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Original Article

Clinico-Epidemiological Characteristics of Severe Cutaneous Adverse Drug Reactions at the Kenyatta National Hospital

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Severe Cutaneous Adverse Drug Reactions (SCARs), Steven-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Drug-Induced Exfoliative Erythroderma, Drug Reactions, Kenya.

ABSTRACT

Severe Cutaneous Adverse Reactions (SCARs) including Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Acute Generalized Exanthematous Pustulosis (AGEP) among others, are rare but potentially fatal drug-induced skin reactions. They pose a significant burden in resource-constrained settings like Kenya, where data on their epidemiology remains limited. Understanding the clinical characteristics of SCARs is crucial for improving patient outcomes, enhancing pharmacovigilance efforts and strengthening drug safety measures in Kenya. The study aimed to describe the clinical and epidemiological characteristics of SCARs, identify clinical phenotypes and describe the drugs associated with SCAR cases at Kenyatta National Hospital (KNH). A hybrid cross-sectional design was employed, comprising both retrospective and prospective data collection. A total of 102 patients were recruited via consecutive sampling. Data was collected through file reviews, clinical examinations, and interviews, focusing on demographics, clinical features and etiologies. Statistical analyses were conducted using SPSS-v26, with ethical approval from the KNH-UoN ERC. SJS/TEN was the most common phenotype (55.9%), followed by Drug-Induced Erythroderma (DIE) (17.6%) and Drug-Induced Erythema Multiforme (DIEM) (11.8%). The mean participant age was 29.4 years, with a slight female predominance (51%). Antimicrobials (60.8%) and anticonvulsants (13.5%) were the main implicated drug classes, with co-trimoxazole, ceftriaxone and carbamazepine identified as common culprits. HIV was the most prevalent comorbidity (23.9%). Common complications included acute kidney injury (11.8%) and drug-induced liver injury (8.8%). In-hospital mortality was 16.7%, with SJS/TEN having the highest case fatality rate (21.05%). SCARs in Kenya exhibit unique clinical and demographic patterns, with high mortality and organ involvement. Antimicrobials and anticonvulsants are major culprits. This underscores the need for early diagnosis, pharmacovigilance, public awareness, and healthcare provider training to improve patient outcomes.

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Future research should explore pharmacogenetics, long-term SCAR sequelae and the role of HIV in these severe reactions.

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INTRODUCTION

A Cutaneous Adverse Drug Reaction (CADR) is an undesired effect of a drug manifestation in the structure of the skin, the appendages, or the mucous membranes. These reactions vary from mild eruptions to severe reactions (Verma et al., 2013). Severe Cutaneous Adverse Drug Reactions (SCARs) encompass a range of rare and potentially fatal reactions that require hospitalization and include Steven-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Acute Generalized Exanthematous Eruption (AGEP) among others (Ardern-Jones & Mockenhaupt, 2019). The incidence of SJS/TEN is estimated at 1-2 cases per million persons annually, with a mortality rate of 9%, 29% and 49% for SJS, SJS/TEN overlap and TEN respectively (Mockenhaupt, 2017). DRESS is often underdiagnosed, with a prevalence among hospitalized patients of 9.63 per 100,000. (Hiransuthikul et al., 2016) AGEP has a reported incidence of 1-5 cases per million annually and the lowest mortality among SCARs (Sidoroff et al., 2001). The incidence of generalized bullous fixed drug eruption (GBFDE) is unknown and varies with the geographical location (Zaouak et al., 2019), while the prevalence of erythema multiforme ranges from 0.01% to 1% (Clark Huff et al., 1983). Drug-induced anaphylaxis (DIA) accounts for approximately 35% of all anaphylaxis cases, with drugs being the primary trigger in adults (Regateiro et al., 2020).

Based on the chronology of symptoms, these reactions can be divided into immediate/acute reactions, which correspond to anaphylaxis and non-immediate/delayed reactions that are primarily T-cell mediated, manifesting days to weeks after drug exposure (Zhang et al., 2019). SJS/TEN is a single disease entity characterized by extensive epidermal necrosis and mucosal involvement. It is divided into SJS, SJS/TEN overlap and TEN based on the extent of skin detachment. The latency period varies, but most cases manifest within 3-4 weeks of drug exposure (Micheletti et al., 2018). DRESS describes a syndrome characterized by a skin eruption, fever, lymphadenopathy, haematological abnormalities and multi-organ involvement, with hepatic dysfunction being the most common complication (Kardaun et al., 2013). AGEP is

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marked by sterile pustules on an erythematous base that begins in the intertriginous areas and later becomes diffuse (Feldmeyer et al., 2016). The lag period is short and mucosal involvement occurs in 20-25% of patients (Owen & Jones, 2021). Drug-induced erythroderma features generalized erythema and scaling affecting 90% of the total body surface area. It accounts for 12% of all cases of exfoliative erythroderma and is characterized by an abrupt onset and resolution once the causative agent is withdrawn (Miyashiro & Sanches, 2020). GBFDE is a severe form of fixed drug eruption(FDE) characterized by vesico-bullous and edematous plaques on erythematous and violaceous skin, involving at least 10% of the body surface area and at least three of six separated anatomic sites (Anderson & Lee, 2021). Drug-induced erythema multiforme major (DIEM) accounts for 10% of cases of erythema multiforme major and is characterized by severe mucosal involvement and acrally distributed target lesions. The lag period ranges from one to two weeks but may be shorter if previously sensitized (Clark Huff et al., 1983). Drug-induced anaphylaxis (DIA) represents a syndrome of symptoms affecting many organ systems, with cutaneous symptoms (urticaria, angioedema, pruritus) often being the initial symptoms, followed by respiratory symptoms in 80-90% of cases (Ensina et al., 2016).

In addition to the previously suspected drugs including antimicrobial sulfonamides (particularly cotrimoxazole), allopurinol, carbamazepine, phenytoin, phenobarbital and non-steroidal anti-inflammatory agents (NSAIDs), the EuroSCAR study identified lamotrigine and nevirapine as triggers in SJS/TEN, while AGEP was found to be linked to antibiotics such as aminopenicillins, pristinamycin, quinolones, anti-infective sulfonamides, as well as antimalarials and terbinafine (Mockenhaupt, 2017). The RegiSCAR study found that 35% of DRESS cases were linked to aromatic anticonvulsants while allopurinol, antibacterial sulfonamides and non-sulfonamide antimicrobials accounted for 18%, 12% and 11% of cases respectively (Kardaun et al., 2013). A study in Brazil identified anticonvulsants, especially carbamazepine, antihypertensives, anti-inflammatory and oral hypoglycemic agents as the culprits in drug-induced erythroderma (Miyashiro & Sanches, 2020). In Taiwan, cephalosporins and tetracyclines were the primary cause of GBFDE (Anderson & Lee, 2021). Drug-induced erythema multiforme major was linked to oxicam NSAIDs, allopurinol, phenobarbital, phenytoin and sulfonamides in the SCAR study (Lerch et al., 2018). Geographical differences exist in the causative agents commonly implicated in drug induced anaphylaxis and in the United States, antibiotics were the most common culprits, followed by analgesics, together accounting for 21.5% of cases (Regateiro et al., 2020).

