ORIGINAL RESEARCH

A Retrospective Analysis of Spontaneously Reported Cutaneous Adverse Drug Reactions At ADR Monitoring Centre of A Tertiary Health Care Teaching Hospital of India

Dr. Jhanvi Vaghela

Department of Pharmacology, Smt. B.K.Shah Medical Institute & Research Centre, Sumandeep Vidyapeeth deemed to be University, Waghodia, Vadodara, Gujarat, India

Corresponding Author
Dr. Jhanvi Vaghela
Department of Pharmacology, Smt. B.K.Shah Medical Institute & Research Centre, Sumandeep Vidyapeeth deemed to be University, Waghodia, Vadodara, Gujarat, India
Email: drjhanvivaghela91@gmail.com

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ABSTRACT

Introduction: Cutaneous adverse drug reactions (ADRs) present a substantial challenge in healthcare, ranging from mild rashes to life-threatening conditions, impacting patient safety and clinical management. Understanding the prevalence, patterns, and causative drugs of cutaneous ADRs in India is critical for optimizing patient care. The Adverse Drug Reaction Monitoring Centre (AMC) plays a pivotal role in assessing drug-related adverse events, utilizing spontaneously reported data to explore real-world drug impact. The objective of this retrospective observational study was to describe clinical patterns, identify associated drugs, and conduct causality assessments for cutaneous ADRs using the WHO causality assessment scale. **Methods**: Data from spontaneously reported cutaneous ADRs between August 2015 to September 2020 at the ADR Monitoring Centre were analyzed. Demographics, clinical characteristics, implicated drugs, and causality were assessed using WHO-UMC criteria. **Results**: Among 164 reported CADRs, 56.7% occurred in males, with a higher prevalence in the 16-30 age group. Maculopapular rash (28.7%) and erythema multiforme (19.5%) were predominant. Antimicrobial drugs (62 cases) and anti-epileptic drugs (30 cases) were frequently implicated. 80% of cases were classified as "serious," with 45.7% experiencing complete resolution. **Conclusion**: The study provides insights into CADR demographics, manifestations, causative drugs, outcomes, and causality assessments. Regional consistency in patterns emphasizes the importance of understanding local variations. The findings underscore the significance of antimicrobial, anti-epileptic, and NSAID drugs, informing vigilant prescribing and monitoring practices. This information is invaluable for healthcare practitioners, aiding in risk identification, intervention planning, and contributing to enhanced drug safety measures. These insights may inform clinical guidelines and contribute to safer drug formulations, addressing the complex landscape of cutaneous ADRs in diverse populations.

Key words: Cutaneous adverse drug reactions, Adverse drug reaction, Pharmacovigilance, Causality assessment, Patient safety

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INTRODUCTION

Cutaneous adverse drug reactions (CADRs) represent a complex and significant concern within the realm of modern healthcare. These reactions, ranging from mild rashes to severe and life-threatening conditions, pose substantial challenges to patient safety, clinical management, and overall public health. As medications play an indispensable role in disease management, understanding the intricacies of adverse reactions, is paramount. Adverse drug reactions (ADRs) constitute a pervasive issue globally, affecting millions of individuals annually. Among these, CADRs are especially noteworthy due to their diverse clinical presentations and potential for severe outcomes. These reactions can manifest as maculopapular rashes, erythema multiforme, pruritus, dermatitis, and, in extreme cases, life-threatening conditions like Stevens-Johnson Syndrome (SJS) and

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toxic epidermal necrolysis (TEN). According to studies, CADRs occur in approximately 2-3% of all hospitalized patients, highlighting the prevalence and clinical significance of these reactions in various healthcare settings.[1] Furthermore, the global impact of CADRs is underscored by their association with increased healthcare costs, significant morbidity, diminished quality of life, and, in rare instances, mortality. Despite the rigorous pre-approval clinical trials conducted for pharmaceutical products, the full extent of drug safety may not become apparent until drugs are widely used in real-world clinical practice.[2]

The Adverse Drug Reaction Monitoring Centre (AMC) plays a critical role in the identification, assessment, and management of drug-related adverse events. These centres serve as repositories of spontaneously reported data, providing valuable insights into the real-world impact of drugs on the population. The utilization of such data offers an opportunity to explore the patterns and characteristics of CADRs, providing a nuanced understanding of the challenges and opportunities for improving drug safety in diverse healthcare landscapes.

