

**CLINICAL AND EPIDEMIOLOGICAL
CHARACTERISTICS OF SEVERE CUTANEOUS
ADVERSE DRUG REACTIONS AT THE KENYATTA
NATIONAL HOSPITAL**

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**Clinical and Epidemiological Characteristics of Severe Cutaneous
Adverse Drug Reactions at the Kenyatta National Hospital**

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Degree of Master of Medicine in Dermatology of the Jomo
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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University

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DEDICATION

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ACRONYMS AND ABBREVIATIONS

ABCD-10	Age, Bicarbonate, Cancer, Dialysis, 10% Body Surface Area
ADR	Adverse Drug Reaction
AGEP	Acute Generalised Exanthematous Pustulosis
AIDS	Acquired Immunodeficiency Syndrome
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
ART	Antiretroviral therapy
AST	Aspartate Aminotransferase
CARD	Cutaneous Adverse Drug Reaction
DIA	Drug Induced Anaphylaxis
DIE	Drug Induced Erythroderma
DIEM	Drug Induced Erythema Multiforme
DILI	Drug Induced Liver Injury
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EM	Erythema Multiforme
FDE	Fixed Drug Eruption
GBFDE	Generalised Bullous Fixed Drug Eruption

HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICU	Intensive Care Unit
KNH	Kenyatta National Hospital
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
SCAR	Severe Cutaneous Adverse Drug Reaction
SJS	Steven Johnson Syndrome
TBSA	Total Body Surface Area
TEN	Toxic Epidermal Necrolysis

DEFINITION OF OPERATIONAL TERMS

Adverse Drug Reaction an undesirable and unintended response to a drug that arises from doses typically employed for the prevention, diagnosis, or treatment of diseases, or for the alteration of normal physiological functions.

Cutaneous Adverse Drug Reaction an undesirable effect from a drug which appears on the skin and its adnexa, including nails, hair and glands.

Drug Reaction with Eosinophilia and Systemic Symptoms a severe, potentially life-threatening reaction involving multiple organ systems, characterised by a rash, fever, lymphadenopathy, liver inflammation, leucocytosis with increased eosinophil count.

Epidermal Necrolysis acute necrosis and detachment of the upper layers of the skin and mucous membrane. It comprises *Steven Johnson Syndrome* and *Toxic Epidermal Necrolysis* which vary in terms of the extent of body surface involved.

Erythroderma a syndrome defined by persistent redness of the skin accompanied by varying degrees of scaling, affecting more than 90% of the total body surface area.

Index Day this is the day of onset of the severe adverse drug reaction.

Lag/Latency Period the timeframe from the administration of the drug to the appearance of clinical signs and symptoms.

Severe Cutaneous Adverse Drug Reaction refers to a potentially fatal reaction that is disabling and requires hospitalisation.

Steven Johnson Syndrome epidermal necrolysis with less than 10% body surface area detachment.

Toxic Epidermal Necrolysis epidermal necrolysis involving more than 30% total body surface area detachment.

Anaphylaxis an acute, potentially fatal, allergic reaction driven by release of mast cell and basophil granules mostly affecting the upper airways.

Acute Kidney Injury defined according to the Acute Kidney Injury Network (AKIN) criteria as an increase in serum creatinine to greater than 1.5 times the baseline or an increase of at least 26.5umol/L within 48 hours.

Drug Induced Liver Injury as per the international DILI expert working group, it is defined as meeting any one of the following criteria: (a) an elevation of $ALT \geq 5$ times the upper limit of normal (ULN=40U/L); (b) an elevation of $ALP \geq 2$ times the ULN; or (c) an elevation of $ALT \geq 3$ times the ULN accompanied by a total bilirubin level exceeding 2 times the ULN(21umol/L).

ABSTRACT

Severe Cutaneous Adverse Reactions (SCARs) are rare but potentially fatal drug-induced skin reactions, including Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and others. They pose a significant burden, especially in resource-constrained settings like Kenya, where data on their epidemiology and risk factors remain limited. This study aimed to describe the clinical and epidemiological characteristics of SCARs in patients at Kenyatta National Hospital (KNH), contributing to pharmacovigilance efforts and drug safety profiles in Kenya. The study's broad objective is to describe the clinical and epidemiological characteristics of patients admitted with SCARs. Specifically, it aimed to determine the clinical phenotypes of SCARs, identify their epidemiological characteristics, and evaluate causality in SCAR cases at KNH. A hybrid cohort design was employed, comprising retrospective and prospective data collection. A total of 102 patients were recruited via consecutive sampling. Data were gathered through file reviews, clinical examinations, and interviews, focusing on demographics, clinical features, etiologies, and co-morbidities. Statistical analyses, including chi-square and Kruskal-Wallis tests, were conducted using SPSS, with ethical approval from the KNH-UoN ERC. SJS/TEN was the most common phenotype (55.9%), followed by Drug-Induced Erythroderma (17.6%) and Drug-Induced Erythema Multiforme (11.8%). Participants had a mean age of 29.4 years, with a slight female predominance (51%). Antimicrobials (60.8%) and anticonvulsants (13.5%) were the most implicated drug classes, with co-trimoxazole, ceftriaxone and carbamazepine identified as common culprits. HIV was the most prevalent comorbidity (23.9%). Significant organ involvement included acute kidney injury (11.8%) and drug-induced liver injury (8.8%). Eosinophilia was associated with DIE (72.2%). Overall in-hospital mortality was 16.8% with the highest case fatality rate recorded in SJS/TEN (21.05%). SCARs in the Kenyan population were characterized by a younger age distribution, predominance of SJS/TEN, and a strong association with antimicrobials and anticonvulsants as the primary culprits. The high rates of organ involvement and in-hospital mortality, with acute kidney injury emerging as a key predictor of mortality, underscore the severity of these reactions. These findings highlight the need for early diagnosis, strengthened pharmacovigilance, and targeted interventions to improve patient outcomes. Future research should explore pharmacogenetics, long-term sequelae of SCARs, and the role of HIV in these severe reactions.

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

A *Cutaneous Adverse Drug Reaction* (CADR) is an undesirable effect of a drug manifestation in the structures or functions of skin, the appendages or the mucous membranes. These reactions account for 30-45% of all *Adverse Drug Reactions* (ADR) and 2% of all hospital admissions (Verma et al., 2013). They vary from mild exanthematous eruptions to *Severe Cutaneous Adverse Drug Reactions* (SCAR)- a group of rare and potentially fatal reactions that are disabling and require hospitalisation. SCARs include *Steven Johnson Syndrome/Toxic Epidermal Necrolysis* (SJS/TEN), *Acute Generalised Exanthematous Pustulosis* (AGEP), *Drug Reactions with Eosinophilia and Systemic Symptoms* (DRESS), *Drug-Induced Anaphylaxis* (DIA), *Generalised Bullous Fixed Drug Eruption* (GBFDE), *Drug-Induced Erythroderma* (DIE) and *Drug-Induced Erythema Multiforme Major* (DIEM) (Ardern-Jones & Mockenhaupt, 2019). The prevalence and clinical phenotypes of SCARs vary across populations due to ethnic and geographical factors (Zhang et al., 2019). Several factors have been associated with CARDs, including age over 60 years, female gender, immune dysregulation (such as immunosuppression and autoimmune disease), pregnancy and underlying diseases such as hepatic failure and renal disease (Mokhtari et al., 2014). Genetic predisposition also plays a role, with HLA-associated hypersensitivity syndromes linked to certain drugs such as abacavir, carbamazepine, nevirapine and allopurinol (Pavlos et al., 2012). Studies have identified multiple drugs as triggers for CADR, particularly antibacterial sulphonamides (especially co-trimoxazole), anticonvulsants, NSAIDs, *Anti-Retroviral Treatment* (ART) and allopurinol. The lag period between drug initiation and reaction onset varies but is typically less than 4 weeks (Mockenhaupt, 2017).

Assessment of drug causality is important as it can be lifesaving and help prevent further damage caused by the drug. Several methods exist and can be broadly classified into 3

group including clinical judgement, algorithmic methods and probabilistic methods(Pande, 2018). In addition to clinical and histological evaluation, specific scoring systems have been devised to aid in diagnosing SCARs, including the AGEp validation score for AGEp (De et al., 2018) and the RegiSCAR criteria, Bocquet's criteria and the J-SCAR criteria for DRESS (D.-H. Kim & Koh, 2014).

Global data highlights variation in SCAR incidence and prevalence in different populations, largely due to genetic differences, emphasizing the need for local epidemiological data. In Kenya, high HIV burden and widespread self-medication contribute to drug reactions(Ocan et al., 2015). SCARs impose significant impacts on patients, affecting them both psychologically and economically due to potential long-term complications. They can lead to scarring, pigment changes, impaired organ function and even cause end organ failure or autoimmune diseases. Despite their rarity, SCARs can be fatal with a case fatality rate of 5-10% for SJS, 30%, for SJS/TEN overlap, 50% for TEN and 10% for DRESS (W. Chung et al., 2016). This underscores the public health importance of studying SCAR epidemiology. Despite efforts to establish systems for reporting ADRs, the number of health facilities reporting these reactions in Kenya remains low(Barry et al., 2020). This study aims to examine the clinical spectrum, suspected drug causes and the epidemiology of SCARs in a tertiary hospital in Nairobi, Kenya.

1.2 Statement of the Problem

Despite the low global incidence, SCARs are lethal with a high mortality ranging between 10-40% and may result in long-term disability. Self-medication is a rising global concern that not only contributes to antibiotic resistance but also increases the risk of adverse drug reactions. Studies indicate that self-medication with antimicrobials, particularly antibacterial and antimalarial drugs, is common in low income countries, with an estimated prevalence of 38.8%(Ocan et al., 2015). This is coupled with a high burden of HIV in Sub-Saharan Africa, which bears 67% of the global HIV burden. The concomitant use of *Anti-Retroviral Treatment* (ART) and medications for opportunistic infections significantly increases the risk of drug reactions - estimated to be 2 to 100 times more common in HIV

infected persons (Lehloenya & Kgokolo, 2014; Moyo et al., 2023). The several international studies that have been conducted on SCARS show varying incidences and prevalence, emphasizing the need for Kenya-specific data given its unique socioeconomic and demographic context. This study aims to evaluate the clinical characteristics of the various SCARs encountered in our setting, identify any potential risk factors and describe the drugs linked with these severe reactions.