The risk factors for SCARs can be categorized as genetic and non-genetic. HLA alleles are well-documented risk factors (Pavlos et al., 2012). Non-genetic factors include extremes of age (Ajayi et al., 2000), female gender, ethnicity, a family or personal history of drug allergy, presence of co-morbidities and polypharmacy. HIV has been identified as a risk factor for TEN independent of drug use (Machoń et al., 2022).

Identifying the causative drug is crucial for SCAR management. Causality assessment methods include expert clinical judgement, algorithmic approaches and probabilistic models (Agbabiaka et al., 2008). The Naranjo algorithm is widely used to establish causality for all cutaneous adverse drug reactions, categorizing reactions as definite, probable, possible or doubtful (Pande, 2018). The Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN) specifically assesses drug causality in SJS/TEN cases (Sassolas et al., 2010). DRESS diagnosis relies on the Bocquet criteria, J-SCAR criteria and RegiSCAR criteria, with the latter being the most comprehensive (Kim & Koh, 2014). The EuroSCAR groups devised the AGEP validation score, incorporating clinical, laboratory and histological parameters (Sidoroff et al., 2001).

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Drug-induced anaphylaxis is diagnosed based on the World Allergy Organization's criteria, which include acute symptom onset and multi-organ involvement (Cardona et al., 2020).

Despite Kenya's efforts to improve pharmacovigilance, underreporting of SCAR cases remains a challenge (Barry et al., 2020). Self-medication with antimicrobials, especially antibacterial and antimalarial drugs is common in low-income countries, with an overall prevalence of 38.8% (Ocan et al., 2015). This, coupled with the high burden of HIV in Sub-Saharan Africa and the concomitant use of ART (Anti-Retroviral Treatment) and treatment for opportunistic diseases, increases the risk of drug reactions, which have been found to be 2- 100 times higher in HIV-infected persons (Lehloenya & Kgokolo, 2014). Given the profound psychological and socioeconomic impact associated with SCARs, understanding the local epidemiology is important for informing supportive care strategies, rehabilitation programs and further research on SCARs in Kenya. A previous study by Irungu et al. at Kenyatta National Hospital focused on SJS/TEN, primarily describing demographic patterns and drug causality. However, SCARs encompass a broader range of severe reactions, each with distinct mucocutaneous and systemic manifestations. This study builds on existing data by providing a comprehensive clinico-epidemiological characterization of SCARs, capturing not only the demographic aspect but also the full spectrum of clinical symptoms, systemic involvement and in-hospital mortality. (Irungu et al., 2017) The study aims to describe the clinical and epidemiological characteristics of SCAR patients at the Kenyatta National Hospital. The specific objectives are to determine the clinical phenotypes of the different SCARs, identify epidemiological characteristics and describe suspected drug associations.

MATERIALS AND METHODS

Study Area

This study was conducted at Kenyatta National Hospital (KNH) in Nairobi, Kenya. Participants were drawn from the dermatology ward and other relevant wards including the Intensive Care Unit (ICU) and the Burns Unit.

Study Design

A hybrid cross-sectional study utilizing both retrospective and prospective data collection. The retrospective arm reviewed patient records of SCAR diagnoses between 2014 and August 2024. The prospective arm enrolled newly admitted SCAR patients from August to December 2024 where data was collected during their hospitalization period. Given the rarity of SCARs, this hybrid design was chosen to maximize case capture and ensure a diverse representation of the different SCAR phenotypes, enhancing the study's ability to comprehensively characterize clinical and epidemiological patterns.

Study Population

The study population comprised patients admitted to KNH with a SCAR diagnosis confirmed by a KNH consultant dermatologist.

Inclusion Criteria:

- Patients admitted to KNH wards between the year 2014-2024.
- Diagnosis of a SCAR confirmed by a KNH consultant dermatologist.
- Consent is provided by patients or guardians (prospective arm).

Exclusion Criteria:

- Clinical diagnosis not confirmed by a dermatologist.
- Patients with differential diagnosis of SCARs including staphylococcal scalded skin syndrome, immunobullous diseases, superficial burns, acute graft versus host disease,

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confirmed lupus erythematosus, pustular psoriasis and erythroderma due to other causes.

- Lack of consent for participation.

Study Sampling

A non-probabilistic consecutive sampling approach was used, enrolling patients until the desired sample size was achieved. The sample size, determined using the Cochran formula, was 102 participants: 48 participants in the retrospective arm and 54 in the prospective arm.

Data Collection Tool

Data was collected using a standardized tool, including interviewer-administered questionnaires, patient file reviews and full-body examination to assess skin lesions and mucosal involvement.

Study Variables

Key variables included:

- Baseline characteristics: Age, gender
- Clinical Features: Prodromal symptoms, latency period, clinical phenotype and systemic involvement
- Drug information: Suspected drug(s), latency period, history of drug reactions and indications for drug use

Data Quality Control and Assurance

Data collection was standardized using a structured tool to ensure methodological consistency. Regular quality checks were conducted and clinical interpretations were validated by consultant dermatologists. Completeness and consistency of data extraction were prioritized.

Data Management, Analysis and Handling

Collected data were securely stored in a locked cabinet accessible only to authorized personnel. Identifiers were anonymized per Kenya's Data Protection Act (2021). Data was analyzed using SPSS v26. Descriptive statistics summarized demographic and clinical data, while inferential analyses included Kruskal-Wallis and Chi-Square tests with statistical significance defined as $p<0.05$.

Ethical Considerations

Ethical approval was obtained from the KNH-UoN Ethics Review Committee, the Department of Dermatology and NACOSTI. Written informed consent was obtained for prospective participants while retrospective data were anonymized and exempted from reconsent. Study protocols adhered to principles of anonymity, confidentiality and transparency, with findings disseminated in aggregated, non-identifiable formats.

RESULTS AND DISCUSSION

Characteristics of Study Participants

A total of 102 patients were enrolled in the study, with 62 retrospective cases and 40 prospective cases. As the number of prospective cases was lower than anticipated, the retrospective arm was expanded (48 to 62 participants) to maintain statistical power and achieve the desired sample size. The adjustment was necessary to ensure a comprehensive representation of SCAR phenotypes without compromising the validity of the study, as key variables were consistently captured across both arms.

Demographic Characteristics

The mean age of participants was 29.4 years (SD=20.5), with a median age of 29.0 years (IQR 35.0). The youngest participant was 0.5 years old, while the oldest was 77 years. Majority of the participants (30.4%) were in the 0-12 age group, followed by 19-30 years (18.6%). There was a slight female predominance compared to males (51% vs 49%). Most participants resided in Nairobi (60.8%), followed by Central (23.5%) and Eastern Kenya (9.8%). The age distribution did not differ between males and females ($p=0.878$) and gender did not differ significantly across age groups. ($p=0.975$) (Table 1)

