ORIGINAL ARTICLE

Incidence and clinical patterns, severity and preventability of cutaneous adverse drug reactions among hospitalized patients in a tertiary centre

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ABSTRACT

Introduction: Cutaneous adverse drug reactions (cADRs) are among the most common manifestations of adverse drug reactions, ranging from mild eruptions to severe, life-threatening conditions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Despite increasing reports from Malaysia's National Pharmaceutical Regulatory Agency, local epidemiological data at the state level remain scarce. This study aimed to determine the incidence, clinical patterns, severity, and preventability of cADRs among hospitalized patients in Hospital Tuanku Ja'afar Seremban (HTJS), and to identify the drugs most frequently implicated and predictors of severe disease.

Materials and Methods: We conducted a prospective, observational cross-sectional study over six months (February–July 2024) at HTJS. Patients admitted with, or developed cADRs during hospitalization secondary to systemic medications were included. Exclusion criteria were allergic/irritant contact dermatitis, chemotherapy-induced alopecia, allergic reactions to radiographic contrast or blood products, and outpatient cases. Data on demographics, clinical features, implicated drugs, severity (modified Hartwig and Siegel scale), preventability (Schumock and Thornton scale), and causality (Naranjo's Algorithm) were collected. Multiple logistic regression identified predictors of severe cADRs.

Results: Among 30,667 admissions, 70 patients met inclusion criteria (incidence: 0.228%). The mean age was 46.2 ± 21.4 years; 55.7% were female and 71.4% Malay. Most cases occurred in medical departments (60%). The commonest reaction patterns were maculopapular eruption (37.1%) and urticaria (35.7%). Antibiotics accounted for 50% of cases, with penicillin being the leading culprit (37.1%), followed by NSAIDs, analgesics, anti-platelet and anti-tuberculosis drugs. Most reactions were of moderate severity (80.0%); one SJS/TEN case was classified as severe according to Hartwig scale. Preventability assessment found 14.3% definitely preventable events, primarily due to re-exposure to known allergens. Multiple logistic regression identified raised eosinophil count (AOR 21.83, p=0.001), mucosal involvement (AOR 29.82, p=0.016), and impaired renal function (AOR 7.98, p=0.024) as independent predictors of severe reactions.

Conclusion: Our study highlights a cADR incidence of 0.228% among hospitalized patients, with antibiotics, especially penicillin group, being the most frequent culprit drug. While most reactions were moderate and not preventable, significant predictors of severity included raised eosinophils, mucosal involvement, and renal impairment. Enhanced vigilance, careful drug selection, and early recognition of high-risk clinical features are crucial to reducing the burden of cADRs in hospital settings.

INTRODUCTION

WHO defines adverse drug reaction as a "response to a drug which is noxious and unintended and occurs at doses normally used in man in any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient".[1] Adverse drug reactions (ADRs) are a significant cause of morbidity and mortality worldwide, contributing to increased hospital admissions, prolonged hospital stays, and elevated healthcare costs.[2] Cutaneous adverse drug reactions are the most common form of ADRs, with incidence ranging from 1% to 3% in hospitalized patients.[3,4] These reactions are variable and can range from mild forms such as maculopapular eruptions and urticaria to severe and potentially life-threatening conditions including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Cutaneous adverse drug reactions can have significant impact on the management of patients and have implications/complications for patient health and can affect the healthcare economy.[2]

In Malaysia, the National Pharmaceutical Regulatory Agency (NPRA) has documented an increasing number of ADR reports over the years, with cADRs constituting a considerable proportion.[5] Despite the rising trend, local data at the state or institutional level, remain limited. Negeri Sembilan, a state in Peninsular Malaysia, is home to several healthcare institutions, including Hospital Tuanku Ja'afar Seremban (HTJS), the primary tertiary referral center in the state. However, no recent comprehensive study has been conducted to evaluate the incidence and clinical spectrum of cADRs in this setting. This gap in knowledge limits efforts to develop local clinical guidelines and pharmacovigilance strategies to reduce the burden of these adverse events.