In India, a country with a vast and diverse population, understanding the prevalence, patterns, and causative factors of CADRs is of paramount importance. The heterogeneity in genetic makeup, cultural practices, and environmental factors within the Indian population can contribute to variations in drug metabolism and response. Furthermore, the widespread use of traditional and alternative medicines alongside conventional pharmaceuticals adds a layer of complexity to drug safety considerations. Studies have indicated that the incidence and characteristics of CADRs may vary across different regions and populations within India.[3] Regional variations in diet, lifestyle, and genetic factors may influence the susceptibility of individuals to specific adverse reactions. Therefore, a comprehensive analysis of CADRs in the Indian context is crucial for tailoring drug safety measures to the unique characteristics of the population. Despite the availability of extensive data from pre-approval clinical trials, the true safety profile of drugs often unfolds in the post-marketing phase. The limitations of clinical trials, such as their relatively small sample sizes and controlled environments, may not fully capture the breadth of adverse reactions that can emerge when drugs are used in a broader patient population with various comorbidities and concomitant medications.[2]

Spontaneously reported data, as collected by AMC, contributes to the ongoing surveillance of drug safety in real-world clinical practice. Cutaneous ADRs, with their potential for widespread impact and varied clinical presentations, demand focused attention within the Indian healthcare context. The current study was planned to address this need by undertaking a retrospective observational analysis of spontaneously reported CADRs at the ADR Monitoring Centre in Vadodara, India. The objectives of the study encompass a thorough exploration of demographic patterns, clinical manifestations, causative drugs, outcomes, severity, and causality assessments using the WHO causality assessment scale.

MATERIALS AND METHOD

The study was conducted at the Adverse Drug Reaction Monitoring Centre located at Smt. B. K. Shah Medical Institute & Research Centre in Vadodara, India. This study employed a retrospective observational design to analyze spontaneously reported cutaneous adverse drug reactions over the five years, from August 2015 to September 2020. The study protocol was subjected to rigorous ethical scrutiny and received approval from the Institutional Ethics Committee of Sumandeep Vidyapeeth deemed to be university. (Approval number: SVIEC/ON/MEDI/RP/20091.

Data collection focused on spontaneously reported CADRs documented at the AMC during the stipulated period. Patient information was systematically retrieved from the CADR reports, which included details on demographics, clinical characteristics, drugs implicated in the reaction, and the duration of drug therapy. The use of spontaneously reported data allowed for the inclusion of diverse cases encountered in real-world clinical settings.

Collected data underwent a comprehensive and systematic analysis to extract meaningful insights into the frequency, severity, and types of CADRs. The demographic distribution of CADRs, including age and gender, was analyzed to identify any notable patterns or variations. The severity of ADRs was classified into categories such as "serious" and "non-serious," with further details on the nature of serious cases. Causative drugs were systematically identified from the ADR reports and categorized based on therapeutic classes. The outcomes of CADRs were assessed in terms of resolution, ongoing cases, and cases lacking improvement. The causality of the reported CADRs was assessed using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) causality assessment criteria. This standardized tool provides a structured approach to determining the likelihood of a causal relationship between the observed adverse event and the implicated drug.

RESULTS

Gender and age distribution of patients

During the study period, a total of 164 cutaneous ADRs were reported. Among these, 93 (56.7%) were reported in males, while 71 (43.3%) were reported in females. (Table 1) The age distribution of ADR cases revealed that the majority of reactions occurred in the age group of 16 to 30 years, accounting for 38.4% of the total reported cases. Following this group, the age group of 31 to 45 years accounted for 28%, in 46 to

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60 years, the incidence of ADRs was 17.7%, 0 to 15 years constituted 9.7% of the reported cases, while those aged more than 60 years represented 6% of the total ADR cases. (Table 1)