1.3 Study Justification

SCARs have profound psychological, medical and socioeconomic impacts as patients tend to develop long term sequelae, which may affect the quality of their lives. In both SJS/TEN and erythema multiforme major, the resolution of the mucosal lesions can lead to significant scarring, which may impede organ function. DRESS has been linked with end-organ failure and the emergence of autoimmune diseases, occurring months to years after the resolution of the initial disease especially thyroid disease with a cumulative incidence of 3.8%. AGEP has been linked to scarring and post-inflammatory hyperpigmentation. The RegiSCAR study also demonstrated a higher death rate 1 year after the acute phase of the severe skin reaction (Kano & Shiohara, 2013; Mockenhaupt, 2017). Given these long-term impacts, this study is essential in providing epidemiological data on SCARs in Kenya. Understanding the burden of these conditions will help improve supportive care strategies, rehabilitation programs and psychosocial interventions for affected patients. In addition, this study will contribute to pharmacovigilance efforts. In Kenya, the department of pharmacovigilance was established in 2004 at the Pharmacy and Poisons board with a vision to develop a system for reporting ADRs. However, the number of health facilities that report individual case safety reports remains low with less than 1% reporting these reactions. Furthermore, this study will provide insights into the safety profile of drugs commonly associated with SCARs and offer a foundation for future research, including pharmacogenetics studies (Barry et al., 2020). A deeper understanding of the local epidemiology of SCARs will also inform healthcare providers on safer prescribing practices, ultimately reducing the incidence of drug-induced reactions and improve patient outcomes.

1.4 Research Questions

The study utilized both retrospective and prospective data to address the following research questions:

1. What are the clinical phenotypes and clinical features of severe cutaneous adverse drug reactions among patients admitted at Kenyatta National Hospital?
2. What are the epidemiological characteristics of patients with severe cutaneous adverse drug reactions at Kenyatta National Hospital?
3. What are the suspected drug associations and drug-related characteristics among patients with severe cutaneous adverse drug reactions at Kenyatta National Hospital?

1.5 Study Objectives

1.5.1 Broad Objective

To describe the clinical, epidemiological and drug-related characteristics of patients admitted with severe cutaneous adverse drug reactions, including those who have developed severe cutaneous adverse drug reactions (SCARs) during their hospitalisation, at the Kenyatta National Hospital.

1.5.2 Specific Objectives

- a) To determine the clinical phenotypes and clinical features of severe cutaneous adverse drug reactions among patients admitted at Kenyatta National Hospital.
- b) To describe the epidemiological characteristics of patients with SCARs at Kenyatta National Hospital.
- c) To describe the suspected drug associations and drug-related characteristics among patients with SCARs at Kenyatta National Hospital.

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology of SCARs

Adverse Drug Reactions (ADRs) contribute to 2-6% of all hospital admissions and affect 10-20% of in-patients (Pirmohamed et al., 1998). The overall incidence of CADR varies by population, with developing countries reporting a higher incidence of 2-5% compared to developed nations (1-3%) (Hina et al., 2021). Hospital-based settings estimate CADR prevalence at 3.6-7 per 1000 hospitalised patients, with an incidence ranging from 0.01% to 3% (Fiszenson-Albala et al., 2003; Hernandez-Salazar et al., 2006). Several large multinational studies in Europe including the SCAR study, (which evaluated cases of SJS/TEN), EuroSCAR (which investigated AGEP and SJS/TEN) and RegiSCAR (assessed SJS/TEN and AGEP and DRESS) have provided important epidemiological insights into SCARs. These studies estimate the incidence of SJS/TEN at 1-2 cases per million persons per year, with a mean age of onset averaging at 53 years. Among those affected, 5% were found to be HIV-positive and mortality rates were 9% for SJS, 29% for SJS/TEN overlap and 49% for TEN, with an overall mortality of 25 % (Mockenhaupt, 2017).

The true incidence of DRESS remains unknown as it is underdiagnosed due to its variable clinical and laboratory presentations but estimates range from 1 in 1000 to 1 in 10000 drug exposures (Cacoub et al., 2011; Shiohara & Kano, 2016). Among hospitalised patients, prevalence is reported as 9.63 per 100,000 inpatients (Hiransuthikul et al., 2016). Studies indicated that DRESS occurs more frequently in black people and women (Calle et al., 2023). A mortality rate of 10% has been reported (Kardaun et al., 2013) though the RegiSCAR study found this to be lower at 1.7%. (Kardaun et al., 2013)

Acute generalized exanthematous pustulosis (AGEP) is similarly rare, with an estimated incidence of 1-5 cases per million per year, with a female predominance (Kardaun et al.,

2013). It exhibits the lowest mortality of all SCARs at 2-5%, typically due to end organ dysfunction(Owen & Jones, 2021).

Erythroderma is rare with an annual incidence of 0.9 per 100,000 inhabitants in the Netherlands and 35 - 71 per 100,000 dermatologic outpatients in India and Singapore respectively(Sigurðsson et al., 2001). It accounts for 1% of all hospital admissions for dermatologic conditions and men are more frequently affected(Salami et al., 2012). The mortality rate ranges from 20-40% but Munyao et. al. found it to be lower at 10% in Kenya.(Munyao et al., 2008)

The incidence of FDE is unknown and varies with the geographical area. A retrospective study in Tunisia estimated an incidence of 0.9 cases per 10000 consultations per year, with bullous FDE accounting for 29.62% of cases(Zaouak et al., 2019). GBFDE primarily affects older patients and has a high mortality of 22%(Lipowicz et al., 2013). Erythema multiforme (EM) has a prevalence of less than 1% but greater than 0.01%, with young adults (20-40 years) being the most affected group (Clark Huff et al., 1983).

Drug-induced anaphylaxis (DIA) incidence ranges from 0.04 to 3.1% and accounts for one in every 4000 emergency visits(Montañez et al., 2017). DIA occurs in approximately 1 in 3000 hospitalised patients. Drugs are the most common cause of anaphylaxis in adolescents and adults as opposed to foods in children. Death due to anaphylaxis is rare and it occurs in 1% of patients admitted with anaphylaxis(Regateiro et al., 2020). Drugs, as triggers of anaphylaxis are associated with fatal cases, accounting for 58.8% of all anaphylaxis related deaths with a fatality rate of 0.65% .

A study from South Africa by Konyana et al. provides insights into regional epidemiology of CADR. In this cohort, SCARs accounted for 68.5% of CADR in the tertiary hospital, with SJS/TEN being the most common phenotype followed by DRESS and AGEP. The affected population has a median age of patients 38 (IQR 28-50) with a female predominance (60%). (Konyana et al., 2024)

2.3 Classification and Clinical Phenotypes

The *European Academy of Allergy and Clinical Immunology* (EAACI), classifies CADR_s based on morphological features, chronology of symptoms and disease extent. (Brockow et al., 2019) Additional frameworks include classification by severity, underlying pathophysiology and the classical ADR classification by Rawlins and Thompson in 1977, which divided reactions into type A (dose-dependent) and type B (dose-independent/idiosyncratic). From an immunological point of view, drug reactions can be immunologically or non-immunologically mediated. Majority (75-80%) are predictable, non-immunological, dose-related toxicities (type A) reactions while 20-25% are unpredictable, abnormal responses to drug (type B/idiosyncratic reactions). These are unrelated to the pharmacological effects or the dose of the drug and can be immunologically and non-immunologically mediated. The Gell and Coombs classification further categorizes immune-mediated reactions into four main groups (Del Pozzo-Magaña & Liy-Wong, 2022; Nayak & Acharjya, 2008).

Chronologically, drug reactions are classified into immediate/acute reactions (includes urticaria, angioedema and/or anaphylaxis) which typically occur within the first hour of exposure and non-immediate/delayed reactions, which are primarily T-cell mediated reactions and manifest days to weeks after drug exposure. These delayed-type reactions can range in severity from mild maculopapular exanthema to SCAR_s(Zhang et al., 2019).

Morphologically, CARD_s can be categorized into exanthematous, bullous, urticarial and pustular types with patterns that do not fit into these groups classified as miscellaneous. These can be further sub-divided into simple and complex diseases, taking into account the presence of systemic features. Simple reactions primarily affect the skin and/or mucosae without systemic symptoms while complex conditions are characterised by systemic symptoms and are potentially lethal(Heelan & Shear, 2013).

SCAR_s therefore refer to those CADR_s which are unpredictable, pose substantial morbidity and mortality and are caused by an immunological mediated inflammatory

reaction with a prominent phenotype in the skin [11]. They include *Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis* (SJS/TEN), *Drug Reaction With Eosinophilia And Systemic Symptoms* (DRESS), *Acute Generalised Exanthematous Pustulosis* (AGEP), *Drug-Induced Erythroderma* (DIE), *Generalised Bullous Fixed Drug Eruption* (GBFDE), *Drug-Induced Erythema Multiforme Major* (DIEM) and *Drug-Induced Anaphylaxis* (DIA)(Ardern-Jones & Mockenhaupt, 2019; Kang et al., 2021). These conditions represent common dermatological emergencies leading to hospital admission(Techasatian et al., 2021).