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This study aimed to determine the incidence, clinical patterns, severity, and preventability of cutaneous adverse drug reactions (cADRs) among hospitalized patients at Hospital Tuanku Ja'afar Seremban (HTJS). The study also determined the drugs most commonly implicated in cADRs and their corresponding reaction patterns. Additionally, it examined the distribution of cADR cases across various clinical departments within HTJS, evaluated the demographic profiles of affected patients, and factors affecting severity.

MATERIALS AND METHODS

This was a prospective, observational cross-sectional study with purposive sampling. Data was collected for 6 months from February 2024 to July 2024, involving patients admitted for cADR or developed cADR during hospitalization in HTJS secondary to systemic medication. An official notification letter was disseminated to the relevant hospital departments and pharmacy department, informing them of the study and the procedures for case reporting. All suspected cADR cases were promptly notified to the dermatology team for evaluation. All the patients satisfying the inclusion criteria were enrolled in the study. The exclusion criteria were allergic or irritant contact dermatitis, chemotherapy induced alopecia, allergic type reaction to radiographic contrast media and blood products. Outpatients and patients in the emergency department who were not admitted were also excluded.

A written informed consent was obtained from either the patient or guardian. All the relevant information regarding the patient including present complaints, past history, laboratory data results, clinical details, treatment received, and final outcome were recorded in data collection form. Data on cADRs like type and pattern, severity, dates on which reaction started and stopped were recorded. Details of suspected medication like generic and brand names, dosages, route, frequency, indication, date of starting, and stopping drug, concomitant drugs with doses and frequency, were also recorded. The patients were followed up till their discharge from hospital to determine outcome.

The collected data were analysed for demographic details, drug details, causality, preventability, and severity of adverse effects. Causality was assessed by using Naranjo's Algorithm, preventability by Schumock and Thornton scale and severity by modified Hartwig and Siegel scale. The Hartwig and Siegel Severity Assessment Scale categorizes adverse drug reactions into mild (levels 1–2), moderate (levels 3–4), and severe (levels 5–7) based on clinical impact and intensive management requirements.

The data were sorted, coded, and entered into Statistical Package for the Social Science (SPSS) for Windows Version 29.0 (SPSS Inc., Chicago, USA) and subsequently analysed. Descriptive statistics were used to calculate the prevalence of cADRs during the study period. Prevalence rate was determined by dividing the number of identified cADR cases by the total number of hospital admissions during the same period. Quantitative variables were expressed as means and standard deviations. Qualitative variables were expressed as frequency and percentage. Multiple logistic regression analysis was conducted to examine the association between risk factors and the likelihood of developing severe disease outcomes. The overall model was statistically significant, χ^2 (4)=31.170, $p<0.001$, indicating that the set of systemic complications meaningfully contributed to predicting severity. The model explained 35.9 of the variance in disease severity according to the Cox & Snell R^2 and 53.6 according to the Nagelkerke R^2, and it correctly classified 82.9 of cases. The Hosmer-Lemeshow goodness-of-fit test yielded a non-significant result, χ^2 (4) = 6.124, p = 0.190, suggesting that the model fits the data well.

RESULTS

A total of 70 patients were identified with suspected cADRs during the 6-month study period. With a total of 30,667 hospital admissions during the same period, the estimated incidence of cADRs was 2.28 per 1,000 admissions, equivalent to 0.228% of all admissions. The prevalence rate was higher in patients hospitalized in medical departments (60.0%) followed by dermatology (15.7%) and paediatric (10.0%). The rest of the department report sparse cases that count for less than 10.0%.

Among the 70 cADR patients, females made up a slightly higher proportion [39 (55.7%)] than males [31 (44.3%)].The ethnicity distribution of patients was predominantly Malay [50(71.4%)], with Indians [10 (14.3%)], Chinese [8(11.4%)], and other ethnicities [2(2.9%)]. This reflects the hospital admission rates: Malays had overall 19,787(64.5%) admissions, followed by Indians with 4,901(15.9%), Chinese with 3,551(11.57%). This distribution reflects the general patient demographic pattern observed in the hospital's catchment area. The mean age of patients was 46.2 ± 21.4 years. The majority of patients were adults aged 19 to 60 years [41(58.6%)], followed by elderly patients above 60 years [21(30.0%)] and paediatric patients aged 0 to 18 years[8 (11.4%)].