Types of clinical manifestations of CADR

The most frequently reported cutaneous ADR was maculopapular rash, accounting for 47 cases (28.7%), followed by erythema multiforme (EM) with 32 cases (19.5%), pruritis with 16 cases (9.8%), and dermatitis with 15 cases (9.1%). Other reported cutaneous ADRs included injection site reaction/rash (8 cases), fixed drug reaction (10 cases), urticaria (3 cases), stria (5 cases), Stevens-Johnson Syndrome (SJS) (3 cases), SJS-TEN (1 case), toxic epidermal necrolysis (TEN) (3 cases), bullous eruption (2 cases), acneiform eruption (3 cases), hyperpigmentation (5 cases), hypopigmentation (1 case), non specified skin lesion (7 cases), skin atrophy (2 cases), and drug reaction with eosinophilia and systemic symptoms (DRESS) (1 case). (Figure 1)

Drugs involved in CADR

Among the causative drugs, antimicrobial drugs were the most frequently implicated in CADRs, accounting for 62 cases. Within this category, β-lactam antibiotics, including Penicillins (4 cases) and Cephalosporins (14 cases) were the most commonly reported, with 18 cases. Fluoroquinolones accounted for a total of 15 cases. Among the antifungal drugs, fluconazole (1 case), ketoconazole (2 cases), clotrimazole (2 cases), itraconazole (1 case), and terbinafine (1 case) were found to be causative agents of total 7 CADRs. The rest of the suspected antimicrobial drugs are shown in Table 2.

Furthermore, anti-epileptic drugs were linked to 30 cases of CADRs, with phenytoin being the most commonly reported (16 cases), followed by carbamazepine (13 cases) and phenobarbitone (1 case). Other CNS drugs, such as clobazam, and paroxetine, were responsible for an additional 4 cases, two each. The analysis also revealed that non-steroidal anti-inflammatory drugs (NSAIDs) were another significant contributor to CADRs, with 24 cases. Among the NSAIDs, nimesulide, paracetamol, and diclofenac were the most frequently reported drugs with 10, 6, and 4 cases, respectively. Corticosteroids were implicated in 23 cases of CADRs. (Table 2)

The outcome of the event

Among the reported cases, 45.7% cases experienced complete resolution of the cutaneous ADRs. Additionally, in 17.7% of cases, ADRs were in the process of resolving. In 14.6% of cases, there was a lack of improvement in the cutaneous reactions. The resolution status was not clear or not reported in 22% of reported CADRs. (Table 3)

The seriousness of the reaction

Out of the total cases, 80% were classified as "serious" ADRs while 20% were categorized as "non-serious" ADRs. Among the serious cases, the majority were associated with either a prolongation of hospitalization or requiring hospitalization (44 cases, 26.8%), followed by cases that required intervention for curing the adverse reaction (39 cases, 23.8%). There were three cases (1.8%) reported as "life-threatening" ADRs and one case (0.6%) resulted in death. (Figure 2)

WHO Causality assessment

Among the reported cases, 93 cases (56.7%) were categorized as "possible" ADRs and 71 cases (43.3%) were classified as "probable/likely" ADRs. (Figure 3).

TABLES & FIGURES

Table: 1 Age and Gender distribution of reported CADRs

	Male	Female	Total
Adverse Drug Reaction Reported	93 (57.7%)	71 (43.3%)	164 (100%)
Age-wise distribution of reported CADRs			
0-15 years	10 (6.1%)	6 (3.7%)	16 (9.8%)
16-30 years	34	29	63 (38.4%)
31-45 years	26	20	46 (28%)
46-60 years	15	14	29 (17.7%)
>61 years	8	2	10 (6.1%)

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Figure: 1 Types of clinical manifestation of CADRs