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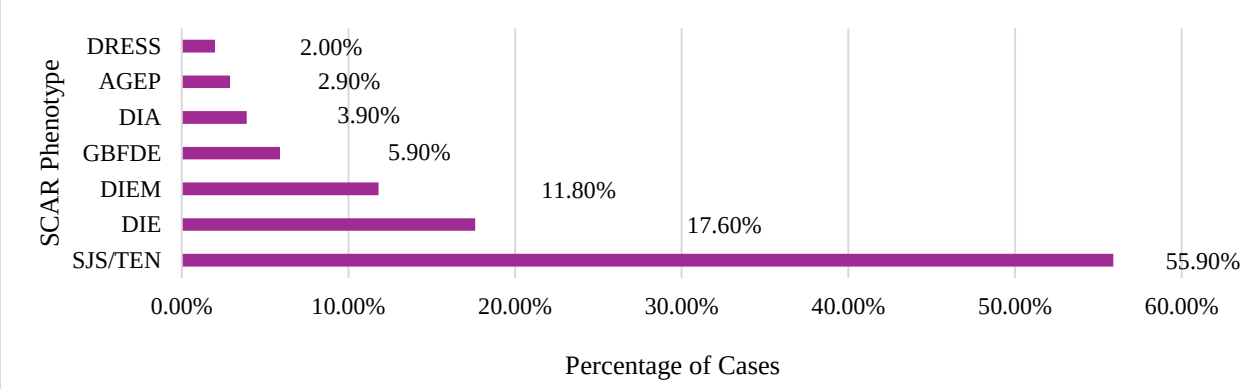
Table 1: Demographic Characteristics of all Study Participants (n=102)

Characteristic	Category	Frequency (n)	Percentage (%)	p-value
Age	0-12	31	30.4	
(Mean 29.426, SD 20.5)	13-18	5	4.9	
Median 29.000, IQR=35.0)	19-30	19	18.6	
	31-40	15	14.7	
	41-50	16	15.7	
	51-60	6	5.9	
	>=60	10	9.8	
Gender	Female	52	51.0	p=0.878
	Male	50	49.0	
Gender vs Age groups				p=0.975
Residence (Regions)	Nairobi	62	60.8	
	Central	24	23.5	
	Eastern	10	9.8	
	North-Eastern	2	2.0	
	Coastal	1	1.0	
	Nyanza	2	2.0	
	Rift Valley	1	1.0	

SCAR Phenotypes and Distribution

SJS/TEN was the most frequent SCAR phenotype (55.9%), followed by DIE (17.6%), DIEM (11.8%), GBFDE (5.9%), DIA (3.9%), AGEP (2.9%) and DRESS (2.0%). (Figure 1).

Figure 1: Percentage Distribution of SCAR Phenotypes in the Study Population



SJS/TEN has the widest age distribution, peaking in the paediatric age group (0-12 years) (35.1%) and 41-50 years (17.5%). DRESS, AGEP and DIA were more common in younger patients, while DIE and GBFDE were prevalent in older age groups. Age distribution differences were significant (p=0.021), but post-hoc analysis was not. (p>0.05) No significant link was found between age groups and SCAR phenotypes. (p=0.381) Gender-wise, DIE and GBFDE had a male predominance while AGEP was exclusive to females. However, these variations were not statistically significant. (p=0.561) (Table 2)

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Table 2: Demographic Characteristics of SCAR Patients

Demographic characteristics	SJS/TEN (n=57)	DRESS (n=2)	AGEP (n=3)	DIE (n=18)	DIEM (n=12)	GBFDE (n=6)	DIA (n=4)	p-value
Mean age (SD)	27.5(19.5)	26.0(12.7)	16.8(14.1)	41.0(20.7)	24.8(16.7)	43.3(25.8)	8.5(13.0)	**0.021***
Median (IQR)	29.0(9-43)	26(21.5-30.5)	24(12.25-25.0)	40.0(26.5-53.75)	24.0(12.25-25.0)	47.0(29.25-59.5)	2.5(1.0-10.0)	
Age group (years)								0.381
0-12	**20 (35.1)**	0 (0)	1 (33.3)	2 (11.1)	4 (33.3)	1 (16.7)	3 (75.0)	
13-18	2 (3.5)	1 (50.0)	0 (0)	1 (5.6)	1 (8.3)	0 (0)	0 (0)	
19-30	9 (15.8)	0 (0)	2 (66.7)	3 (16.7)	3 (25.0)	1 (16.7)	1 (25.0)	
31-40	9 (15.8)	1 (50.0)	0 (0)	3 (16.7)	2 (16.7)	0 (0)	0 (0)	
41-50	**10 (17.5)**	0 (0)	0 (0)	3 (16.7)	1 (8.3)	2 (33.3)	0 (0)	
51-60	3 (5.3)	0 (0)	0 (0)	2 (11.1)	1 (8.3)	0 (0)	0 (0)	
> 60	4 (7.0)	0 (0)	0 (0)	4 (22.2)	0 (0)	2 (33.3)	0 (0)	
Gender								
Female	29 (50.9)	1 (50)	3 (100)	8 (44.4)	6 (50)	2 (33.3)	3 (75.0)	0.561
Male	28 (49.1)	1 (50)	(0)	10(55.6)	6 (50)	4 (66.7)	1 (25.0)	
Female: Male ratio	1:0.97	1.1	1	1:1.25	1:1	1:2	1:0.33	

This table presents the demographic characteristics of participants across different SCAR phenotypes. *Post-hoc analysis did not show any statistical difference between the SCAR phenotypes in age distribution.

Clinical Characteristics

Prodromal Symptoms

Prodromal symptoms were common (70.6%, n=72) with pruritus (35.3%) and constitutional symptoms (28.4%) being the most common. Less common symptoms included respiratory (11.8%) and neurological symptoms (2.9%) (Table 3). No significant association was found between symptom type and SCAR phenotype (p>0.05) (Data not shown).

Table 3: Frequency and Percentage of Prodromal Symptoms in SCAR Patients

Clinical presentation	Frequency (n)	Percentage (%)
Pruritus	36	35.3
Constitutional symptoms	29	28.4
Respiratory symptoms	12	11.8
Paraesthesia	9	8.8
Gastrointestinal symptoms	4	3.9
CNS symptoms	3	2.9
Musculoskeletal symptoms	3	2.9
Other	3	2.9

Latency Period

The mean latency period was 7.08 days (SD=9.87), with a median of 4 days. DIE had the longest latency period (18.4 days), while GBFDE had the shortest (1.5 days). The difference in latency period across SCAR phenotypes was statistically significant (p=0.0015) (Table 4).

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Table 4: Mean Latency Period among SCAR Phenotypes