The majority of patients did not have pre-existing skin conditions, with only 3 patients (4.3%) reporting an underlying skin disease. A history of prior cADRs was documented in 13 patients (18.6%), while 4 patients (5.7%) had a history of atopy, such as asthma, allergic rhinitis, or eczema. Chronic comorbid conditions were present in a subset of patients. Autoimmune diseases and malignancies were each reported in 6 patients (8.6%), as was chronic kidney disease (CKD). A single patient (1.4%) was found to have an RVD (retroviral disease) infection. Only 9 patients (12.9%) did not have any co-morbids (no known medical illness). The majority of patients, 41 (58.6%) were hospitalized for 7 days or less. The mean length of hospital stay was 10.31 ± 9.96 days. The number of concurrent medications ranged from 0 to 12. The number of concurrent medications among patients had a mean of 3.69 ± 2.91. The median number of concurrent medications was 3.0, with an interquartile range (IQR) of 3.0. (Table I)

Moderate severity reactions accounted for 56 (80.0%) cases. This typically required medical intervention or hospitalization but were not life-threatening. Mild reactions

Table I: Demographic and clinical characteristics of patients with cADR

Characteristics	n (%)
Gender	
Male	31 (44.3)
Female	39 (55.7)
Ethnicity	
Malay	50 (71.4)
Indian	10 (14.3)
Chinese	8 (11.4)
Other	2 (2.9)
Age group	
Paediatric (0-18)	8 (11.4)
Adult (19-60)	41 (58.6)
Elderly (>60)	21 (30.0)
Comorbidities	
Underlying skin disease	3 (4.3)
History of cADR	13 (18.6)
History of Atopy	4 (5.7)
RVD infection	1 (1.4)
Autoimmune disease	6 (8.6)
Malignancy	6 (8.6)
CKD	6 (8.6)
No comorbids	9 (12.9)
Concurrent medications	
0-4	48 (68.6)
5-9	19 (27.1)
>10	3 (4.3)
Number of cADRs reported by department	
Dermatology	11 (15.7)
Medical	42 (60.0)
O & G	5 (7.1)
Paediatric	7 (10.0)
Rehab	1 (1.4)
Surgical	4 (5.7)
Length of hospital stay	
≤7 days	41 (58.6)
7–14 days	13 (18.6)
>14 days	16 (22.9)

Table II: Causality, preventability and severity of cADR among the study population

Parameters	n (%)
Severity of cADR (Hartwig Scale)	
Mild (1-2)	13 (18.6)
Moderate (3-4)	56 (80.0)
Severe (5-7)	1 (1.4)
Causality (Naranjo Adverse Drug Reaction Probability Scale)	
Possible (1-4)	11 (15.7)
Probable (5-8)	51 (72.9)
Definite (>8)	8 (11.4)
Preventability (Schumock and Thornton scale)	
Definitely preventable	10 (14.3)
Not preventable	60 (85.7)

were reported in 13 (18.6%) patients, involving self-limiting cutaneous eruptions that resolved with drug discontinuation and minimal supportive care. Only one (1.4%) patient with SJS fell in the severe category. The modified Schumock and Thornton criteria classified 10 reactions (14.3%) as definitely preventable, and 60 reactions (85.7%) were considered not preventable. 51(72.86%) patients had a probable causality score (5–8), 11 (15.7%) patients were assessed as possible (score 1–4), and 8 (11.43%) patients were classified as definite (>8) according to the Naranjo Adverse Drug Reaction Probability Scale. (Table II)

The onset of cADRs varied across clinical patterns. Urticaria had the earliest onset, typically occurring within less than 1 to 6 days (mean 0.40 ± 1.32 days), reflecting its nature as an immediate hypersensitivity reaction. AGEP and cutaneous vasculitis also presented early, within 2 to 7 days and 2 days, respectively. In contrast, maculopapular eruptions (MPE) showed a broader onset window ranging from 2 to 21 days (mean 7.62 ± 4.89), while TEN/SJS developed between 2 and 17 days (mean 8.67 ± 7.64), indicating their delayed hypersensitivity mechanisms. Fixed drug eruption, erythroderma, and DRESS had longer latency periods in this