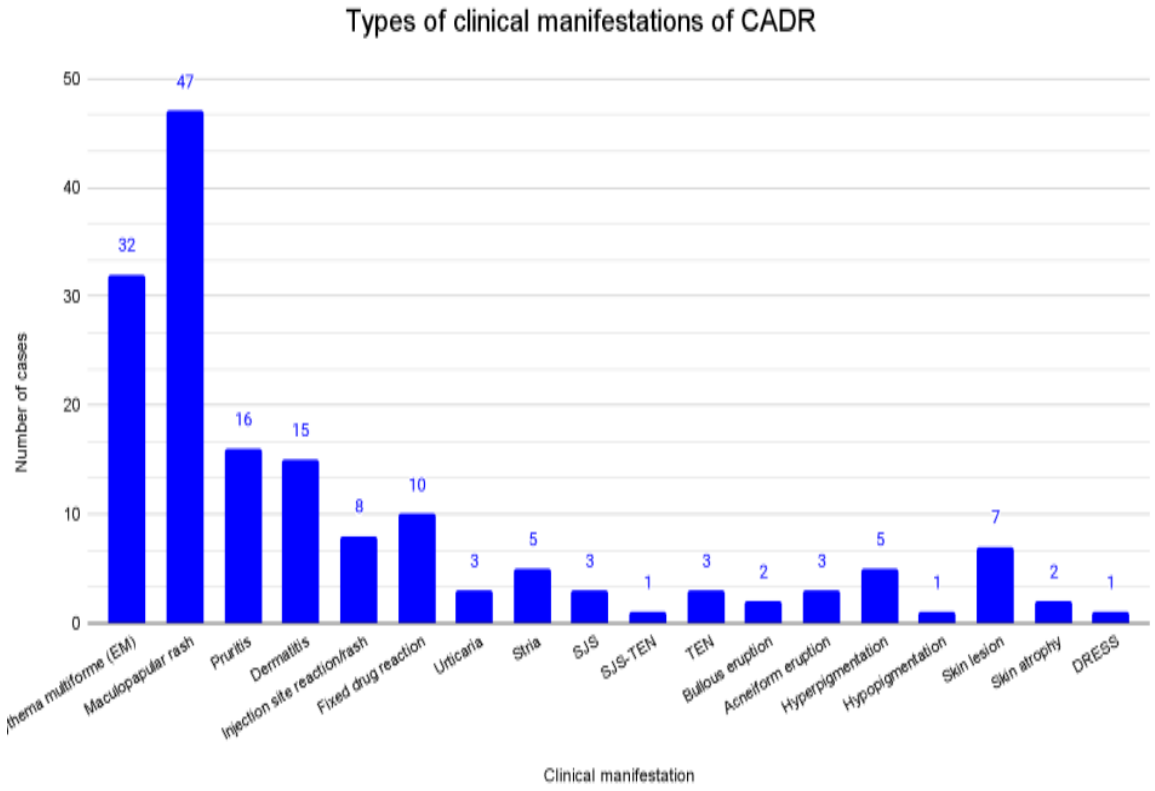

Table 2: Distribution Of Causative Drugs And Their Respective Drug Classes

Drug class	No of ADR reported	Causative Drugs
Antimicrobial Drugs	58	
B-Lactams	18	Penicillins (4), Cephalosporins (14)
Fluoroquinolones	15	Levofloxacin (3), Ofloxacin (11), Ciprofloxacin (1)
Sulfonamides	3	Sulphasalazine (1), Cotrimoxazole (2)
Macrolides	4	Azithromycin (3), Clarithromycin (1)
Antitubercular Drugs	4	
Antileprotic Drugs	5	Dapsone (5)
Antimalarial Drugs	2	Chloroquine (2)
Antifungal Drugs	7	Fluconazole (1), Ketoconazole (2), Clotrimazole (2), Itraconazole (1), Terbinafin (1)
NSAIDs	24	Ibuprofen (1), Diclofenac (4), Aspirin (2), Paracetamol (6), Nimesulide (10), Naproxen (1)
Anticonvulsants	30	Carbamazepine (13), Phenytoin (16), Phenobarbitone (1)
Antidepressant-Anxiolytic		Clobazam (2), Paroxetine (2)
Corticosteroids	23	Betamethasone (7), Beclomethasone (6), Clobetasone (8), Fluticasone (2)
Miscellaneous Drugs	19	Ondansetron (6), Ranitidine (1), Pantoprazole (1), Immunosuppressant (4), Immunoglobulines (1), Iron Preparation (1), Fexofenadine & Montelukast (1), Tramadol (1), Multivitamins (2), Heparin (1)

Table 3: Outcome of reported CADRs

OUTCOME	Number of ADRs (%)
Recovered	75 (45.7%)
Recovering	29 (17.7%)
Not recovered	24 (14.6%)
Unknown	36 (22%)

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Figure: 2 Seriousness of CADRs