Steven-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS and TEN), first described in 1922 and 1956 respectively(Roujeau & Stern, 1994), are considered to be a single disease entity characterised by extensive detachment of the epidermis, erythematous skin and mucous membrane erosions. They differ based on the extent of skin detachment with SJS involving less than 10% of the *Total Body Surface Area* (TBSA), TEN involving more than 30% of the TBSA and SJS/TEN overlap involving 10-30% TBSA. The lag period varies, with a median time of less than 3-4 weeks and majority of the cases will have presented less than 8 weeks following the introduction of the offending drug(Mockenhaupt, 2014; Owen & Jones, 2021). However, in cases of a previous exposure to the trigger, the lag time is shorter at 4.1days after re-exposure(Miliszewski et al., 2016). Prodromal symptoms consisting of a headache, pain in the skin, cough, sore throat, generalised malaise and myalgia occur 1 to 3 days prior to onset of cutaneous symptoms(Owen & Jones, 2021). The initial presentation of the cutaneous symptoms is a tender erythematous irregularly shaped dusky-red macule with or without atypical targets lesions that first appears on the trunk and spreads over 3-4 days to the face, neck and limbs. The scalp and palms are spared which differentiates it from other drug eruptions. The lesions rapidly coalesce leading to sheets of skin detachment which leave erythematous, denuded, oozy dermis. Gentle lateral pressure on the adjacent normal appearing skin leads to separation of the epidermis; known as *Nikolsky Positive Sign* [18]. Only necrotic skin that is detached (exhibiting blisters and erosions) and detachable (*Nikolsky Positive Sign*) skin is considered when calculating the TBSA involved(Owen &

Jones, 2021). In 80% of the cases, two or more mucous membranes are involved and often precede the skin lesions. The disease progresses over 7 to 10 days. Visceral involvement consists of a transient elevation of the liver and/or renal enzymes as well as necrosis of the bronchial and gastrointestinal tract epithelium (Duong et al., 2017). The ulcerated mucocutaneous lesions may heal with extensive scarring that affects organ function of the eyes, genitalia, lungs, oesophagus, the skin and its appendages. Therefore, long term follow up of patients is required after symptoms resolve (Kano & Shiohara, 2013).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) coined by Bocquet et al in 1996 to describe a syndrome characterised by a severe eruption, fever, lymphadenopathy, haematological abnormalities and organ involvement (Bocquet et al., 1996). The fever may precede the rash by up to 2 weeks and there may be a prodrome with upper respiratory tract symptoms (Owen & Jones, 2021). The cutaneous eruption is a morbilliform rash with a follicular accentuation that first affects the face and upper trunk and spreads caudally. It becomes infiltrated and indurated with oedematous follicular accentuation. Oedema of the face, often marked in the periorbital region with pinhead-sized pustules is the most characteristic early lesion. If the causative agent is not withdrawn, the eruption becomes generalised into erythroderma. Notably, the lesions can be polymorphic and bullae on the wrists, urticaria, purpura and targetoid lesions may develop. Mucosal involvement may occur although it may be mild. Tender lymphadenopathy occurs in 70-75% of cases and bilateral swelling of the salivary glands may be seen. Haematological abnormalities include leucocytosis with atypical lymphocytes and eosinophilia (60-70%). The most common visceral manifestation seen is liver in 50-60% of the cases and it could present as a transaminitis (51%) and hepatomegaly although fulminant liver failure can occur and is the leading cause of mortality. Other organs involved include the kidneys (30%), lung (25%), heart, brain, gastro-intestinal system, thyroid, nervous system and pancreas. The organ preferentially affected is likely determined by the causative agent and even after drug withdrawal; the resolution of symptoms in one organ may be succeeded by the development of failures in other organs (Bocquet et al., 1996; Calle et al., 2023; Shiohara & Kano, 2016; Walsh &

Creamer, 2011). However, no pathognomic pattern of skin rash has been reported(Cacoub et al., 2011). DRESS may manifest 3 weeks to 3 months after drug initiation, may persist despite drug withdrawal and may paradoxically worsen upon. It has also been reported to develop in patients receiving anticonvulsants for up to 40years (Criado et al., 2012), (Shiohara & Kano, 2016). More than 11% of DRESS patients experience long term sequelae which could be a continuation of the organ dysfunction that occurs during acute disease or may appear later, months to years after the acute disease. In younger patients, the sequela tends to present as autoimmune diseases while older patients develop organ failure. (Schunkert & Divito, 2021).

Acute Generalised Exanthematous Pustulosis (AGEP) described by Beylot et. al.(1980) begins as very acute oedematous erythema in the intertriginous areas or face and becomes diffuse. This is followed by an acute eruption with hundreds of small (pinhead sized, <5mm) non-follicular sterile pustules on the erythematous base, arising first in the face and skin folds and spreading rapidly on the trunk and limbs. (Sidoroff et al., 2001). Although rare, marked oedema of the face, purpura lesions on the legs and atypical targets, blisters and vesicles may develop. Mucosal involvement occurs in 20-25% of patients and is usually mild and limited to one mucosal region(Owen & Jones, 2021). The lag period in AGEP tends to be short, usually occurring within 48 hours of drug intake but this may vary for different drugs(Owen & Jones, 2021). In the EuroSCAR study, the lag period was found to be 1 to 5 days where antibiotics were found to be associated with a shorter latency period of 1 day but this was prolonged to 11 days for non-antibiotic related cases(De et al., 2018). During the initial stages of disease, elevated C-reactive protein, fever, leucocytosis due to increased levels of neutrophils occurs. Additionally, 30% of patients present with eosinophilia and 75% of patients develop hypocalcaemia, likely due to reduced albumin(Feldmeyer et al., 2016). Organ involvement occurs in 17% of cases with lymphadenopathy and involvement of the liver, kidney and lung(De et al., 2018). AGEP follows a mild, typically self-limiting course with skin lesions typically resolving spontaneously within 2weeks with a distinctive collarette-shaped desquamation in the region where pustules were previously present(Feldmeyer et al., 2016). Variants and

overlap syndromes including AGEP-DRESS overlap and TEN-AGEP as well as localised forms (*Acute Localised Exanthematous Pustulosis*) have been described (De et al., 2018).

Erythroderma refers to a severe syndrome marked by persistent erythema of the skin, often accompanied by varying degree of scaling affecting more than 90% of the total body surface area. It is dermatological emergency that represents a cutaneous inflammatory state associated with skin barrier dysfunction and metabolic changes (Tso et al., 2021). It has diverse aetiologies with *Drug-Induced erythroderma* (DIE) accounting for 12% of all cases of exfoliative dermatitis. The onset of drug induced erythroderma is abrupt and resolves promptly on withdrawal of causative agent which differentiates it from other causes of erythroderma (Miyashiro & Sanches, 2020). It presents as pruritus and patches of erythema which progressively increase in size to form extensive erythema which covers most of the body. The scaling begins 2-6 days after erythema and the scales tend to be large in acute disease and small in chronic disease. Hair loss and nail dystrophy may occur in erythroderma of long duration. It resolves over 2-6 weeks with generalised exfoliation. Widespread loss of pigmentation, oedema of the lower limbs, organomegaly, lymphadenopathy, periorbital oedema, hypothermia with resulting bradycardia and hypotension as well as hyperthermia, weight loss and cardiac failure may develop (Sehgal et al., 2004).

Fixed Drug Eruption (FDE) is a term coined by Brocq in 1894 to describe a reaction that is characterised by a solitary, well-defined erythematous to violaceous, round to oval patch, plaque or bullae with a dusky centre that reappear at the same location whenever a medication is consumed; with subsequent exposures resulting in increase in number of lesions and sites involved. It is classified based on its clinical morphology into localised (pigmenting, bullous), non-pigmenting, mucosal, generalised and *Generalised Bullous Fixed Drug Eruption* (GBFDE) (Patel et al., 2020). The lesions may also present as vesicles and bullae leaving erosions and usually, the resulting hyperpigmentation may persist for weeks to months after acute inflammation (Anderson & Lee, 2021). GBFDE refers to a severe form of FDE characterised by several vesico-bullous and oedematous plaques on erythematous and violaceous skin, involving at least 10% of the TBSA and at

least three of six separated anatomic sites(Anderson & Lee, 2021; Zaouak et al., 2019). In one study in Tunisia, 55% of all bullous FDEs were generalised bullous fixed drug eruptions(Zaouak et al., 2019). The lag period is rapid, ranging from 1-24 hours and mucosal involvement occurs in 66% of GBFDE and it typically tends to be mild. In addition, patients generally lack prodromal symptoms and these three features help differentiate it from SJS/TEN (Anderson & Lee, 2021; Patel et al., 2020) GBFDE is yet to be reported in children(Heelan & Shear, 2013).

In 1866, Hebra described an acute, self-limited disease characterised by symmetrical, evolving skin lesions located mostly on the extremities with a tendency to recur and termed it *Erythema Multiforme* (EM). The typical primary lesion is a round erythematous macule that becomes papular then enlarges to form a plaque with concentric changes in colour known as a target lesion. The central area may exhibit blistering, epidermal necrosis without blistering, appear beefy red and in people of colour, it may appear dark grey. EM is divided into EM major and EM minor based on the severity of mucosal lesions. These are seen in 25-60% of all EM lesions. In EM major, mucosal involvement is more severe with at least 2 surfaces affected while EM minor, it is absent or limited to one surface. Additionally, the classic acral distribution on the dorsal surfaces and extensor aspect of extremities typifies EM minor while EM major tends to be more variable and centralised. *Drug Induced EM* (DIEM) accounts for less than 10% of the cases and is most often an EM major. The lag period is 1-2 weeks but could be shorter if previously sensitised(Clark Huff et al., 1983; Sokumbi & Wetter, 2012).