Table III: Characteristics of cADR among the study population

Duration to cADR onset	**range and mean(SD) in days**	
MPE	2 -21	7.62 (4.89)
Urticaria	< 1 – 6	0.40 (1.32)
Fixed drug eruption	4	4.00 (0.00)
Cutaneous vasculitis	2	2.00 (0.00)
Erythroderma	14	14.00 (0.00)
AGEP	2-7	3.00 (1.77)
DRESS	21-56	33.60 (15.18)
TEN/SJS	2-17	8.67 (7.64)
Clinical manifestations of cADR	**n (%)**	
MPE	26 (37.1)	
Urticaria	25 (35.7)	
Fixed drug eruption	1 (1.4)	
Cutaneous vasculitis	1 (1.4)	
Erythroderma	1 (1.4)	
AGEP	8 (11.4)	
DRESS	5 (7.1)	
TEN/SJS	3 (4.3)	
Drug implicated in various cADR		
Antibiotics, total	35 (50.0)	
Bactrim	3 (4.3)	
Cephalosporin	4 (5.7)	
Meropenem	1 (1.4)	
Penicillin	26 (37.1)	
Vancomycin	1 (1.4)	
Anti-TB, total	5 (7.1)	
Akurit-4	5 (7.1)	
Anticonvulsant, total	3 (4.3)	
Lamotrigine	2 (2.9)	
Sodium valproate	1 (1.4)	
Urate-lowering, total	3 (4.3)	
Allopurinol	3 (4.3)	
NSAIDS, total	7 (10)	
Diclofenac	2 (2.9)	
Etoricoxib	1 (1.4)	
Ibuprofen	1 (1.4)	
Mefenamic acid	1 (1.4)	
Naproxen	2 (2.9)	
Other analgesics, total	7 (10)	
Fentanyl	1 (1.4)	
Paracetamol	3 (4.3)	
Paracetamol/Ibuprofen	1 (1.4)	
Tramadol	2 (2.9)	
Antiviral, total	1 (1.4)	
Acyclovir	1 (1.4)	
Antifungal, total	1 (1.4)	
Fluconazole	1 (1.4)	
Immunosuppressant, total	1 (1.4)	
Methotrexate	1 (1.4)	
Anticoagulant, total	1 (1.4)	
Rivaroxaban	1 (1.4)	
Anti-platelet, total	6 (8.6)	
Aspirin	6 (8.6)	

study. DRESS, in particular, had the most delayed onset, occurring between 21 and 56 days (mean 33.60 ± 15.18).

Antibiotics were the most frequently implicated drug class, accounting for a total of 35(50%) cases, with penicillins being the most common culprit (26 cases, 37.1%). Other antibiotics included cephalosporins (5.7%), bactrim (4.3%), vancomycin (1.4%), and meropenem (1.4%).

NSAIDs and analgesics were the second most frequently implicated drug classes. Diclofenac and naproxen each accounted for 2 cases (2.9%), while etoricoxib, ibuprofen, and mefenamic acid were each implicated in 1 case (1.4%). For other analgesics, paracetamol was the most common, contributing 3 cases (4.3%), followed by tramadol with 2 cases (2.9%), and fentanyl and the combination of paracetamol/ibuprofen with 1 case each (1.4%).

Antiplatelet agents, namely aspirin, were implicated in 8.6% of all cases. Anti-tuberculosis drugs, specifically Akurit-4, contributed to 7.1% of cases. Among anticonvulsants, lamotrigine (2.9%) and sodium valproate (1.4%) were implicated. Allopurinol used for gout management, was responsible for 4.3% of cADRs. Less frequently implicated

Table IV: Reaction patterns, drug groups, and specific culprit drugs in cADR patients