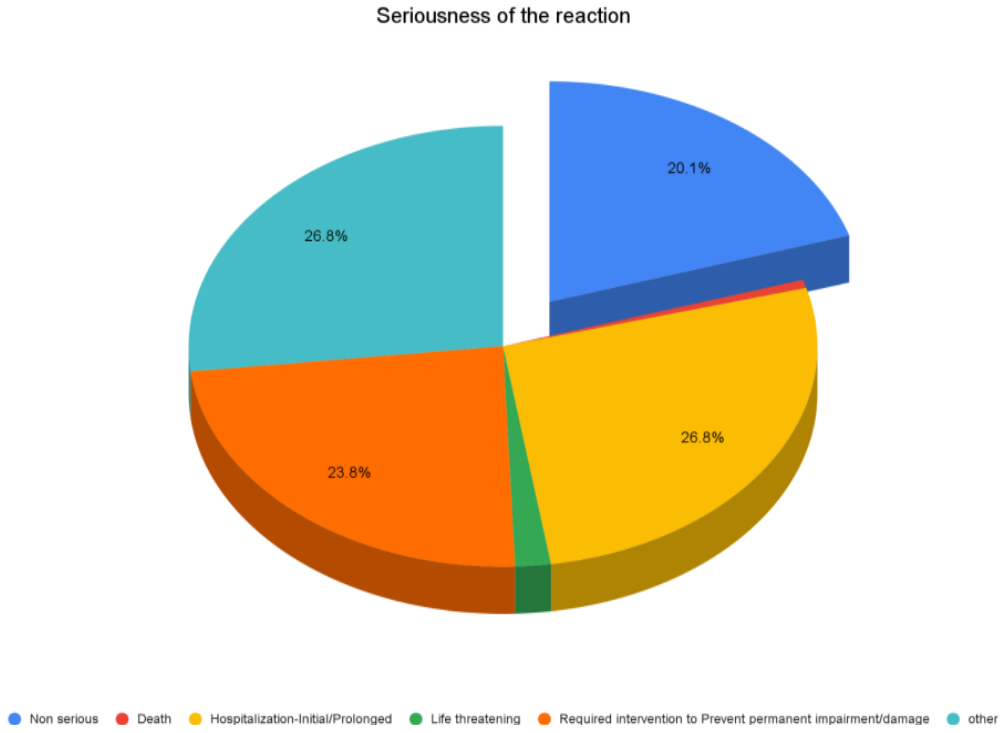
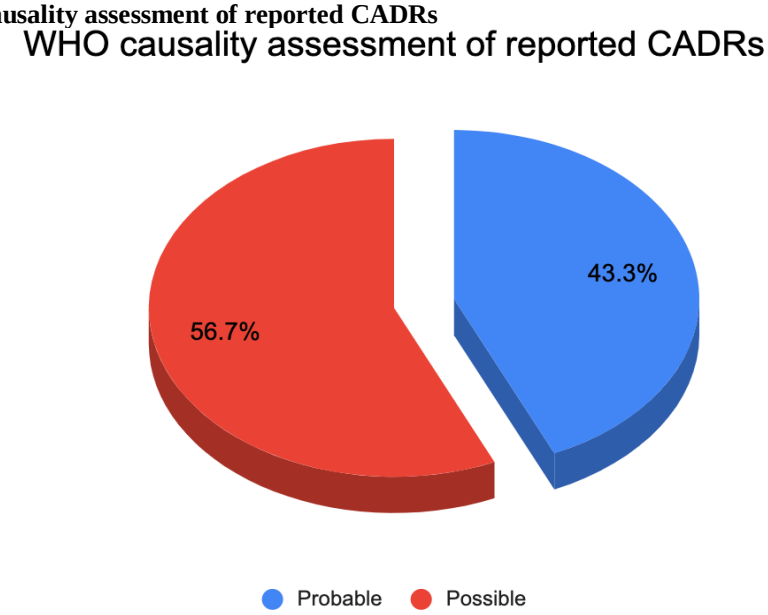