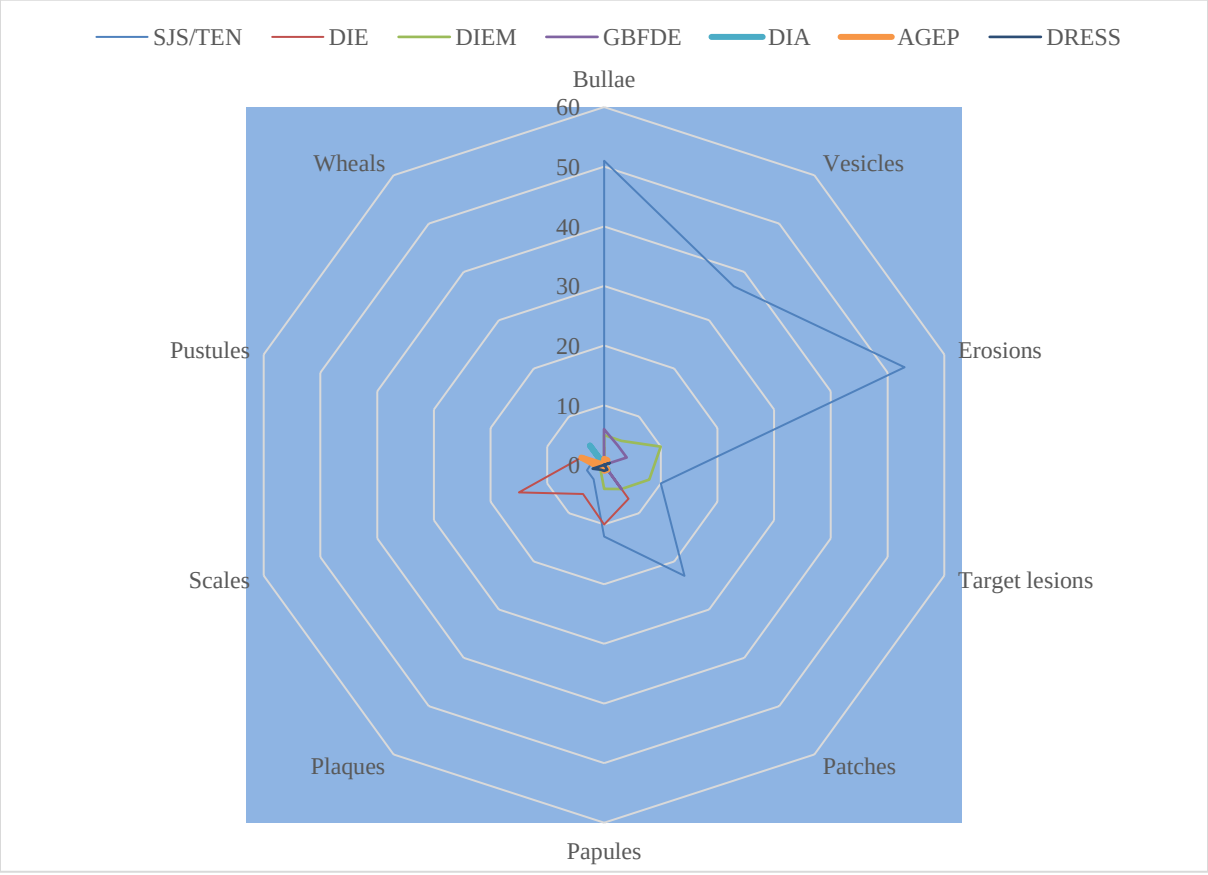
Disease Phenotype	Mean (days)	SD	p-value
Overall participants (n=99)	**Mean 7.08** **Median** 4.00 (IQR 9) **Min**=0, **max**=60	(SD 9.869)	**0.0015*** **(Kruskal-Wallis)**
SJS/TEN (n=55)	5.04	4.91	
DIE (n=17)	18.41	17.59	
DIEM (n=12)	4.75	5.72	
GBFDE (n=6)	1.50	0.83	
DIA (n=4)	4.50	6.35	
AGEP (n=3)	2.67	1.52	
DRESS(n=2)	9.5	6.36	

The table shows the mean latency period among the different SCAR phenotypes. *Pairwise comparison showed a significant difference between DIE and SJS/TEN (P<0.0001), with DIE having a longer latency period

Cutaneous Involvement was observed in all participants, with bullae (64.7%), erosions (63.7%) and macules (51.0%) being the most common. AGEP was characterized by pustules and DIA by wheals. (Figure 2).

Mucocutaneous Symptoms

Figure 2: Distribution of Cutaneous Lesions Across SCAR Phenotype



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This radar chart illustrates lesion patterns across SCAR phenotypes. SJS/TEN had the highest prevalence of erosions, bullae and vesicles while target lesions were seen in DIE. The visualization highlights the variation of clinical presentation among the different SCAR subtypes.

Mucositis was present in 80.8% of participants with 61.8% presenting with involvement of two or more sites and 19.6% a single site. Oral mucosa was the most affected (74.5%), followed by conjunctiva (54.9%). SJS/TEN and DIEM had extensive mucosal involvement, while AGEP and DIA had none. The number of sites affected varied significantly across SCAR phenotypes ($p<0.0001$) as did conjunctival involvement ($p<0.0001$) (Table 5).

Table 5: Mucosal Involvement Across SCAR Phenotypes

Mucosal site	SJS/TEN (n=57)	DRESS (n=2)	AGEP (n=3)	DIE (n=18)	DIEM (n=12)	GBFDE (n=6)	DIA (n=4)	p-value
Number of sites								
None	2(3.5)	1(50.0)	3(100)	9(50.0)	0(0)	1(16.7)	4(100)	**0.000*[1]**
1	10(17.5)	1(50.0)	0(0)	5(27.8)	1(8.3)	2(33.3)	0(0)	
2 or more	45(78.9)	0(0)	0(0)	4(22.2)	11(91.7)	3(50.0)	0(0)	
Oral	51(89.5)	1(50.0)	0(0)	7(38.9)	12(100)	5(83.3)	0(0)	0.0752
Conjunctiva	42(73.7)	0(0)	0(0)	4(22.2)	10(83.3)	0(0)	0(0)	**0.000*[2]**
Genital mucosa	18(31.6)	0(0)	0(0)	0(0)	6(50.0)	1(16.7)	0(0)	0.230
Urethral mucosa	2(3.5)	0(0)	0(0)	0(0)	2(16.7)	0(0)	0(0)	0.365
Anal mucosa	10(17.5)	0(0)	0(0)	0(0)	2(16.7)	0(0)	0(0)	0.368
Nasal mucosa	4(7.0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.772

The table presents the distribution of mucosal involvement across SCAR phenotypes.

***[1]**Pairwise post-hoc analysis showed that the number of sites affected was higher in SJS/TEN and DIEM. ***[2]**Pairwise post-hoc analysis showed SJS/TEN was more frequently affected ($p=0.002$).

Extracutaneous Manifestations

61.8% of the participants reported extracutaneous symptoms, with constitutional symptoms being the most common (45%). SJS/TEN exhibited the highest frequency and diversity while GBFDE had a lower frequency. (Figure 3) Statistical analysis did not show any difference in the presence of extracutaneous symptoms across the diseases. (Data not shown).