Reaction Pattern (n)	Drug Group – n (%)	Specific Drugs (n)
MPE (26)	Antibiotics – 17 (65.4)	Penicillin (10), Bactrim (3), Cephalosporin (2), Vancomycin (1), Meropenem (1)
	Anti-TB – 1 (3.8)	Akurit-4 (1)
	Anticonvulsants – 2 (7.7)	Lamotrigine (2)
	Antigout – 1 (3.8)	Allopurinol (1)
	Analgesics – 1 (3.8)	Tramadol (1)
	Antifungal – 1 (3.8)	Fluconazole (1)
	Immunosuppressant – 1 (3.8)	Methotrexate (1)
	Anticoagulant – 1 (3.8)	Rivaroxaban (1)
	Antiplatelet – 1 (3.8)	Aspirin (1)
Urticaria (25)	Antibiotics – 10 (40.0)	Penicillin (9), Cephalosporin (1)
	NSAIDs – 5 (20.0)	Aspirin (5), Diclofenac (2), Ibuprofen (1), Mefenamic acid (1), Naproxen (1)
	Analgesics – 4 (16.0)	Paracetamol (2), Tramadol (1), Fentanyl (1)
	Antiviral – 1 (4.0)	Acyclovir (1)
	Antiplatelet – 5 (20.0)	Aspirin (5)
Fixed drug eruption (1)	NSAIDs – 1 (100)	Etoricoxib (1)
Cutaneous vasculitis (1)	Antibiotics – 1 (100)	Penicillin (1)
Erythroderma (1)	Anti-TB – 1 (100)	Akurit-4 (1)
AGEP (8)	Antibiotics – 6 (75.0)	Penicillin (5), Cephalosporin (1)
	Anti-TB – 1 (12.5)	Akurit-4 (1)
	Analgesics – 1 (12.5)	Paracetamol (1)
DRESS (5)	Anti-TB – 2 (40.0)	Akurit-4 (2)
	Anticonvulsant – 1 (20.0)	Sodium valproate (1)
	Antigout – 1 (20.0)	Allopurinol (1)
	NSAIDs – 1 (20.0)	Naproxen (1)
TEN/SJS (3)	Antibiotics – 1 (33.3)	Penicillin (1)
	Antigout – 1 (33.3)	Allopurinol (1)
	Analgesics – 1 (33.3)	Paracetamol/Ibuprofen (1)

drugs included antivirals (acyclovir), antifungals (fluconazole), immunosuppressants (methotrexate), and anticoagulants (rivaroxaban), each contributing a small proportion of cases at 1.4% respectively. (Table III)

The analysis of drug-specific associations with various cADR revealed that maculopapular eruptions (MPE) and urticaria were the most frequently observed manifestations, involving 26 (37.1%) and 25 (35.7%) patients respectively. MPE was most linked to penicillin, which accounted for 10 out of 26 cases (38.5%). Other drugs implicated in MPE were Bactrim (3 cases), cephalosporins (2 cases), lamotrigine (2 cases), and several single-drug cases such as Akurit-4, allopurinol, aspirin, fluconazole, meropenem, methotrexate, rivaroxaban, tramadol, and vancomycin (each with 1 case). In urticaria, penicillin was again the leading cause (9 cases, 36%), followed by aspirin (5 cases, 20%). Other drugs included diclofenac (2 cases), paracetamol (2 cases), and one case each involving acyclovir, cephalosporin, fentanyl, ibuprofen, mefenamic acid, naproxen, and tramadol.

Fixed drug eruption (FDE) and cutaneous vasculitis were each observed in a single case, linked to etoricoxib and penicillin, respectively. Erythroderma was reported in one patient and was attributed to Akurit-4. Acute generalized exanthematous pustulosis (AGEP) was associated with penicillin (5 out of 8 cases, 62.5%), Akurit-4, cephalosporin, and paracetamol (1 case each). DRESS syndrome was predominantly caused by Akurit-4 (2 cases), followed by allopurinol, naproxen, and sodium valproate (1 case each). Toxic epidermal necrolysis/Stevens-Johnson syndrome (TEN/SJS) was reported in 3 patients and was associated with allopurinol, a paracetamol/ibuprofen combination, and penicillin. (Table IV)