The *World Allergy Organisation* (WAO) defines anaphylaxis as a severe, life-threatening systemic hypersensitivity reaction that is acute with potentially fatal airway, breathing or circulatory problems and is usually, but not always associated with skin and mucosal changes(Cardona et al., 2020). *Drug-Induced Anaphylaxis* (DIA) accounts for 35% of anaphylaxis cases and it may be IgE or non-IgE mediated(Regateiro et al., 2020). Like other types of anaphylaxis, DIA represents a syndrome of different symptoms that involve multiple organ systems and they may develop alone, simultaneously or subsequently. Cutaneous symptoms (pruritus, flushing, urticarial, angioedema) and mucous membrane

involvement are often the initial symptoms and this is followed by respiratory symptoms. These symptoms are present in 80-90% of patients(Ensina et al., 2016; Ring et al., 2010). Cardiovascular and gastrointestinal symptoms can also occur. A prodrome comprising of paraesthesia of the palms and soles, anxiety, diaphoresis, headache has been described(Ring et al., 2010). In Korea, cardiovascular symptoms were found to be more frequent in DIA while skin manifestations were more common in food induced anaphylaxis(S.-Y. Kim et al., 2018).

2.4 Aetiology

SJS/TEN is primarily drug-induced, although 25% of adult cases and 50% of pediatric cases are not drug induced(Ardern-Jones & Mockenhaupt, 2019). A nationwide multicentre study conducted in Korea - one of the largest studies on SCARs globally- identified 149 drugs responsible for SCARs. Allopurinol, carbamazepine, vancomycin, anti-tuberculosis agents were the four leading causes of both SJS/TEN and DRESS. Some drugs showed a strong phenotype preference: all carbonic anhydrase inhibitors, 84% of NSAIDs and 83% acetaminophen-related cases were associated with SJS/TEN while all dapsone, 81% of anti-tuberculosis agents and 78% glycopeptide antibiotic-related cases were linked to DRESS. SCARs due to carbonic anhydrase inhibitors have only been reported in Japanese, Chinese and Koreans populations, reflecting the high frequency of the HLA-B*59.01 allele in these regions(Kang et al., 2021). Similarly, the EuroSCAR identified nevirapine and lamotrigine, alongside well-established culprits as culprits in SJS/TEN(Mockenhaupt et al., n.d.). In India, antimicrobials were the most common triggers, followed by antiepileptic drugs and NSAIDs(Pudukadan & Thappa, 2004). A Kenyan study attributed 94.8% of SJS/TEN cases to sulphonamides(22.9%), nevirapine(16.5%), ciprofloxacin (11%), penicillin(7.3%), while infections – primarily HIV, herpes simplex virus-1 and mycoplasma pneumonia- accounted for the remaining cases (Irungu et al., 2017).

DRESS was initially termed ‘anticonvulsant hypersensitivity syndrome’ due to its association with long-term use of anticonvulsants(Shiohara & Kano, 2016). This has been

reflected in studies like the RegiSCAR study which found that aromatic antiepileptic drugs accounted for 35% of DRESS cases, followed by allopurinol(18%), antibacterial sulphonamides(12%) and non-sulphonamide antimicrobials, particularly vancomycin and minocycline(11%) (Kardaun et al., 2013). Similarly, Cacoub et. al. reported that antiepileptic - including carbamazepine, phenobarbital and lamotrigine accounted for a third of all drugs implicated in DRESS(Cacoub et al., 2011). A Tunisian study found that carbamazepine-induced DRESS accounted for 0.7% of all drug reactions and 31% of DRESS cases (Ksouda et al., 2017). Minocycline rarely causes DRESS but is a common cause of DRESS in patients with higher Fitzpatrick skin phenotypes(Shiohara & Kano, 2016). Some drugs have been associated with specific organ involvement: allopurinol with kidney injury, sulfasalazine with hepatitis, minocycline with lung involvement with myocarditis and ampicillin with myocarditis(Schunkert & Divito, 2021).

Over 90% of AGEP cases are drug-induced, with a minority being linked to infections(Owen & Jones, 2021) especially in the paediatric population (Heelan & Shear, 2013). The EuroSCAR study identified pristinamycin, aminopenicillins, quinolones, antimalarials, anti-infective sulfonamides, terbinafine and diltiazem as the most implicated drugs. Drugs with a weaker association were corticosteroids, macrolides, oxicam NSAIDs and antiepileptic drugs (except valproic acid). This study also disputed the etiological role of infections, suggesting that preceding infections led to the prescription of anti-infectives, which were the true AGEP triggers. (Sidoroff et al., 2007). Unlike SJS/TEN and DRESS, AGEP is not commonly associated with antiepileptics or allopurinol(Kardaun et al., 2013). Contact sensitivity to topical agents, spider bites, malignancy and pregnancy has been suggested to have a role in AGEP but the evidence is limited(De et al., 2018).

Both systemic and topical medications can precipitate erythroderma. Allopathic, herbal, homeopathic, ayurvedic treatment, as well as home remedies have been incriminated(Sehgal et al., 2004). In Brazil, anticonvulsants (especially carbamazepine), antihypertensives, anti-inflammatories and oral hypoglycemics were identified as the main culprits (Miyashiro & Sanches, 2020). Similar findings were reported in other

studies, consistently implicating carbamazepine (Akhyani et al., 2005; Munyao et al., 2008). However, in HIV-positive patients, anti-tuberculosis and herbal drugs are the leading causes of erythroderma (Morar et al., 1999).

More than 100 drugs can cause FDE with intravenous contrast and vaccines also implicated (Patel et al., 2020). Oral administration is more likely to cause FDE than parenteral administration (Goutham & Rajendran, 2020). Earlier studies implicated identified co-trimoxazole as the primary trigger, followed by tetracyclines, methimazole, phenylbutazone and paracetamol (Mahboob & Haroon, 1998). In Taiwan, NSAIDs were the most common cause of all FDEs, while antibiotics including cephalosporins and tetracyclines, were the primary triggers for GBFDE (C.-H. Lee et al., 2012).

The SCAR study identified oxicam NSAIDs, allopurinol, phenobarbital, phenytoin, antibacterial sulphonamides and chlormezanone as the main causes of erythema multiforme. Vaccinations in infants and newer drugs, such as Tumour Necrosis Factor-alpha (TNF- α) inhibitors, antitumour agents, exogenous sex hormones and topical treatments like imiquimod 5% have also been implicated (Lerch et al., 2018). In India, sulphonamides followed by metamizole were the primary causes of drug-induced EM (DIEM) (Panthalla et al., 2019). Shivhare et al. reported NSAIDs, paracetamol, carbamazepine, cefixime and diclofenac as triggers for DIEM (Shivhare et al., 2023).

Geographical variations in (DIA) are likely influenced by genetic predisposition and local prescription practices. In the United States, antibiotics were the most common culprits (accounting for two-thirds of cases) followed by analgesics (21.5%), with amoxicillin being most frequently implicated antibiotic. Black patients had a higher incidence of angiotensin-converting enzyme inhibitors related reactions than white patients, a trend also observed in European studies. In Latin America, NSAIDs were the leading triggers, followed by antibiotics then anaesthetic agents (Regateiro et al., 2020). Yu et al reviewed the *FDA Adverse Event Reporting System* (FAERS) database (2009-2019) and found that antibiotics, monoclonal antibodies, NSAIDs, acetaminophen and intra-operative agents accounted for 14.87%, 13.06%, 8.83%, 8.59% of all DIA cases respectively. Six drugs

were associated with over 20% of anaphylaxis-related deaths, including Iopamidol (29%), ceftriaxone(28%), fluorescein (28%), aprotinin (27%), cefoperazone (27%) and Lapine T-lymphocyte immune globulin(24.49%)(Yu et al., 2021). In Korea, exposure to iodinated contrast media, antibiotics (cefaclor) and muscle relaxants (tolperisone) was linked to increased anaphylaxis risk (Ahn et al., 2022).

2.5 Risk Factors

Several genetic and non-genetic risk factors increase the risk of SCARs(Guerra, n.d.). Human leukocyte antigen (HLA) polymorphisms are the predominant genetic risk factor, varying by population, drug and the phenotype of SCAR induced(Tempark et al., 2022).

Age-related risk has also been documented, with the very young and elderly patients at higher risk due to immaturity of enzymes responsible for drug metabolism leading to decreased drug clearance in the younger patients and impaired organ function in the older patients(Ajayi et al., 2000). Female predilection of ADR has been attributed to hormonal influence on drug metabolism(Nicolson et al., 2010). Ethnicity, a family personal or history of drug allergy, concurrent drug use for example lamotrigine and valproic acid and radiation therapy increase the risk of CADRs (W.-H. Chung et al., 2014), (Orozco, 2003), (Vázquez et al., 2018), (Ferreira et al., 2011). While co-morbidities do not directly induce drug reactions, the presence of underlying diseases like psychiatric disorders, autoimmune diseases, neoplasms and polypharmacy increases susceptibility (Machoń et al., 2022). Interestingly, HIV is an risk factor for TEN, independent of use of antiretroviral agents, anti-tuberculosis and sulfa-containing drugs(Guerra, n.d.). A hospital-based stud linked female gender, advanced age (>60 years), intensive care unit (ICU) hospitalization, obesity and immune dysregulation (such as systemic lupus erythematosus, thyroid disease, antiphospholipid syndrome) to CADR(Orozco, 2003). Drug induced anaphylaxis, in particular, is influenced by age, cardiorespiratory comorbidities, atopy and certain medications including angiotensin-converting enzyme inhibitors and beta-blockers and systemic mastocytosis. Additionally, hypertension, antidepressant use, vigorous exercise and physiological stress have been linked to anaphylaxis(Regateiro et al., 2020). Demir

et. al. found that parenteral drug administration -particularly intravenous route- and atopy increase the risk of DIA(Demir et al., 2019).