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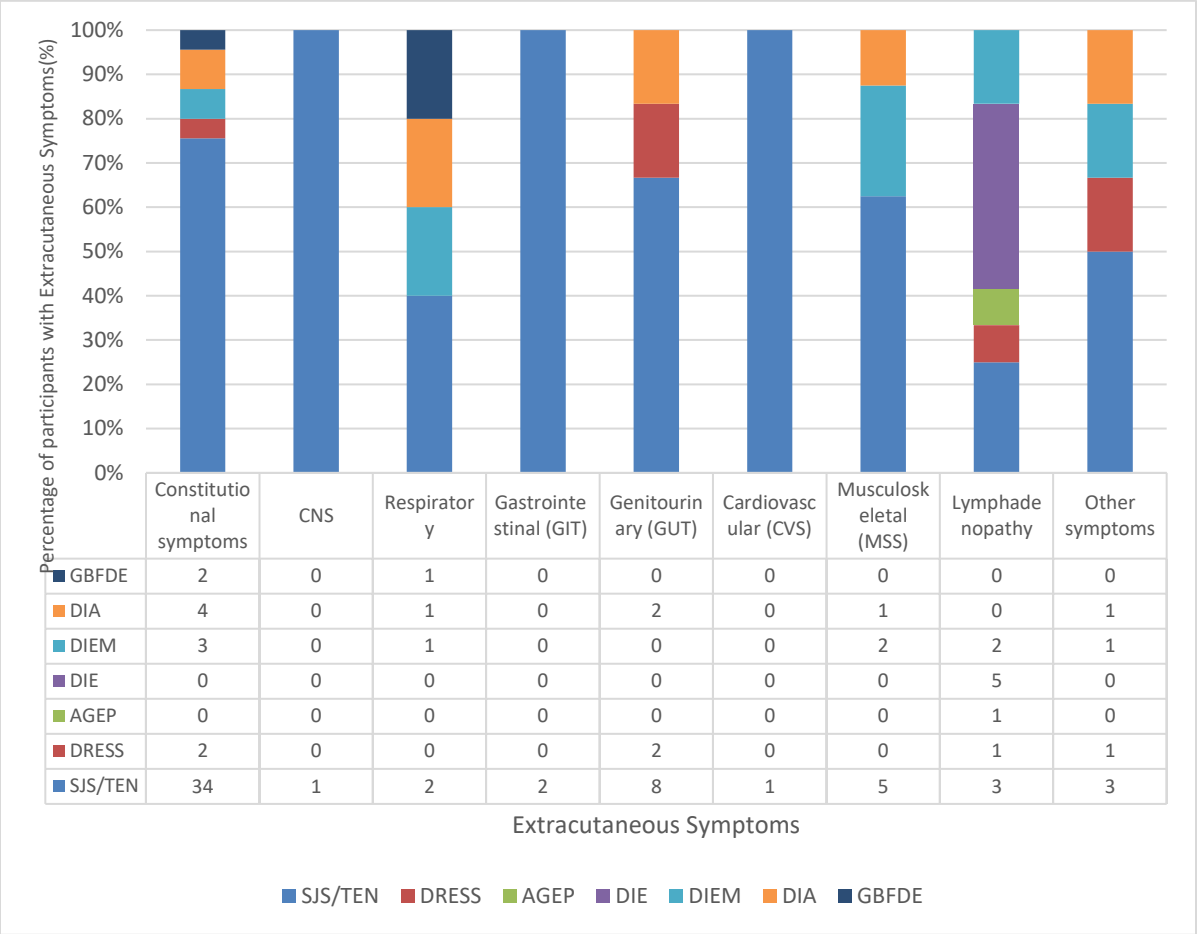
Figure 3: Distribution of Extracutaneous Symptoms Across SCAR Phenotypes



	Constitutional symptoms	CNS	Respiratory	Gastrointestinal (GIT)	Genitourinary (GUT)	Cardiovascular (CVS)	Musculoskeletal (MSS)	Lymphadenopathy	Other symptoms
GBFDE	2	0	1	0	0	0	0	0	0
DIA	4	0	1	0	2	0	1	0	1
DIEM	3	0	1	0	0	0	2	2	1
DIE	0	0	0	0	0	0	0	5	0
AGEP	0	0	0	0	0	0	0	1	0
DRESS	2	0	0	0	2	0	0	1	1
SJS/TEN	34	1	2	2	8	1	5	3	3

This stacked bar chart illustrates the distribution of extracutaneous symptoms across different SCAR phenotypes. The x-axis represents symptom types while the y-axis shows the percentage of participants with symptoms per phenotype.

Systemic Involvement per Laboratory Assessment

Renal and liver function tests identified acute Kidney Injury (AKI) in 11.8% of the participants, though it showed no significant association with any SCAR phenotype ($p = 0.448$). Drug-Induced Liver Injury (DILI) was present in 8.8%, with a significant association with DRESS. ($p<0.0001$). Eosinophil levels varied across SCAR phenotypes ($p<0.001$), with DIE strongly linked to eosinophilia ($p <0.0001$), while TEN cases had the lowest eosinophil counts ($p=0.0006$). (Data not displayed)

Co-morbidities among the Study Participants

More than 57.8% of participants had an underlying medical condition, with HIV (23.9%), hypertension (15.5%) and psychiatric disorders (14.1%) being the most common. (Figure 4) SJS/TEN and DIE had the highest comorbidity burden, while AGEP had none. No statistically significant association was found between comorbidities and SCAR phenotypes. (Data not shown).

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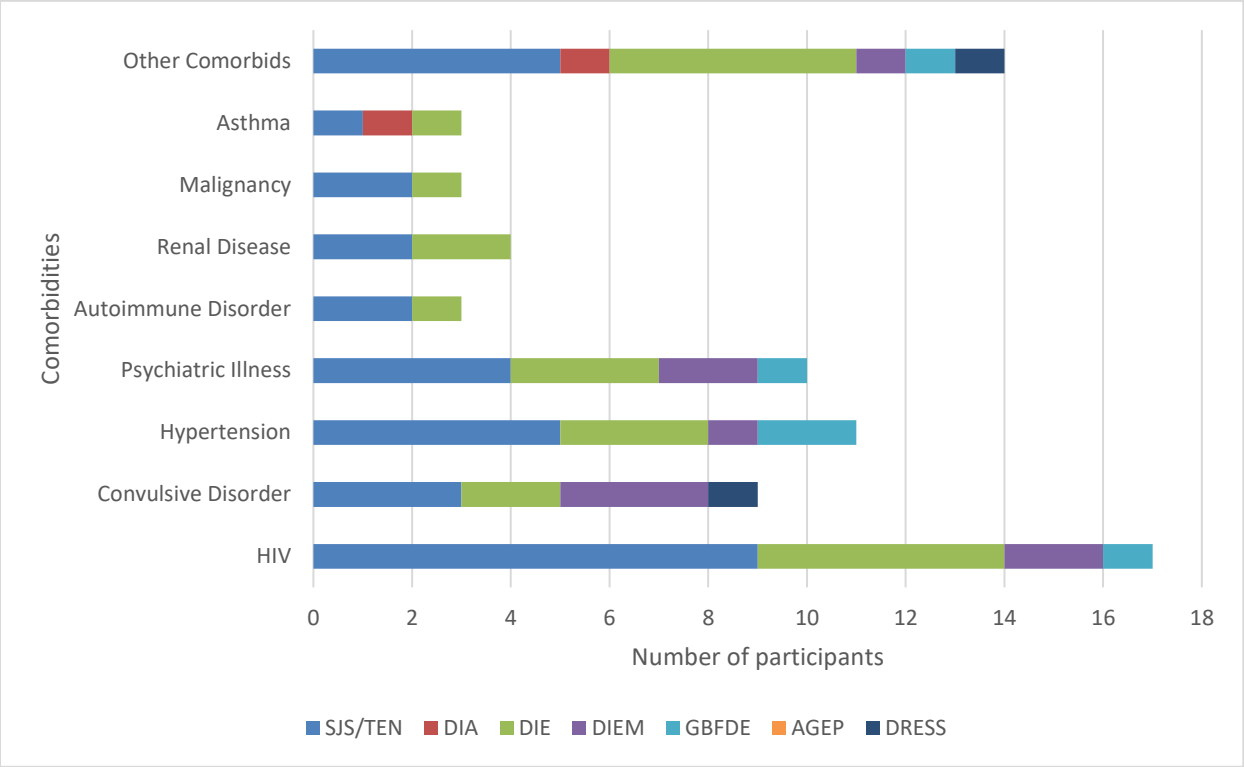
Figure 4: Distribution of Comorbidities Across SCAR Phenotypes



The bar chart illustrates the distribution of comorbidities among SCAR phenotypes. (x-axis: number of participants with each comorbidity, y-axis: list of the different co-morbidities)