Figure: 3 WHO causality assessment of reported CADRs



DISCUSSION

In the present study, the gender distribution of CADRs revealed a higher prevalence in males (56.7%) compared to females (43.3%). Such gender-based variations in drug reactions have been documented in literature and could be influenced by genetic, hormonal, or environmental factors. The age distribution patterns are equally intriguing, with a substantial majority of CADRs occurring in the age group of 16 to 30 years (38.4%). This age bracket is often associated with increased medication usage, potentially due to higher likelihood of drug usage in this age group, coupled with increased susceptibility to skin-related reactions during adolescence and young adulthood.[5] These findings align with the outcomes presented in the study conducted by Sharma et al which shows a male-to-female ratio of 1.7:1.2 and a common age group of 21-30 years.[6] However, there are several other studies in which females were commonly affected or equally affected. [7,8] The variability in gender and age distribution across different studies suggests the complex interplay of multiple factors influencing CADRs. The diverse clinical manifestations of CADRs, as identified in the study, underscore the complexity of skin reactions to drugs. The most frequently reported manifestation

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was maculopapular rash, followed by erythema multiforme, pruritis, and dermatitis. Interestingly, these findings align with a study conducted by Modi et al and Gohel et al in the nearby geographic region of Gujarat. [2,9,10] Such regional consistency emphasizes the importance of understanding local patterns of CADRs, aiding clinicians in promptly identifying and addressing these common presentations. The diversity in reported CADRs underscores the intricate nature of skin reactions to drugs, emphasizing the necessity for individualized management strategies.[11] The spectrum of reported manifestations includes severe conditions such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, highlighting the potential gravity of CADRs. These severe manifestations, although less common, necessitate heightened vigilance due to their association with significant morbidity and mortality. Antimicrobial drugs, particularly β-lactam antibiotics and fluoroquinolones, emerged as the most frequently implicated in CADRs. This emphasizes the need for cautious prescribing and close monitoring, especially considering the widespread use of these medications in various clinical settings. The involvement of anti-epileptic drugs, NSAIDs, and corticosteroids underscores the importance of vigilant surveillance when using these classes of drugs, particularly in patients prone to skin sensitivities.[2,12,13] The identification of specific drugs within these classes, such as phenytoin, nimesulide, and fluconazole, provides targeted information for clinicians to consider in their prescribing practices. This detailed analysis contributes to pharmacovigilance efforts, aiding in the development of safer prescribing guidelines. The outcomes of CADRs revealed that 45.7% of cases experienced complete resolution, showcasing the manageability of many reactions with appropriate intervention. However, the 14.6% of cases lacking improvement underscores the challenges in managing certain reactions, potentially due to delayed recognition or inadequate treatment strategies. The 17.7% of cases in the process of resolving emphasizes the dynamic nature of skin reactions, necessitating ongoing monitoring and care. The severity of CADRs, as categorized by the study, highlights the clinical significance of these reactions. The majority of cases were classified as "serious," with notable proportions associated with hospitalization, interventions, and, in rare cases, life-threatening outcomes or death. This underscores the critical need for awareness, rapid intervention, and appropriate medical management to mitigate the potential severity of CADRs.

The application of the World Health Organization (WHO) causality assessment provided a structured approach to evaluating the likelihood of ADRs being attributed to specific drugs.[14] The study found that 56.7% of cases were categorized as "possible" ADRs, and 43.3% as "probable/likely" ADRs. This distribution aligns with similar observations in the literature, reinforcing the utility of the WHO causality assessment in informing decisions regarding drug continuation, discontinuation, or alternative choices. The strength of this study lies in its comprehensive analysis of various aspects of CADRs, providing a nuanced understanding of these reactions in a diverse patient population. However, it is essential to acknowledge certain limitations, such as the retrospective nature of the study and the potential underreporting of CADRs, which may impact the generalizability of the findings.

CONCLUSION

In conclusion, the study's results contribute significantly to our understanding of CADRs in terms of their demographics, manifestations, causative drugs, outcomes, seriousness, and causality assessment. This information serves as a valuable resource for healthcare practitioners, enabling them to identify at-risk populations, predict common manifestations, and implement appropriate interventions. Moving forward, these insights could inform clinical practice guidelines, enhance patient safety measures, and potentially contribute to the development of safer drug formulations. However, the potential underreporting of cutaneous ADRs is one of the limitations of our study that needs to be considered when interpreting and applying these findings.

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