to develop CADR. Yet in our study, only one CADR in the pediatric age group was reported. This may be because our super specialty hospital does not have a dedicated pediatric OPD.

Women have up to 1.7 times higher risk of developing CADR which is attributed to gender-related differences in pharmacokinetic and hormonal characteristics [7]. Goutham and Rajendran, have shown that female sex is considered a risk factor for CADR [8]. Similar observations have been found in our study with 52% of females and 48% of males reporting CADR.

Maculopapular rash (63%) was the most commonly observed CADR in our study. This is in agreement with studies by Jha *et al*., Jayanthi R *et al*., and Hina *et al*. where the frequency varied from 26% to 69% [9-11]. The second most common CADR reported in our study is urticaria (8%) followed by FDEs (4.4%). Similar findings were reported by Hina *et al*. (with 10% Urticaria and 5% FDE cases). However, in contrast to our findings, Roge *et al*., have reported a higher incidence of FDEs (42%) than urticaria (10%) [12]. This may be due to the differences in the drug utilization patterns and pharmacogenetic variability in drug response in the differing population subgroups. While Roge *et al*. had studied CADR in a tertiary care center in Central India, our findings are mainly from the south Indian population [12].

In our study, 16% serious CADR have been reported. This corroborates with findings by Modi *et al*. and Rajendran *et al*. who have reported 10% and 13% of serious CADR, respectively [13,14]. Among the serious CADR reported in our study, three cases of SJS (6%) and one case of TEN were reported, which were mainly caused by antimicrobials. Previous studies by Jha *et al*. show a similar trend with 6% of SJS cases [7]. However, higher incidences of life-threatening CADR (19% SJS cases) have been reported by Sushma *et al*. [15]. This may be because the study by Sushma *et al*. was of longer duration (9 years) and most of the SJS and other severe CADR were reported to be caused by antiepileptics.

Antimicrobials (42%), especially beta-lactams (n=82) and fluoroquinolones (n=13) were the major suspected medications as seen in our study. Similar findings have been shown in studies by Jayanthi *et al*. and Roge *et al.* where antimicrobials accounted for 37% and 41% of all the CADR, respectively [10,12]. However, Roge *et al*. have shown that both amoxycillin and sulfa drugs (Cotrimoxazole) were equally implicated in causing CADR. In contrast in our study, the incidence of CADR was found to be low with sulfa drugs. This may be attributed to the rampant use of beta-lactams rather than sulfa drugs in our hospital.

NSAIDs such as tramadol, paracetamol, and aceclofenac were the second most common suspected medications accounting for up to 9% of all CADR in our study. As per a systematic review by Patel *et al*., the rate of CADR due to NSAIDs is higher, that is, up to 20% among all offending

drugs [6]. This may be due to the widespread over-the-counter use of NSAIDs. CADR, especially urticaria, occurs more commonly due to inhibition of prostaglandin synthesis, thereby resulting in the increased synthesis and release of leukotrienes.

In our study, in 76% of the cases, the drugs were withdrawn and 33% of patients had recovered while 52% were recovering during the reporting of CADR. The latency period for the majority of CADR was within 1 day to 1 week post-drug exposure mainly for antimicrobials and NSAIDs. As most of the drug reactions are immunologically mediated, hence prompt withdrawal of the drugs resulted in better outcomes. Similar findings were reported in studies by Jayanthi *et al*. [10].

Most of the CADR have been classified as possible or probable on causality assessment in our study. No CADR has been reported as "Certain" as rechallenge with the suspected drug was not done in any case. Majority of the drugs were reported as "Possible" because concurrent use of other medications and the underlying disease pathology could not be ruled out during causality assessment. Studies by Modi *et al*. too have shown a maximum possible relationship with drugs (65%) followed by probable as per WHO-UMC criteria [13].

CONCLUSION

Our study provides important insight regarding CADR among the patients of our hospital. A wide spectrum of clinical presentations of CADR has been reported. Furthermore, our study highlights that timely diagnosis of CADR and prompt withdrawal of suspected medication can be lifesaving. However, the limitations of our study are that it is cross-sectional, of a short duration, and that not all details were captured in the ADR reporting form, especially pertaining to past history of any drug reactions. Moreover, rechallenge testing especially in non-serious CADR cases may better help in the assessment of causality and preventability, which was not done in our study. Hence, large-scale, prospective pharmacovigilance studies are the need of the hour, which may help us in a better understanding of CADR and the drugs causing them so that steps may be undertaken to prevent such CADRs in the future.