Drug Information: Classes, Associations and Implicated Agents

Nearly a quarter of the participants (n=22, 21.6%) had multiple drug exposures. Causality was primarily assessed through expert opinion, supplemented by the Naranjo algorithm in select cases. Antimicrobials (n=62, 60.8%) were the most frequently implicated drug class, followed by anticonvulsants (n=15, 13,5%) and analgesics (n=14, 12.6%). Less common drug classes included antipsychotics, hormonal drugs, anti-gout agents and vaccines. (Figure 5)

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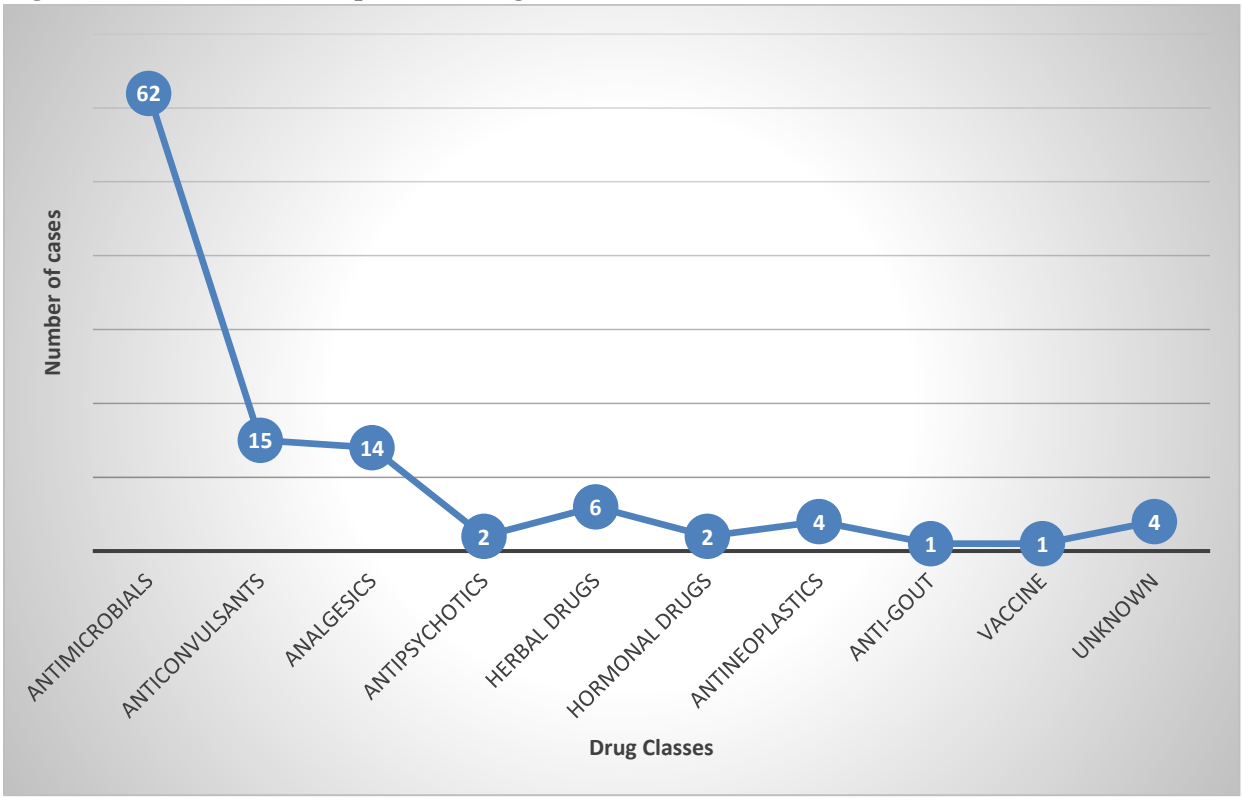
Figure 5: Distribution of Implicated Drug Classes in SCARs



The line chart illustrates the distribution of drug classes implicated in SCARs among study participants.

Among the antimicrobials, antibiotics were the most frequently used, with B-lactam antibiotics and sulfonamides Antibiotics were the predominant culprits across SCAR phenotypes, except for DRESS and DIE, where aromatic anticonvulsants were the leading triggers. SJS/TEN, DIEM and GBFDE were mainly associated with B-lactam antibiotics and sulfonamides, with NSAIDs also contributing significantly. In the less frequent phenotypes, DIA and AGEP, B-lactam antibiotics remained the primary trigger, with hormonal drugs also playing a role in both conditions. Statistical analysis found a significant difference in antimicrobials across SCAR phenotypes (p=0.001) with antibiotics also varying significantly (p=0.021). (Table 6) Further subgroup analysis showed SJS/TEN was significantly linked to antibiotics (p=0.003) though no subclass association was found, while DIE had a strong link to antibiotics (p=0.032), particularly anti-TBs (p=0.032). Aromatic anticonvulsants were associated with SJS/TEN(p=0.012), DRESS (p=0.011) and DIE(p=0.022). GBFDE was significantly linked to nitroimidazoles (p=0.019) and paracetamol (p=0.001). *(These sub-group analyses are not shown)*

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Table 6: Distribution of Implicated Drug Classes Across SCAR Phenotypes

Drug Class	SJS/TEN (n=57)	DIE (n=18)	DIEM (n=12)	DRESS (n=2)	AGEP (n=3)	GBFDE (n=6)	DIA (n=4)	p-value
Antimicrobials	45	5	5	0	2	4	1	**0.001**
1. Antibiotics	**37**	**4**	**5**	**0**	**1**	**4**	**1**	**0.021**
i. B-lactams	**17**	2	2	0	1	1	2	
ii. Sulfonamides	**12**	0	3	0	0	2	0	
iii. Fluoroquinolones	7	0	1	0	0	0	0	
iv. Tetracyclines	1	0	0	0	0	0	0	
v. Glycopeptide	1	0	0	0	0	0	0	
vi. Nitroimidazole	3	0	0	0	0	2	0	
vii. Anti-TBs	0	2	0	0	0	0	0	
2. Antifungals	2	0	0	0	1	0	0	0.087
a. Azole antifungals	2	0	0	0	1	0	0	
b. Non-azole antifungals	1	0	0	0	0	0	0	
	1	0	0	0	0	0	0	
3. Antivirals	7	1	0	0	0	0	0	
4. Antimalarials	1	0	0	0	0	0	0	
5. Others								
Antipsychotics	**1**	**1**	**0**	**0**	**0**	**0**	**0**	0.940
Anti-convulsant	4	6	3	2	0	0	0	
a. Aromatic anti-convulsant	3	6	3	2	0	0	0	
b. Non-aromatic anti-convulsant	1	0	0	0	0	0	0	
Analgesics	**5**	**3**	**3**	**0**	**0**	**2**	**1**	0.449
a. NSAIDs	5	2	3	0	0	0	1	
b. Paracetamol	0	0	0	0	0	2	0	
Hormonal drugs	**0**	**0**	**0**	**0**	**1**	**0**	**1**	0.623
Herbal drugs	**3**	**2**	**0**	**0**	**0**	**0**	**1**	0.543
Anti-neoplastic agents	**3**	**1**	**0**	**0**	**0**	**0**	**0**	0.959
a. Anti-metabolites	3	1	0	0	0	0	0	
b. Alkylating agents	1	0	0	0	0	0	0	
Vaccine	**1**	**0**	**0**	**0**	**0**	**0**	**0**	0.992
Anti-gout	**0**	**1**	**0**	**0**	**0**	**0**	**0**	0.581
Unknown	**2**	**1**	**1**	**0**	**0**	**0**	**0**	0.967

The table shows the distribution of implicated drug classes and their sub-groups among the disease phenotypes.