Three risk factors were found to significantly predict severe cADRs after adjusting for other variables. The odds of severe disease were approximately 22 times higher among patients with raised eosinophils (AOR=21.832, 95 CI: 3.637 to 131.050, p=0.001), while those with mucosal involvement had nearly 30 times higher odds of severity (AOR = 29.815, 95 CI: 1.888 to 470.810, p=0.016). Additionally, patients with impaired renal function had almost 8 times higher odds of developing severe disease (AOR=7.977, 95 CI: 1.320 to 48.207, p). Although fever was associated with increased odds of severity (AOR=5.385, 95 CI: 0.956 to 30.328), the result did not reach statistical significance (p=0.056). (Table V)

DISCUSSION

Cutaneous adverse drug reactions remain a major challenge in hospital practice due to their frequency, varied presentations, and potential severity. The incidence in our study was lower than that reported in local retrospective studies (~1%) [6,7] likely due to our study design and exclusion criteria. Some other studies have included broader definitions of cADRs such as those caused by topical agents, radiocontrast media, blood products and outpatients which were excluded from our cohort. Our inclusion of all hospitalized patients across various departments, including lower risk groups, may have diluted incidence compared to studies focused on high-risk populations such as internal medicine inpatients (0.4%).[8] Nevertheless, higher cADR rates

Table V: Multiple Logistic Regression for severe cADRs

Risk factors		Non -severe caDR (%) (n=53)	Severe caDR %() (n=17)	Univariate analysis		p-value	Multivariate analysis p-value
				Crude OR	95 CI		
Sex	Male#	23 (43.4)	8 (47.1)	1	-	-	-
	Female	30 (56.6)	9 (52.9)	-0.863	0.288, 2.582	0.791	
Race	Malay#	39 (73.6)	11 (64.7)	1	-	0.655	-
	Chinese	5 (9.4)	3 (17.6)	2.127	0.438,10.328	0.349	
	Indian	8 (15.1)	2 (11.8)	0.886	0.164,4.793	0.889	
	Other	1 (1.9)	1 (5.9)	3.545	0.205,61.381	0.384	
Underlying Skin Disease	No#	3 (5.7)	17 (100.0)	1	-	-	-
	Yes	50 (94.3)	0 (0)	0.000	0.000	0.999	
History of CADR	No#	44 (83.0)	13 (76.5)	1	-	-	-
	Yes	9 (17.0)	4 (23.5)	1.504	0.398,5.690	0.547	
History of Atopy	No#	47 (88.7)	17 (100.0)	1	-	-	-
	Yes	6 (11.3)	0 (0)	1.042	0.101,10.729	0.973	
RVD Infection	No#	51 (96.2)	14 (82.4)	1	-	-	-
	Yes	2 (3.8)	3 (17.6)	0.000	0.000	1.000	
Autoimmune Disease	No#	50 (94.3)	16 (94.1)	1	-	-	-
	Yes	3 (5.7)	1 (5.9)	0.600	0.065,5.526	0.652	
Malignancy	No#	52 (98.1)	17 (100.0)	1	-	-	-
	Yes	1 (1.9)	0 (0)	0.000	0.000	0.999	
CKD	No#	48 (90.6)	16 (94.1)	1	-	-	-
	Yes	5 (9.4)	1 (5.9)	1.633	0.272,9.814	0.592	
Systemic Complications: Fever	No#	47 (88.7)	10 (58.8)	1	-	-	0.056
	Yes	6 (11.3)	7 (41.2)	5.483	1.515,19.849	0.010	
Systemic Complications: lymphadenopathy	No#	51 (96.2)	14 (82.4)	1	-	-	-
	Yes	2 (3.8)	3 (17.6)	5.464	0.830,35.968	0.077	
Liver Dysfunction	No#	48 (90.6)	11 (64.7)	1	-	-	-
	Yes	5 (9.4)	6 (35.3)	5.236	1.350,20.313	0.017	
Renal Dysfunction	No#	47 (88.7)	10 (58.8)	1	-	-	0.024*
	Yes	6 (11.3)	7 (41.2)	5.483	1.515,19.849	0.010	
Raised Eosinophils	No#	49 (92.5)	9 (52.9)	1	-	-	0.001**
	Yes	4 (7.5)	8 (47.1)	10.889	2.699,43.932	0.001	
Mucosal Involvement	No#	52 (98.1)	13 (76.5)	1	-	-	0.016*
	Yes	1 (1.9)	4 (23.5)	16.000	1.646,155.495	0.017	
Causative Drug Category	Antibiotics #	28 (52.8)	7 (41.2)	1	-	-	-
	Anti-TB	1 (1.9)	4 (23.5)	16.00	1.537,166.533	0.020	
	Anticonvulsant	2 (3.8)	1 (5.9)	2.000	0.158,25.342	0.593	
	Antigout	1 (1.9)	2 (11.8)	8.000	0.631,101.369	0.108	
	NSAIDs	6 (11.3)	1 (5.9)	0.667	0.069,6.474	0.727	
	Analgesics	5 (9.4)	2 (11.8)	1.600	0.255,10.045	0.616	
	Others (combined)	10 (18.9)	0 (0)	0.000	0.000	1.000	
Age Group	Paed#	5 (9.4)	3 (17.6)	1	-	-	-
	Adult	35 (66.0)	6 (35.3)	0.286	0.054,1.522	0.142	
	Elderly	13 (24.5)	8 (47.1)	1.026	0.191,5.507	0.976	
Concurrent Medications	0–4#	37 (69.8)	11 (64.7)	1	-	-	-
	5–9	13 (24.5)	6 (35.3)	1.552	0.478,5.045	0.464	
	>10	3 (5.7)	0 (0)	0.000	0.000	0.999	