2.6 Assessment of Causality

Assessment of causality refers to identifying a causal link between a drug and a drug reaction. This is a crucial yet complex part of pharmacovigilance, where attempts are made to identify the exact drug responsible for causing an ADR (Pande, 2018). It is important in management of the patient as well in drug monitoring for better evaluation of the risk/benefit profile of drugs. The assessment relies on four key principles: temporal relationships with the drug reaction; biological plausibility; de-challenge; and re-challenge. (Sassolas et al., 2010). Causality assessment methods are broadly classified into three categories: global introspection (clinical judgment), algorithms-based assessment and probabilistic methods (Pande, 2018). Global introspection also known as expert/clinician judgement, involves experts determining causality based on clinical knowledge and experience. Four published methods exist in this category, including assessment methods used by the Swedish regulatory agency, the World Health Organisation and Uppsala Monitoring Centre (WHO-UMC), The French causality assessment method and one by Arimone et al.'s approach, where 5 experts independently assess the probability of drug causation(Agbabiaka et al., 2008). Algorithms-based methods provide structured step-by-step instructions to classify ADRs as definite, probable, possible or unlikely(Agbabiaka et al., 2008; Pande, 2018). The Naranjo algorithm (Table 2-1), established in 1981, is the most widely used tool for causality assessment across all adverse drug reactions(Son et al., 2011). Probabilistic (Bayesian) methods utilize a statistical approach to establish drug causality. These include the *Bayesian Adverse Reaction Diagnostic Instrument* (BARDI), which calculates the probability of drug causation based on epidemiological and clinical data(Agbabiaka et al., 2008).

Table 2.1: Naranjo Algorithm

Interrogation	Yes	No	Do Not Know
Are there previous confirmed reports of reaction?	+1	0	0
Did the adverse event appear after the drug was administered?	+2	-1	0
Did the adverse reaction improve following discontinuation of the medication or administration of a specific antagonist?	+1	0	0
Were there other plausible causes for the reaction?	-1	+2	0
Did the adverse reaction recur upon administration of placebo?	-1	+1	0
Was the drug found in the blood or other fluids in toxic concentrations?	+1	0	0
Did the reaction worsen with increasing dosage? Or did it improve with dosage reduction?	+1	0	0
Did the adverse reaction recur upon re-administration of the drug?	+2	-1	0
Has the patient experienced a similar reaction to the medication or a related agent in the past?	+2	0	0
Was the adverse event supported by other objective evidence?	+1	0	0

Source: (Bereda et al, 2021)

Interpretation: Score ≤ 0 , probability doubtful, 1- 4; possible, 5-8; likely/probable, ≥ 9 ; definite probability

For cases of SJS/TEN, the *Algorithm of Drug Causality for Epidermal Necrolysis* (ALDEN) is employed to determine the culprit drug, assigning scores based on six criteria as shown in Table 2.2.

Table 2.2: Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN)

Criteria	Possible Score
Time elapsed between initial drug intake and onset of reaction (index day)	-3 to +3
Presence of drug in the body on the index day	0 to -3
Prechallenge/rechallenge outcome with the suspected drug	-2 to +4
Outcome of rechallenge	0 to -2
Drug reputation for causing SJS/TEN	-1 to +3
Other potential etiological alternatives	-1, if applicable

Source: (Shanbhag et al, 2020)

Interpretation: ≥ 6 : very probable, 4-5: probable, 2-3: possible, 0-1: unlikely and ≤ 0 : very unlikely

2.7 Diagnostic Criteria

In 1996, Bocquet et al. proposed a criteria for the diagnosis of DRESS, comprising three key elements: (1) a cutaneous drug eruption, (2) haematological irregularities (eosinophilia $\geq 1.5 \times 10^9/L$ or the presence of atypical lymphocytes) and (3) systemic manifestations (lymph node enlargement ≥ 2 cm in diameter/hepatitis/interstitial nephritis/interstitial pneumonitis/carditis). A diagnosis is established if at least three of these criteria are met. (Bocquet et al., 1996). Subsequently, the J-SCAR (Table 2.3) and RegiSCAR (Table 2.4) diagnostic criteria were developed in 2006 and 2007, respectively and the primary distinction between the two is that J-SCAR requires laboratory evidence of the reactivation of human *Herpes Type 6* (HHV-6) for the diagnosis of DRESS to be made while RegiSCAR does not. A comparative study by Kim et al. evaluated the suitability of these three diagnostic criteria and found that Bocquet's criteria was the simplest to apply in the clinical setting and the RegiSCAR criteria, while accurate, was complex, making its use difficult in clinics. The J-SCAR was deemed too strict, making diagnosis difficult. As a result, it was recommended that Bocquet's and RegiSCAR criteria be used complementarily when diagnosing suspected cases of DRESS (D.-H. Kim & Koh, 2014).

Table 2.3: J-SCAR Criteria

1. Appearance of a maculopapular rash more than 3 weeks after initiation with a limited number of drugs
2. Persistence of clinical symptoms after discontinuation of the triggering drug
3. Fever more than 38 °C
4. Abnormal liver function tests (ALT exceeding 100U/L) ^a
5. Abnormalities in leukocyte count
a) Leucocytosis ($>11 \times 10^9/L$)
b) Presence of atypical lymphocytes ($>5\%$)
c) Eosinophilia ($>1.5 \times 10^9/L$)
6. Lymphadenopathy
7. Reactivation of HHV-6.

Source: (Shiohara et al, 2017)

Note: Diagnosis is verified by the presence of all seven criteria (typical DiHS) or 5 of the 7 (atypical DiHS). ^a can be replaced with other organ involvement.

Table 2.4: RegiSCAR Criteria

Score	-1	0	1	2
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes		
Lymphadenopathy		No/U	Yes	
Eosinophilia				
- Eosinophil count			$0.7 - 1.499 \times 10^9 \text{ L}^{-1}$	$\geq 1.5 \times 10^9 \text{ L}^{-1}$
- Eosinophil count, if leukocytes $< 4.0 \times 10^9 \text{ L}^{-1}$			10 % - 19.9%	$\geq 20\%$
Atypical lymphocytes		No/U	Yes	
Skin involvement				
- Skin rash extent (%TBSA)		No/U	$> 50\%$	
- Skin rash suggesting DRESS	No	U	Yes	
- Biopsy suggesting DRESS	No	Yes/U		
Organ involvement				
- Liver		No/U	Yes	
- Kidney		No/U	Yes	
- Muscle/heart		No/U	Yes	
- Pancreas		No/U	Yes	
- Other organs		No/U	Yes	
Resolution ≥ 15 days	No/U	Yes		
Evaluation of other potential causes				
- Antinuclear antibody				
- Blood cultures				
- Hepatitis A/B/C serology				
- Chlamydia/mycoplasma serology				
- If none positive and ≥ 3 of the above negative		Yes		

Source: (Cacoub et al, 2011; Sibbald et al, 2023)

U: unclassifiable or unknown.

Interpretation: Score < 2 : no case, 2-3: possible case, 4-5: probable case, > 5 : definite case.

In 2001, the EuroSCAR group developed the AGEP validation score, which assesses the morphology of skin lesions, presence of fever, clinical progression, laboratory and histological findings, as detailed in Table 2.5.

Table 2.5: AGEP Validation Score of the EuroSCAR Study Group

Morphology	
Presence of pustules	
- Typical	+2
- Compatible	+1
- Insufficient	0
Presence of erythema	
- Typical	+2
- Compatible	+1
- Insufficient	0
Distribution pattern	
- Typical	+2
- Compatible	+1
- Insufficient	0
Post-pustular desquamation	
- Yes	+1
Absent/insufficient	0
Course	
Mucosal involvement	
- Present	-2
- Absent	0
Acute Onset (≤ 10 days)	
- Present	0
- Absent	-2
Resolution ≤ 15 days	
- Present	0
- Absent	-4
Fever $\geq 38^{\circ}\text{C}$	
- Present	+1
- Absent	0
PMN $\geq 7000/\text{mm}^3$	
- Present	+1
- Absent	0
Histology	
- Other disease	-10
- Not Representative/No Histology	0
- Presence of exocytosis of PMN	+1
- Presence of subcorneal and/or intra-epidermal non-spongiform or NOS pustule(s) with papillary edema or subcorneal and/or intra-epidermal spongiform or NOS pustule(s) without papillary edema	+2
- Presence of spongiform subcorneal and/or intra-epidermal pustule(s) with papillary edema	+3

Source: (Sidoroff et al, 2001)

Interpretation: ≤ 0 : no AGEP, 1-4: possible, 5-7: probable, 8-12: definite

In 2005, the US National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAD/FAAN) proposed a diagnostic criteria for anaphylaxis which was later revised by the *World Allergy Organisation* in 2020 to address certain limitations in the original criteria (Table 2.6)

Table 2.6: The World Allergy Organisation’s Criteria for the Diagnosis of Anaphylaxis

Anaphylaxis is highly probable when any one of the following 2 sets of criteria is met:	
1.	An abrupt onset of symptoms (minutes to several hours) characterised by concurrent involvement of the skin, mucous membranes or both
	And at least One of the following:
	Respiratory compromise (for example dyspnoea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
	Decreased blood pressure or associated symptoms or end-organ dysfunction such as hypotonia (collapse), syncope, incontinence
	Severe gastrointestinal symptoms (for example severe crampy abdominal pain, repetitive vomiting) particularly following exposure to non-food allergens.
2.	Sudden onset of hypotension or bronchospasms or laryngeal involvement after exposure to a known or highly likely allergen for that individual (occurring within minutes to hours), even in the absence of typical skin manifestations.

Source: (Cardona et al, 2020)

2.8 Conceptual Framework

This study was guided by a descriptive conceptual framework illustrating the relationship between patient-related factors, drug-related factors, clinical phenotypes and outcomes patients admitted with SCARs at Kenyatta National Hospital. Patients-related factors included epidemiological characteristics such as age and sex and underlying co-morbidities. Drug-related factors included the suspected culprit drug, concurrent medications, indication for drug use, previous drug allergy, mode of drug acquisition and lag period. These factors influenced the development of specific SCAR phenotypes, their clinical presentation and systemic involvement, which in turn determine in-hospital outcomes.