Notably, co-trimoxazole was the most common culprit drug (n=16), followed by ceftriaxone (n=9), carbamazepine (n=7) and herbal medication (n=6). (Figure 6).

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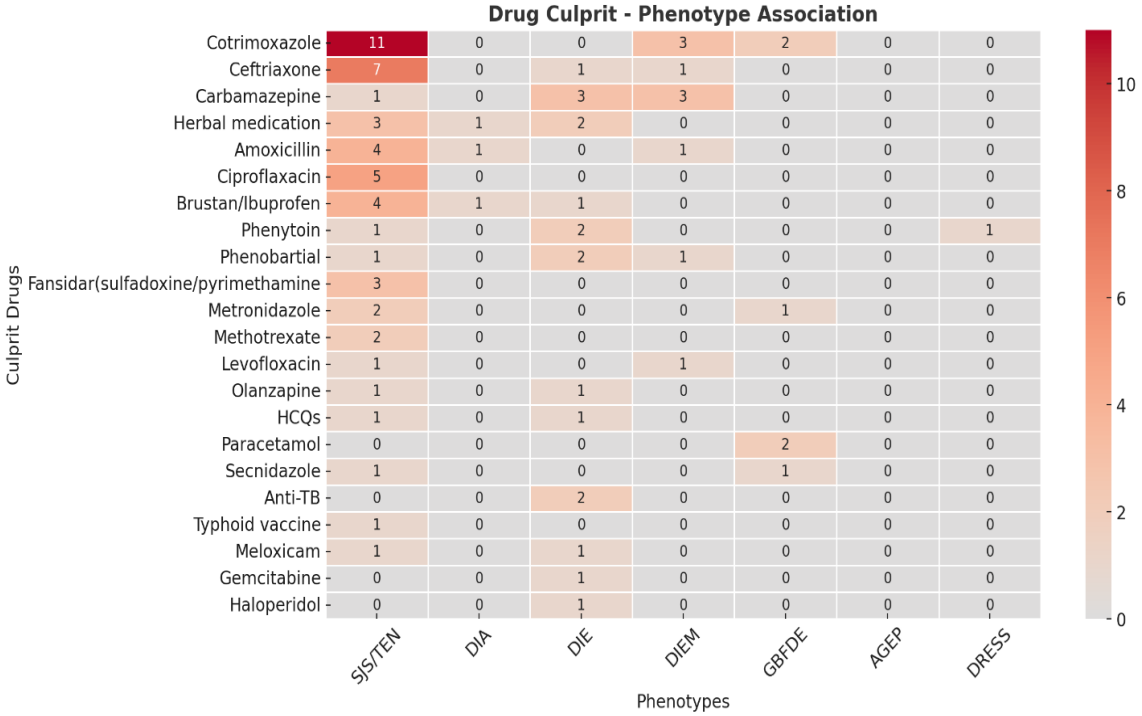
Figure 6: Drug Culprit-Phenotype Association in SCARs



The heatmap illustrates the distribution of culprit drugs across different SCAR phenotypes. The y-axis represents the identified culprit drugs, while the x-axis denotes the various SCAR phenotypes. The varying heat intensities highlight the frequency of drug-phenotype association, with darker shades indicating a higher number of cases.

Drug Indications, Prescription Mode and Drug Allergies

Acute illness (<6 weeks duration) was the primary indication for drug use in 67.3% of the participants. GBFDE, SJS/TEN, DIA and DIEM were more frequently observed in patients taking drugs for acute illness, while DIE and DRESS were linked with chronic drug use. These differences were statistically significant. ($p<0.0001$) Most patients (75.2%) obtained drugs via prescription while 22.8% acquired them over the counter. The mode of acquisition did not differ significantly among the SCAR phenotypes ($p=0.492$).

A history of drug allergy was reported in 36.3% of participants, most frequently in SJS/TEN cases. Statistical analysis showed a statistically significant difference in past allergies across phenotypes ($p=0.012$). (Table 7) GBFDE was significantly associated with past drug allergies ($p=0.0036$). (Data not shown)

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Table 7: Summary of Indication for Use, Mode of Drug Acquisition and Drug Allergies Among SCAR Phenotypes

Drug Class	SJS/TEN	DIE	DIEM	DRESS	AGEP	GBFDE	DIA	p-value
Indication for drug use								**0.000**
< 6 weeks	44	5	7	0	2	5	3	
> 6 weeks	10	13	5	2	0	1	1	
Drug acquisition:								0.492
Over the Counter	12(21.4)	5(27.8)	1(8.3)	0(0)	0(0)	4(66.7)	1(25.0)	
Prescribed	42(75.0)	13(72.2)	11(91.7)	2(100)	3(100)	2(33.3)	3(75.0)	
	2(3.6)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	
Positive history of drug reaction	22	4	4	1	0	6	0	**0.012**

In-Hospital Mortality

The overall in-hospital mortality rate was 16.7% with the highest case fatality in SJS/TEM (21.05%). No deaths were reported in DRESS, AGEP or DIA. Differences in mortality across SCAR phenotypes were not statistically significant (p=0.785). (Table 8) Additional analysis indicated that elevated creatinine levels (p=0.0039), older age (p=0.022) and anti-TBs were significantly associated with in-hospital mortality. (Data not shown)

Table 8: In-hospital Mortality and Case Fatality Rates among SCAR Phenotypes

	SJS, SJS/TEN, TEN (n=57)	DRESS (n=2)	AGEP (n=3)	DIE (n=18)	DIEM (n=12)	GBFDE (n=6)	DIA (n=4)	p-value
Outcome								0.785
Discharge	45(78.9)	2(100)	3(100)	15(83.3)	11(91.7)	4(83.3)*	4(100)	
In-hospital mortality	12(21.1)	0(0)	0(0)	3(16.7)	1(8.3)	1(16.7)	0(0)	
Case Fatality Rate (%)	21.05	0.00	0.00	16.67%	8.33%	20%	0.00	

The table summarizes patient outcomes across SCAR phenotypes, categorizing them as either discharge (Alive) or in-hospital mortality(deceased) *One patient was excluded due to ongoing hospitalization at the time of study completion.

DISCUSSION

Severe Cutaneous Adverse Drug reactions (SCARs) are rare but potentially fatal drug-induced reactions with diverse clinical presentations. This study found that SCAR patients were significantly younger than those in previous studies (Mockenhaupt, 2017). Paediatric cases (30.4%) were more prevalent than prior reports (Singh et al., 2021), likely due to the referral hospital setting. A slight female predominance was observed, consistent with earlier findings (Guzman & Paliza, 2018). Most participants resided in Nairobi, reflecting referral patterns that may underrepresent cases from other areas. SJS/TEN was the most common SCAR phenotype, aligning with findings from India (Tee et al., 2022) and Jamaica (Guzman & Paliza, 2018) while DRESS was the least common at 1.7%, lower than reports from Korea. Antibiotics were the most implicated drug group, consistent with prior studies in black populations, while allopurinol, commonly implicated in Asian populations, was rare (Kang et al., 2021). Organ involvement was common, with Acute Kidney Injury (AKI) and Drug-Induced Liver injury (DILI) observed in 11.8% and 8.3% of cases, respectively. All DRESS cases exhibited DILI. A higher proportion of patients (36.3%) reported prior drug reactions, highlighting poor awareness of drug avoidance. Co-morbidities mirrored prior studies,

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with HIV being the most prevalent, reflecting the disease burden in Kenya (Pudukadan & Thappa, 2004). Unlike global trends where SCARs occur in older adults with chronic illnesses, this study found that most cases were linked to acute disease, often requiring antibiotics, particularly among children.