#Reference **p-value< 0.001*p-value<0.05

were noted in medical-based departments (internal medicine, dermatology, paediatrics), consistent with findings from France and Singapore[3,9] likely reflecting better awareness and reporting among clinicians.

Demographic patterns in our cohort were consistent with both local and international studies.[6,7,9,10] A slight female predominance was observed, consistent with studies from Singapore and India[9,10] which has been linked to differences in pharmacokinetics, hormonal and immunological factors.[11] Adults aged 19–60 formed the majority of affected patients, a finding mirrored in Malaysian studies and international cohorts,[6,7,10] likely due to higher rates of drug exposure, polypharmacy, healthcare utilization and the dominant age group requiring inpatient treatment.

Latency periods in this study reflected expected immunological mechanisms and are key to identifying the culprit drug through temporal relationship. Urticaria showed rapid onset, while DRESS exhibited delayed presentation. Most reactions were deemed not preventable (85.7%) The presence of preventable cases reinforces the need for meticulous allergy enquiry and safer prescribing practices.

Maculopapular eruptions (MPE) and urticaria were the most common patterns, similar to trends reported globally.[3,6,7,9,10,12] The relative frequency of MPE and urticaria may also reflect their shorter latency, and greater likelihood of detection and reporting compared to other cADRs. Often it was challenging to differentiate from viral exanthems, particularly in febrile patients receiving antimicrobials. Infection-related immune

alteration may contribute to drug hypersensitivity [13,14] often driven by skin-resident memory T cells that have been primed either by prior sensitization or cross-reactivity with viral antigens. [15]

Penicillin were the most frequently implicated drugs, causing diverse reaction types from mild maculopapular eruptions and urticaria to life-threatening SCARs such as AGEP and SJS/TEN. This aligns with their widespread use and strong immunogenic potential. This may be explained by how penicillin-haptenated peptides can form intracellularly and extracellularly, activating multiple T-cell pathways that result in various clinical phenotypes.[15] Nonsteroidal anti-inflammatory drugs (NSAIDs) and other analgesics were the second and third most commonly implicated drug classes after antibiotics, reflecting their widespread inpatient use and established link to both immunologic and non-immunologic cADRs.[16] Urticaria was the most frequent clinical presentation for NSAIDs among our patients. Urticaria and angioedema are well recognized presentations of NSAIDs induced cutaneous reaction consistent with previous studies.[6,7,9,10] Nonallergic hypersensitivity reactions, particularly NSAID-induced urticaria/angioedema (NIUA), accounted for most NSAID-related cases in Southeast Asia, with diclofenac, mefenamic acid, and paracetamol commonly implicated.[17] These trends may reflect both prescribing practices and genetic susceptibility, as suggested by pharmacogenomic research.[17]

Although paracetamol is generally regarded as low risk, emerging data has link it to severe reactions such as SJS/TEN.[18] While no association was found in France, up to a ninefold increased risk was reported in Germany, Italy, and Portugal, where paracetamol is more frequently used as an antipyretic. [19] This may reflect confounding by indication, as infections themselves can predispose to SCARs[20] Paracetamol was implicated in one SJS/TEN case in our study, underscoring the importance of careful assessment even for widely used over-the-counter medications.