Independent variables

Epidemiological Factors: Age,
Gender

Co-morbidities: HIV, renal
disease

Drug-related factors: Suspected
drug, indication for drug use,
history of prior allergy, lag
period

Dependent variables

SCAR phenotype

Clinical features

Systemic involvement

Outcomes:

-In-hospital Outcome
(discharge, in-hospital
mortality)

Figure 2.1: Conceptual Framework

CHAPTER THREE

METHODOLOGY

3.1 Study Design

This study is a hybrid cross-sectional study utilizing both retrospective and prospective data collection. The retrospective arm involved a review of patient records diagnosed with SCARs between 2014 and August 2024 while the prospective arm enrolled newly admitted SCARs patients between August 2024 and December 2024, with data collected during their hospitalization period. For both study arms, data was collected at a single point in time – during hospitalization. In the prospective arm, all relevant clinical data, including patient status at discharge, was recorded during the hospitalization period without subsequent tracking after discharge. The use of a hybrid design was intended to maximise case capture for a rare condition such as SCARs. The retrospective arm provided a larger sample size over an extended period, while the prospective arm allowed for more detailed and standardized data collection. Data from both arms were pooled for analysis, as the variables of interest were comparable across both datasets. However, no formal comparison between retrospective and prospective cohorts was performed as the study was designed to provide a descriptive analysis of SCAR characteristics rather than to compare temporal cohorts.

3.2 Study Site

This study was conducted at the *Kenyatta National Hospital* (KNH), situated in Nairobi, Kenya. KNH is a public, tertiary, referral hospital and the largest in East Africa, with a bed capacity of 1,800. Study participants were drawn from the dermatology ward and other relevant wards, including medical and paediatric wards, *Intensive Care Unit* (ICU) and the burns unit.

3.3 Study Population

The study population comprised patients admitted to KNH and diagnosed with a severe cutaneous adverse drug reaction by a KNH consultant dermatologist.

3.4 Eligibility Criteria

3.4.1 Inclusion Criteria

- Patients admitted to Kenyatta National Hospital wards between year 2014-2024 (retrospective arm) and between August 2024 and December 2024 (prospective arm)
- The diagnosis of a severe cutaneous adverse drug reaction confirmed by a KNH consultant dermatologist.
- Consent provided by patients or guardians (prospective arm).

3.4.2 Exclusion Criteria

- Clinical diagnosis not confirmed by a dermatologist.
- Patients with confirmed alternative diagnosis that may clinically mimic SCARs including staphylococcal scalded skin syndrome, immunobullous diseases, superficial burns, acute graft versus host disease, confirmed lupus erythematosus, pustular psoriasis and erythroderma due to other causes.
- Lack of consent for participation.(Prospective arm)

3.5 Study Sampling

3.5.1 Sampling Technique

A non-probabilistic consecutive sampling approach was used, enrolling all eligible patients until the desired sample size was achieved. This technique was appropriate given the rare nature of SCARs.

3.5.2 Sample Size Determination and Formula

The sample size was calculated using the Cochran formula. Given the absence of prevalence data on all severe cutaneous adverse drug reactions in Kenya, prevalence rates from a comparable study conducted in Malaysia was utilised as proxy. Tee et. al. conducted a retrospective study on SCARs including SJS/TEN, DRESS, AGEP, acute erythroderma and GBFDE over a period of 5years and 3months. The calculated incidence rate was 0.18%.

Prevalence = incidence rate x average disease duration

$$\text{Prevalence} = 0.18 \times 5.25$$

$$\text{Prevalence} = 0.945$$

In determining the sample size, the Cochran's formula for Sample Size Calculation in Survey Research was used.

$$n = \frac{Z^2 p(1 - p)}{e^2}$$

Where:

n = required sample size

Z = Z-score corresponding to the desired confidence interval for the study, a 95% confidence level will be employed which corresponds to a Z score of 1.96

p = prevalence rate of 0.945

e = margin error of 0.05

$$n = \frac{1(1.96)^2 \times 0.945 \times (1 - 0.945)}{(0.05)^2}$$

$$n = 79.88(80)$$

To account for non-response and missing data, adjustments were made, resulting in a total sample size of **102** participants as demonstrated below:

The original **total sample size** was **80**, which was to be split equally between the prospective and retrospective arm = **40** for each arm.

Prospective arm:

The estimated non-response rate was 20%

Adjusted sample size = $n / (1 - \text{non-response rate})$

= $40 / 0.8$

= 50

Retrospective arm

The estimated missing data rate was 22%

Adjusted sample size = $n / (1 - \text{missing data rate})$

= $40 / 0.78$

= 52

The combined adjusted sample sizes = $50 + 52 = 102$

C. T. Tee, N. H. Abdullah, P. Kristummoonthy, and C. S. Lee, “Severe Cutaneous Adverse Reactions: A 5-year retrospective study at Hospital Melaka, Malaysia, from December 2014 to February 2020(Tee et al., 2022).

The larger retrospective sample compared to the prospective arm reflects both the rarity of SCARs and the limited duration of prospective recruitment. To maximize case capture, a prolonged retrospective period (2014–2024) was utilised; however, inclusion was restricted to files with sufficient clinical data, leading to the exclusion of records with substantial missing information. Additionally, limited availability of older records, further constrained case identification. These factors necessitated extending the retrospective

period to achieve the required sample size. In contrast, the prospective arm involved active case identification across multiple wards allowing for more efficient capture of SCAR cases over a shorter period. This contributed to a higher number of cases observed during the prospective phase despite its shorter duration.

3.6 Data Collection

Data collection was initiated after obtaining approval from the Department of Dermatology and the Kenyatta National Hospital (KNH) Ethics Review Committee. For the prospective arm, participants were recruited from KNH wards following informed consent; those who declined were excluded. Data was gathered via interviewer-administered questionnaires, patient file reviews, and full-body examinations to evaluate lesion types, affected body surface area, and mucosal involvement. Outcomes were recorded at a single time point, the hospitalization period, with the final status categorized as:

- Recovery: Discharge from hospital during the data collection period
- In-hospital mortality: Defined as death occurring during the hospitalization period
- Ongoing hospitalization: Patients still admitted at the time of study completion.

These patients were not categorized under final outcomes.

For the retrospective arm, patient files were identified using ICD-10 and ICD-11 codes from KNH records. The same standardised data collection tool was used to systematically extract clinical data in both the retrospective and prospective arms to ensure consistency of variables across datasets. All data collection was paper-based and conducted by the principal investigator and trained research personnel.

3.7 Pre-Test

A pre-test was conducted to pilot data collection tools and procedures, allowing identification and resolution of potential issues before the main study.

3.8 Data Variables

The study collected data on demographic factors, clinical features, aetiology and associated co-morbidities, as summarized in Table 3.1 below.

Table 3.1: Data Variable

Objective	Variables	Source of Data
Baseline Characteristics	Demographic factors: - Age - Gender Residence: County Ethnicity (self-identification)	Patient's file
Clinical Features	1. Prodromal symptoms 2. Type of Severe cutaneous adverse drug reaction 3. Associated co-morbidities: Convulsive disorder, psychiatric diseases, Hypertension, Diabetes, Renal diseases, Hepatic diseases, HIV, malignancy, autoimmune diseases 4. Concomitant symptoms including systemic involvement	Patient's file
Aetiology	Drug cause: 1. Suspected drugs 2. Other drugs taken concurrently 3. Lag periods 4. History of previous drug allergies 5. Indication for drug use	Patient's file

3.9 Data Quality Control and Assurance

Data collection was standardised using a structured tool to ensure methodological consistency. In the prospective cohort, regular quality checks were conducted to maintain accuracy and adherence to protocols, with emphasis on minimising variability in clinical interpretations and subjective assessments. Initial assessments were conducted by the principal investigator and in cases of uncertainty, confirmation was sought from a consultant dermatologist, who provided the final determination. In the retrospective cohort, quality assurance prioritised completeness and consistency of extracted records. Any gaps or ambiguities in medical records were systematically identified, documented, and addresses using systematic methods. All data underwent completeness and clarity verification prior to analysis.

3.10 Data Management and Analysis

Collected data was securely stored in a locked cabinet accessible only to authorised personnel. Identifiers were anonymised to comply with Kenya's *Data Protection Act (2021)*. Data cleaning addressed outliers, missing values, and coding inconsistencies; categorical variables were numerically coded for analysis. Statistical analysis was performed using **SPSS v26**, with results visualised in tables, charts, and graphs. Descriptive statistics summarised demographic/clinical profiles and medication-related data. Inferential analyses employed:

- **Kruskal-Wallis tests** to compare non-parametric medians
- **Chi-square/Fisher's exact tests** (as appropriate) to assess associations between categorical variables
- Statistical significance was defined as $p < 0.05$.

3.11 Data Handling

Available case analysis was employed, where for each analysis, only cases with complete data for a specific variable under consideration were included. In the prospective arm, missing data was minimal due to real-time data collection. In the retrospective arm, some variables, particularly laboratory tests, were missing due to incomplete records (*Missing Completely At Random* {MCAR}) or because certain tests were not performed based on clinical decision-making (*Missing At Random* {MAR}). Efforts were made to include files with minimal missing data. Including files with excessive missing data could introduce information bias, while excluding too many cases might affect representativeness. To balance this, available case analysis was used, ensuring a minimal proportion of missing data to preserve statistical power. However, this approach may still introduce bias, which is acknowledged as a study limitation.

The nature of missing data was assessed to differentiate between true absence of variables (documented as negative) and incomplete reporting. Absence was recorded when a

variable was documented as negative or not present, while missing data referred to instances where no information was available due to lack of documentation. No imputation methods were applied as the study was primarily descriptive and the use of imputation could introduce additional bias given the relatively small sample size.