The mean age for SJS/TEN patients (27.5 years) was lower than in the US (49 years) (Micheletti et al., 2018) and EuroSCAR (53.4 years). The latency period (5.04 days) was shorter than previously reported (Mockenhaupt, 2017). Mucositis was common and cutaneous lesions included bullae, vesicles and erosion consistent with earlier studies. (McNish et al., 2024) Co-trimoxazole was the most implicated drug, followed by ceftriaxone while allopurinol was absent in this cohort. HIV was the most common co-morbidity, but occurred at lower rates than in a multi-centre African study, though higher than in Europe. Nevirapine was implicated in only one case, lower than reported in SJS/TEN cases among people living with HIV (PLHIV), likely due to its infrequent use as first-line HAART in Kenya. (Saka et al., 2013)

DIE patients had a mean age of 41 years, younger than the 67 years reported by Kliniec et al. The DIE latency period, previously reported to range from days to weeks, was the longest in this study at 18.41 days. (Kliniec et al., 2024) Eosinophilia was frequent (72.2%) aligning with prior findings. (Khaled et al., 2010) Anti-TB drugs and aromatic anticonvulsants were significantly associated with DIE, with carbamazepine being the most common culprit (Miyashiro & Sanches, 2020). Among patients with eosinophilia, two had organ involvement due to allopurinol and anticonvulsants, both known as DRESS. As erythroderma is a typical presentation of DRESS, it is plausible that these patients may have DRESS but were not evaluated according to the RegiSCAR criteria. 29.4% of DIE patients in this study were HIV positive and in Nigeria, it was found that erythroderma in HIV patients was primarily caused by ART and sulfonamides (Salami et al., 2012) while Zhu et al. identified antivirals followed by anti-TBs as the major culprits in HIV patients (Zhu et al., 2021). In contrast, in this study, anticonvulsants and anti-TBs were the most common causes of DIE among PLHIV.

GBFDE had a short latency period (1.5 days), consistent with prior studies. Patients were older (mean 43 years), aligning with earlier research (Brahimi et al., 2010). Mucositis was more frequent (83.3%) compared to 66.7% in previous reports, and 50% of cases involved two or more mucosal sites, as previously reported (Lipowicz et al., 2013). Nitroimidazoles and paracetamol were significantly associated with GBFDE, differing from a French multicentric study that identified NSAIDs and paracetamol as the main triggers. Prior drug reactions were more common than in previous research. (C.-H. Lee et al., 2012)

In DIEM, most patients (66.7%) were under 30 years, consistent with prior studies. Sulfonamides, NSAIDs and aromatic anticonvulsants were implicated in equal frequency, aligning with Panthalla et al., who identified sulfonamides as the most common cause. Mucositis was severe, with 91.6% of patients exhibiting involvement of multiple mucosal sites (Panthalla et al., 2019).

AGEP showed a female predominance, consistent with the EuroSCAR study but the mean age was significantly lower (16.3 years). No patients had prior drug reactions, making this rapid onset despite a lack of sensitization unexplainable (Mockenhaupt, 2017). The youngest patient (6 months) was the study's overall youngest. Paediatric AGEP cases are rare and are typically linked to infections rather than drug use but in drug-induced cases, antibiotics are the main trigger as was seen in this case. Antibiotics, especially B-lactams were the primary trigger, with ketoconazole and hormonal contraceptives identified as causative agents, the latter being a novel finding (E. Y. Lee & Koh, 2021). Additionally, no organ involvement, lower than in prior studies (Creadore et al., 2022). Generalized pustular psoriasis was ruled out based

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on the lack of psoriasis history, sudden drug onset and absence of a drug known to trigger pustular psoriasis. Furthermore, skin biopsies were performed in two patients, both revealing features consistent with AGEP.

DRESS accounted for 2% of cases, significantly lower than the 50% previously reported (Guzman & Paliza, 2018). The latency period (9.5 days) was shorter than the RegiSCAR (mean 22 days) (Kardaun et al., 2013). A strong association with aromatic anticonvulsants and DILI was noted. Genetic links between HLA-A*31:01 and carbamazepine-induced DRESS/DILI have been identified in European and Asian populations, but African data remain limited (Devarbhavi & Raj, 2019). The relatively low frequency of DRESS in this study may be attributed to the protean nature of its cutaneous manifestations and suboptimal use of diagnostic criteria.

DIA primarily affected the pediatric groups (mean age 8.5 years), contrary to previous studies. A female predominance was observed, though the cause remains unclear. Antibiotics and analgesics were the leading triggers, and asthma, a known risk factor was present in one patient (Regateiro et al., 2020). One case involved a progestin-only contraceptive, a rare cause of anaphylaxis, suggesting hormonal influences may be more complex than previously thought (Foer et al., 2016). The low DIA prevalence (3.9%) likely reflects referral biases.

CONCLUSION

This study provides key insights into the epidemiology, clinical presentations and drug causality of SCARs in a Kenyan referral hospital, highlighting notable differences from global trends. SCAR patients were significantly younger, with a higher proportion of paediatric cases, likely due to referral patterns and frequent antibiotic use for acute infections. SJS/TEN was the most common phenotype while DRESS was the least frequent. Antibiotics, particularly sulfonamides and B-lactams were the leading drug classes with anticonvulsants, NSAIDs and hormonal drugs also playing a role. Organ involvement, especially acute kidney injury (AKI) and drug-induced liver injury (DILI) was common, especially in SJS/TEN. The high prevalence of prior drug reactions (36.3%) highlights poor drug avoidance awareness, increasing the risk of severe recurrence. While HIV was the most common co-morbidity, its impact on SACR severity remains uncertain. Unlike global trends where SCARs mainly affect older adults with chronic illnesses, this study found that most cases were linked to acute illnesses. The findings underscore the need for stronger pharmacovigilance, patient education and stricter drug avoidance measures. Further genetic research is necessary to enhance early detection, risk stratification and prevention strategies for SCAR patients in Kenya.

Recommendations

Kenyan healthcare facilities should enhance pharmacovigilance by implementing mandatory SCAR reporting and ensuring clinicians are trained to identify early symptoms. This will help prevent escalation of reactions and misdiagnosis, which often leads to the addition of unnecessary medication that may worsen the reactions. Safer prescribing practices, particularly for antimicrobials, can be enforced while restricting over-the-counter sales of high-risk drugs to prevent misuse. Antimicrobials stewardship should be promoted to curb inappropriate drug use. Lastly, patient education on drug allergy awareness is crucial to prevent repeated exposure to offending drugs, which can lead to severe or fatal reactions.

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Data Availability

The dataset supporting this study is available upon reasonable request.

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Conflict Of Interest

The authors declare no conflict of interest.

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