ACKNOWLEDGMENT

The authors would like to acknowledge the National Coordination Centre-PvPI for their logistic and technical support and the faculty of other departments of NIMS, Hyderabad, for referring the ADRs to AMC, PVPI.

AUTHORS' CONTRIBUTION

Study conception and design: Usharani Pingali. Data collection: Ankita Panigrahy, Asiya Begum, Amal Sajeev. Analysis and interpretation of results: Ankita Panigrahy, Usharani Pingali, Asiya Begum. Draft and manuscript preparation: Usharani Pingali, Mekala Padmaja, Ankita Panigrahy.

CONFLICTS OF INTEREST

None.

FUNDING

This study received no specific grant from any funding agency.

DISCLAIMER

1. Data from VIGIFLOW (software of PVPI) have been used in the study
2. There is only a likelihood that the suspected reactions were drug-related and it is not the same in all cases
3. The views of the authors expressed in the manuscript are personal and it does not represent the opinion of NCC-PVPI or its scientific committee/group or other regulatory agencies.

REFERENCES

1. Safety of Medicines: A Guide to Detecting and Reporting Adverse Drug Reactions: Why Health Professionals Need to Take Action. World Health Organization. Available from: https://www.who.int/publications/i/item/WHO-EDM-QSM-2002-2
2. Malhotra S, Kaur B, Kaur I. A prospective study of clinical spectrum of cutaneous adverse drug reactions and their incidence in Indian population. IP Indian J Clin Experimental Dermatol. 2021 May 15;7(2):143-7.
3. Fact Sheet No293. Medicines: Safety of Medicines-Adverse Drug Reactions. Geneva: World Health Organization; 2008.
4. Keche Y, Gaikwad N, Dhaneria S. Preventability, predictability, severity and causality assessment of adverse drug reactions reported from a teaching hospital in Chhattisgarh: A retrospective analysis. J Family Med Prim Care. 2021;10(7):2541-5.
5. Kumar M, Manjhi PK, Singh S, Soni, Singh DK, Deo S. Appraisal of inter-rater agreement among assessment scales and retrospective analysis of validated reports of cutaneous adverse drug reactions at tertiary care hospital in Eastern India. J Clin Diagn Res. 2021;2(2):FC17-22.
6. Patel TK, Thakkar SH, Sharma D. Cutaneous adverse drug reactions in Indian population: A systematic review. Indian Dermatol Online J. 2014 Dec;5(Suppl 2):S76-86.
7. Sportiello L, Capuano A. Sex and gender differences and pharmacovigilance: A knot still to be untied. Front Pharmacol. 2024;15:1397291.
8. Goutham S, Rajendran N. Patterns of cutaneous drug reactions: A review. J Basic Clin Appl Health Sci. 2019;2(4):134-7.
9. Jha N, Alexander E, Kanish B, Badyal DK. A study of cutaneous adverse drug reactions in a tertiary care center in Punjab. Indian Dermatol Online J. 2018;9:299-303.
10. Jayanthi CR, Bedwal A, Rajarathna K. Cutaneous adverse drug reactions from a teaching hospital in Bengaluru: An observational study to determine the spectrum and outcome. Natl J Physiol Pharm Pharmacol. 2017;1:476-481. doi:10.5455/njppp.2017
11. Hina A, Masood S, Jamil S, Tabassum S, Jalil P, Ghulam U, *et al*. Prevalence of clinical spectrum of cutaneous adverse drug reactions in patients presenting at a tertiary care hospital in Pakistan. Cureus. 2021;13(4):e14568.
12. Roge RP, Mukhi JI, Mamidwar SM, Rokade PR, Supekar BB. Clinical patterns of cutaneous adverse drug reactions in tertiary care centre of central India: A cross-sectional study. Indian J Drugs Dermatol. 2023;9:28-33.
13. Modi A, Desai M, Shah S, Shah B. Analysis of cutaneous adverse drug reactions reported at the regional ADR monitoring center. Indian J Dermatol. 2019 May-Jun;64(3):250.
14. Rajendran L, Thyvalappil A, Sridharan R, Ajayakumar S, Deep S, Divakaran B. A study of cutaneous adverse drug reactions in a tertiary care center in South India. Clin Dermatol Review. 2021;5:173-7.
15. Sushma M, Noel MV, Ritika MC, James J, Guido S. Cutaneous adverse drug reactions: A 9-year study from a South Indian Hospital. Pharmacoepidemiol Drug Saf. 2005l;14:567-70.