3.12 Ethical Considerations

Ethical approval was obtained from the KNH-UoN Ethics Review Committee, the Department of Dermatology, and National Commission for Science, Technology, and Innovation (NACOSTI). Administrative approval from KNH facilitated access to anonymised hospital records. Written informed consent (English/Swahili) and minor assent forms were obtained prospectively, detailing study objectives, risks/benefits, and investigator contact information. Participants in the prospective arm were informed of their right to withdraw from the study at any point without impact on their medical care. Patient safety was prioritised throughout the study and all clinical management decisions were made independently of study participation under the supervision of the attending clinical team. Participation in the study did not interfere with standard patient care. Retrospective data, being fully anonymised, were exempted from reconsent per institutional guidelines. All data were stored in password-protected systems, accessible exclusively to the Principal Investigator. Study protocols adhered to:

1. **Anonymity:** No personally identifiable information retained
2. **Confidentiality:** Secure storage and restricted access
3. **Transparency:** Clear communication of data use in publications

Findings were disseminated in aggregated, non-identifiable formats.

CHAPTER FOUR

RESULTS

4.1 Characteristics of the Study Participants

A total of 102 patients were enrolled in the study. For the retrospective arm, 62 patient files from individuals diagnosed with SCARs between 2014 and 2024 were reviewed while 40 patients were recruited prospectively. Due to lower-than-expected prospective recruitment, the retrospective sample was increased to maintain the overall sample size. The adjustment does not compromise the validity of the study, as key variables of interest are not influenced by whether data was collected retrospectively or prospectively. Study findings are presented below in line with the study objectives.

4.2 Clinical Phenotypes and Clinical features of SCARs

4.2.1 Clinical Phenotype

To address Objective 1, which examined the clinical phenotypes and clinical features of SCARs, the distribution of disease phenotypes and associated clinical characteristics were analysed. The most common disease phenotype in the study was the SJS/TEN spectrum, observed in over half of the participants (n=57, 55.9%). Within this group, the majority had TEN (n=41, 40.2%) while 10 participants (9.8%) had SJS/TEN overlap and 6 participants (5.9%) had SJS. Drug induced exfoliative erythroderma (DIE) was the second most prevalent phenotype, found in 18 patients (17.6%) followed by drug induced erythema multiforme (DIEM) and GBFDE in 12 and 6 participants respectively. The least common were DIA, DRESS, AGEP which were present in 4(3.9%), 2(2.0%) and 3(2.9%) of the participants respectively (Figure 0-1). Regarding diagnostic criteria, the RegiSCAR criteria and the AGEP validation score were applied to assess one patient each for DRESS and AGEP respectively. The WAO criteria was not used in the study.

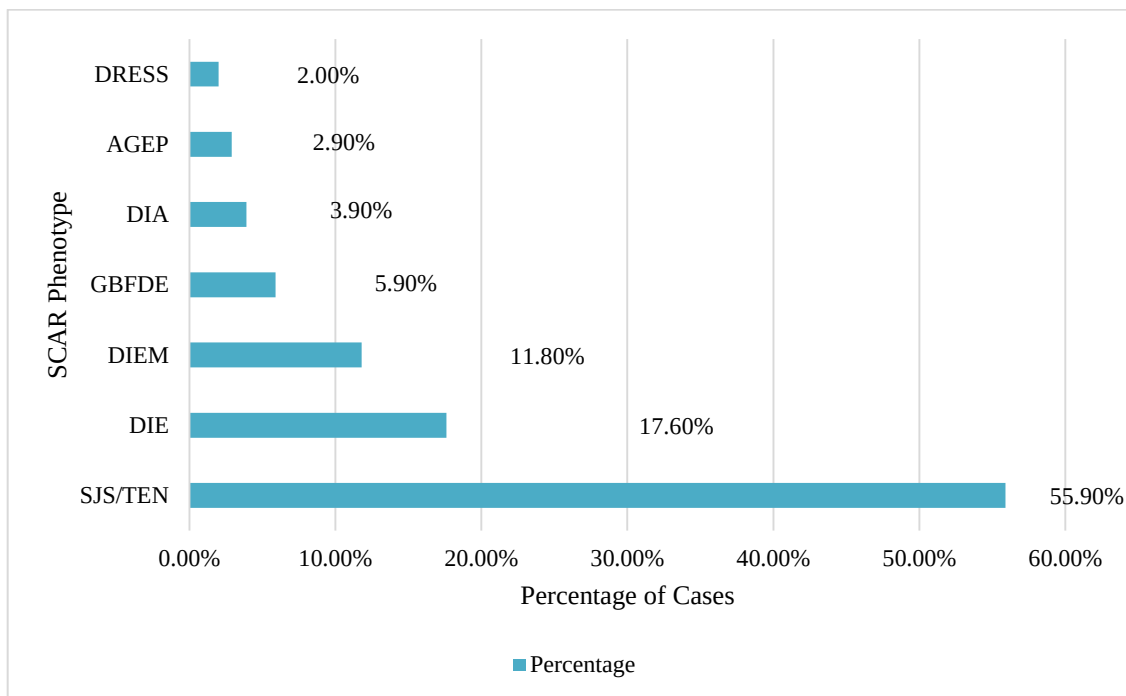


Figure 4.1: Percentage Distribution of SCAR Phenotypes in the Study Population

Figure 4.1 illustrates the percentage distribution of SCAR phenotypes in the study population. SJS/TEN was the predominant SCAR phenotype, accounting for over half of all cases, with other phenotypes occurring at substantially lower frequencies.

The X-axis represents the percentage of cases, while the Y-axis lists the SCAR phenotypes.

4.2.2 SCAR Phenotypes and Age Distribution

Notably, SJS/TEN had the widest age distribution with the largest proportion of cases occurring in the paediatric age group (0-12 years) at 35.1% (n=20) followed by a significant proportion in the 41-50 age group (17.5%). DRESS, AGEP, and DIA were primarily seen in younger patients, with DIA affecting the youngest participants (mean age: 8.5 years). In contrast, DIE and GBFDE were more frequent in older age groups where GBFDE was particularly notable for affecting older adults with 66.6% of cases occurring in those above 40 years. (Figure 4.2)

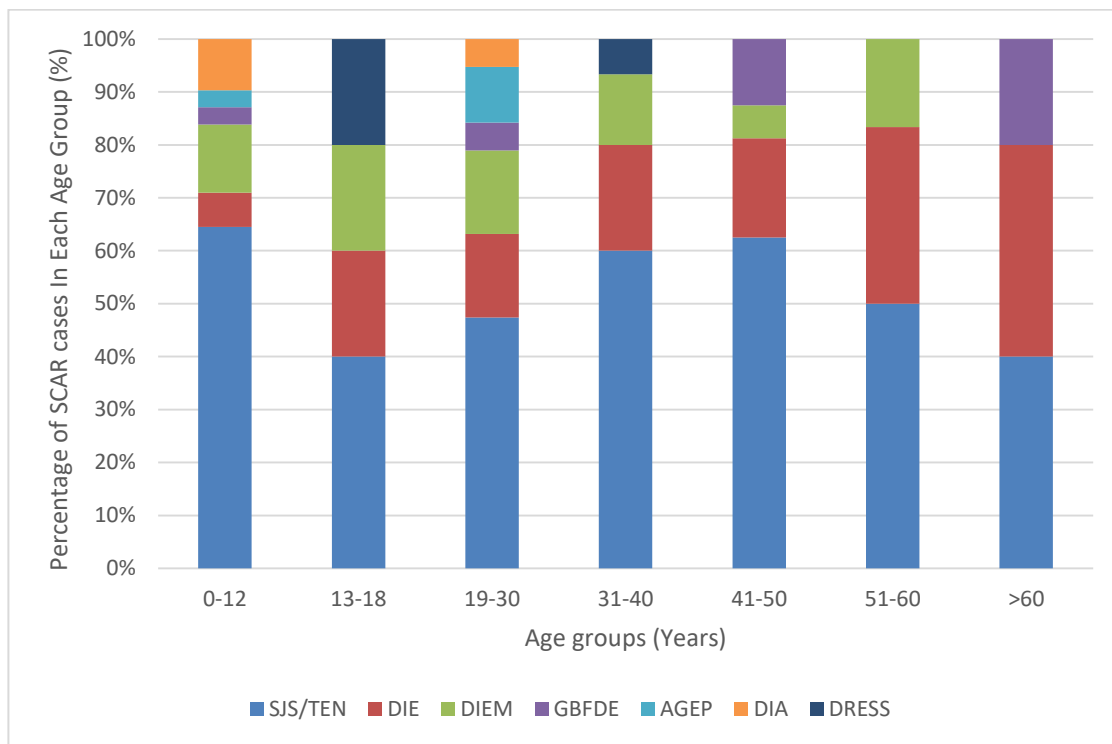


Figure 4.2: Distribution of SCAR Phenotypes by Age Group

Figure 4.2 illustrates the distribution of SCAR phenotypes across different age groups using a 100% stacked bar chart. SCAR phenotypes demonstrated variable age distributions, with SJS/TEN spanning all age groups while other phenotypes showed clustering within specific age categories. The X-axis represents age groups (years) while the Y-axis represents the percentage of SCARs within each age group {Each bar represents 100% of SCAR cases for that specific age group}

A Kruskal-Wallis test revealed a statistically significant difference in age distribution among SCAR phenotypes ($p=0.021$). Post-hoc pairwise comparisons using the Mann-Whitney U test showed no statistically significant difference between any specific SCAR phenotypes. ($p>0.05$) To further examine the relationship between age group categories and SCAR phenotypes, a Chi-square test ($p=0.381$) was conducted. However, small sample sizes in certain SCAR phenotypes may have limited the test's ability to detect

significant differences, even though some SCAR phenotypes appeared more common in specific age groups. (Table 4.1)

4.2.3 SCAR Phenotypes and Gender Distribution

Regarding gender distribution, DIE showed a slight male predominance while GBFDE had a clear male majority. Conversely, DIA was predominantly observed in females with AGEF exclusively affecting females. In contrast, SJS/TEN, DRESS and DIEM showed a near-equal gender distribution. A Chi-square test was performed to assess the statistical significance of these differences and the results were not significant ($p=0.561$). (Table 4.1).