Allopurinol was responsible for several SCARs, particularly SJS/TEN and DRESS, reaffirming its status as a high-risk agent in this country.[21–23] A 15-year Malaysian study reported a SCAR incidence of 2.5 per 1000 new users, with SJS being most common (46.8%).[24] Genetic predisposition plays a key role, with HLA-B*58:01 allele increasing susceptibility. The highest prevalence is seen among Chinese, followed by Malays, consistent with our cohort's ethnic distribution.[25] Current local guidelines do not recommend routine genetic screening due to cost-effectiveness concerns, but caution is warranted when prescribing allopurinol.[26] The lower frequency of allopurinol-induced SCARs in our study compared to earlier Malaysian reports [6–8] may reflect improved clinical awareness and risk reduction strategies.

Anticonvulsants were less frequently implicated but still caused both mild and severe reactions. Lamotrigine and sodium valproate were involved in 2.9% and 1.4% of cADRs, respectively. Aromatic anticonvulsants like phenytoin and carbamazepine have been linked to SCARs in previous studies.[8–10] A Malaysian study noted a decline in carbamazepine-induced SCARs after 2016, likely due to the implementation of HLA-B15:02 screening and a shift in prescribing practices.[27] This decline in carbamazepine use was accompanied by an increased use of sodium valproate and lamotrigine, which may explain the continued presence of cADRs and SCARs associated with these agents.

We also identified five cADR cases related to anti-TB therapy, all involving Akurit-4. Reaction types included MPE, AGEP, erythroderma, and DRESS. These findings are consistent with earlier Malaysian and Indian data[28,29] Notably, recent NPRA safety alerts highlighted the risk of ethambutol-induced DRESS[30], underscoring the need for continued vigilance in TB pharmacovigilance as Malaysia has one of the higher TB incidence rates in Southeast Asia, particularly among high-risk populations such as the elderly, immunocompromised, and migrant communities.[31,32]

Most cADRs in our study were of moderate severity, consistent with Malaysian and international data [8,10] The Hartwig scale did not always align with SCAR classifications, as many SCAR cases (about one-quarter) were rated moderate due to the absence of ICU need, only one SJS/TEN case required intensive care. Penicillin was the most frequently implicated drug in SCARs, including AGEP and one SJS/TEN case. Other culprits included allopurinol, Akurit-4, NSAIDs, and paracetamol.

We identified raised eosinophil count, mucosal involvement, and renal impairment as significant predictors of severe cADRs, with mucosal involvement being the strongest predictor. Other risk factors that have been identified in the literature included age over 60 years [8] concomitant drug use, delayed onset and generalized skin involvement.[10] Our findings highlight the added value of integrating laboratory parameters, such as eosinophil count and renal function for a more precise risk stratification and early identification of patients at higher risk, trigger prompt escalation of care, and potentially improve outcomes by enabling earlier interventions.

This study was conducted at a single tertiary center over a 6-month period, which may limit the generalizability of findings as it may not fully represent the broader population particularly in other settings with different drug formularies or prescribing practices. Underreporting and under-recognition of cADRs are possible, especially for milder cases that may have been missed. Patients with short hospital stays (e.g., for elective procedures or deliveries) may have developed cADRs only after discharge and were not captured. The causality assessment in cases involving polypharmacy remains a challenge, particularly in the absence of drug rechallenge.

CONCLUSION

Our data underscore the continued dominance of antibiotics, NSAIDs, analgesic and anti-tuberculosis drugs as key culprits, and highlight the role of systemic complications in driving disease severity. The reduced incidence of anti-gout and anticonvulsant-related reactions observed in this study is likely attributable to increased prescriber awareness and greater caution exercised during the initiation of these high-risk medications.

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