Table 4.1: Demographic Characteristics among the Different SCARs

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)								
0-12	20 (35.1)	0 (0)	1 (33.3)	2 (11.1)	4 (33.3)	1 (16.7)	3 (75.0)	0.381
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	

Table 4.1 above summarizes the demographic distribution of participants across different SCAR phenotypes. Age distribution differed significantly across SCAR phenotypes ($p=0.021$), although post-hoc pairwise comparisons did not identify any statistically significant differences between specific groups. In contrast, gender distribution did not vary significantly across phenotypes ($p=0.561$)

4.2.4 Prodromal Symptoms

Prodromal symptoms were common, reported in 70.6% (n=72) of the participants (*Retrospective: n=33, Prospective: n=39*). A total of 99 responses were recorded as participants could report multiple symptoms. Pruritus was the most frequently reported symptoms (35.3%), followed by constitutional symptoms 29 (28.4%). Other notable symptoms included respiratory symptoms (11.8%) and paraesthesia (8.8%) (Table 2.2).

Table 4.2: Frequency and Percentage of Prodromal Symptoms

Clinical presentation	Frequency	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

Table 4.2 highlights that pruritus (35.3%) and constitutional symptoms (28.4%) were the predominant prodromal features, with all other symptoms reported less frequently.

A statistical analysis was conducted to determine whether specific prodromal symptoms were significantly associated with SCAR phenotypes. The results showed no statistically significant associations between prodromal symptoms and SCAR phenotypes. (Table 4.3)

Table 4.3: Distribution of Prodromal Symptoms among SCAR Phenotypes

Clinical presentation	SJS/TEN (n=57)	DRESS (n=2)	AGEP (n=3)	DIE (n=18)	DIEM (n=12)	GBFDE (n=6)	DIA (n=4)	P value
Pruritus	7(12.3)	0(0)	0(0)	10(55.6)	1(8.3)	0(0)	1(25.0)	0.467
Constitutional symptoms	20(35.1)	1(50.0)	1(33.3)	2(11.1)	3(25.0)	1(16.7)	1(25.0)	0.558
Respiratory symptoms	10(17.5)	0(0)	0(0)	1(5.6)	0(0)	0(0)	1(25.0)	0.396
Paraesthesia	7(12.3)	0(0)	0(0)	0(0)	1(8.3)	0(0)	1(25.0)	0.549
Gastrointestinal symptoms	4(7.0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0.772
CNS symptoms	2(3.5)	0(0)	0(0)	1(5.6)	0(0)	0(0)	0(0)	0.971

Clinical presentation	SJS/TEN (n=57)	DRESS (n=2)	AGEP (n=3)	DIE (n=18)	DIEM (n=12)	GBFDE (n=6)	DIA (n=4)	P value
Musculoskeletal symptoms	0(0)	0(0)	0(0)	2(11.1)	1(8.3)	0(0)	0(0)	0.268
Other	2(3.5)	0(0)	0(0)	0(0)	1(8.3)	0(0)	0(0)	0.892

Table 4.3 shows that prodromal symptoms differed across the different SCAR phenotypes. However, there was no statistically significant association between prodromal symptoms and SCAR phenotypes, with similar distributions observed across disease groups ($p>0.05$).

4.2.5 Muco-Cutaneous Symptoms

4.2.5.1 Cutaneous Signs and Symptoms

Cutaneous symptoms were described in all study participants. Bullae were the most predominant cutaneous symptom, occurring in 66 participants (64.7%), followed by erosions in 65 participants (63.7%) and macules in 52 participants (51.0%). The least common cutaneous symptoms were pustules in (n=8, 7.8%), plaques (n=6, 5.9%) and wheals (n=4, 3.9%) (Table 4.4)

Table 4.4: Distribution of Cutaneous Symptoms among Study Participants

Cutaneous Symptoms	Frequency(n)	Percentage (%)
Bullae	66	64.7
Erosions	65	63.7
Macules	52	51.0
Vesicles	47	46.1
Patches	43	42.2
Papules	28	27.5
Scales	22	21.6
Target Lesions	18	17.6
Pustules	8	7.8
Plaques	6	5.9
Wheals	4	3.9

Table 4.4 shows that bullae and erosions were the most common cutaneous symptoms, followed by macules and vesicles, with other lesions occurring less frequently.

Erosions, bullae and vesicles were common in SJS/TEN, DIEM and GBFDE while scales and papules were more frequent in DIE. Wheals and pustules were notably associated with DIA and AGEF respectively. (Figure 4.3) Statistical analysis revealed significant variation in the types of lesions observed across the disease phenotypes ($p < 0.05$). (Data not shown)

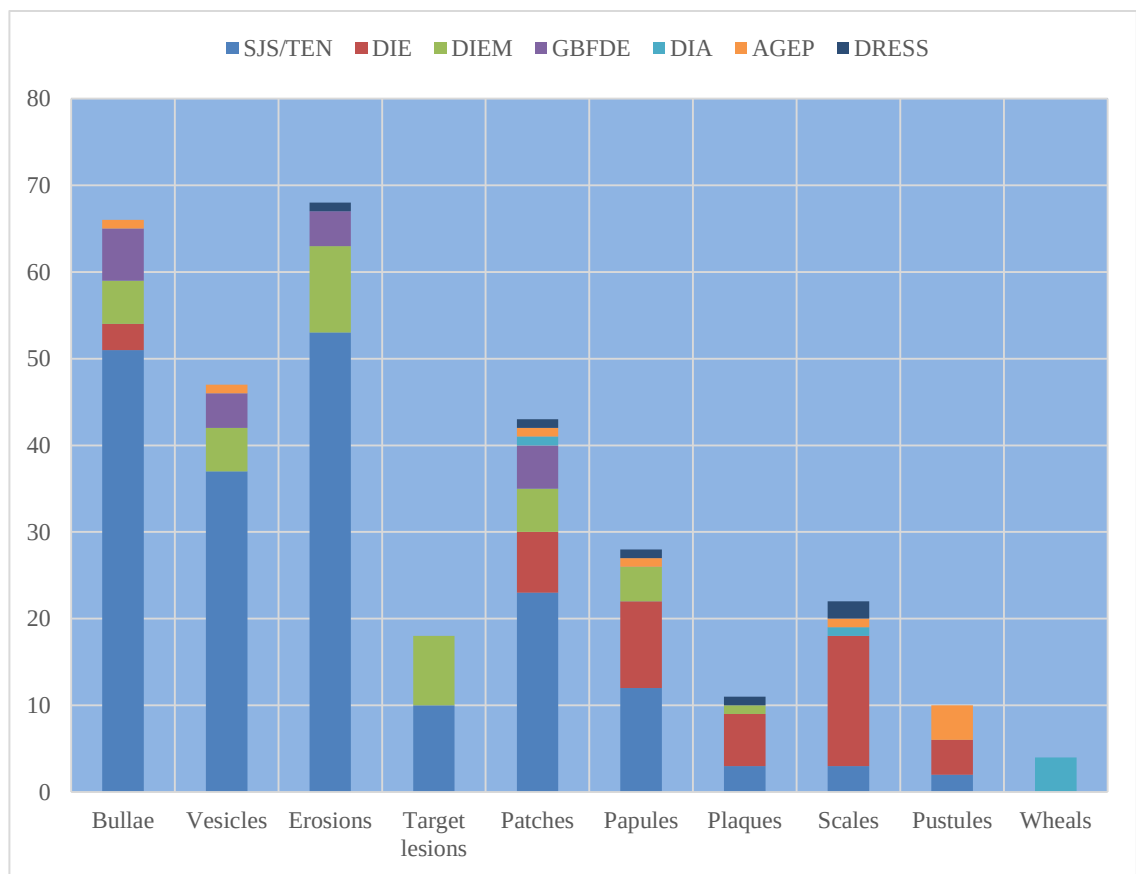


Figure 4.3: Distribution of Cutaneous Symptoms by Phenotypes

Figure 4.3 illustrates the distribution of cutaneous lesions across different SCAR phenotypes. Erosions, bullae and vesicles were predominant in SJS/TEN while DIE exhibited a higher frequency of scales and papules. DIEM and GBFDE also showed notable occurrence of bullae and vesicles but at a lower frequency. Wheals and pustules were primarily observed in DIA and AGEF respectively. The visualization highlights the variation of clinical presentation among the different SCAR subtypes.

4.2.5.2 Mucositis

Mucosal involvement was assessed in all study participants. A significant number of participants (n=83, 81.4%) reported mucositis. Of these, 61.8% (n=63) presented with mucosal involvement in two or more sites while 19.6% (n=20) had only one mucosal membrane affected. The oral mucosa was the most commonly affected site (74.5%), followed by the conjunctiva in 56 participants (54.9%) and genital mucosa in 25 participants (24.5%). Less commonly affected sites included urethral mucosa (20.6%), anal mucosa (11.8%) and nasal mucosa (3.9%) (Table 4.5).

Table 4.5: Distribution of Mucosal Involvement across Different Sites

Mucosal site	Frequency	Percentage (%)
None	19	18.6%
1 site	20	19.6%
2 or more sites	63	61.8%
Oral mucosa	76	74.5%
Conjunctiva	56	54.9%
Genital mucosa	25	24.5%
Urethral mucosa	21	20.6%
Anal mucosa	12	11.8%
Nasal mucosa	4	3.9%

Table 4.5 shows that the oral mucosa was the most frequently affected site (74.5%), followed by conjunctival involvement (54.9%), while other mucosal sites were less commonly involved.

Among the different phenotypes, SJS/TEN and DIEM displayed extensive mucosal involvement, affecting multiple sites while DIE, DRESS and GBFDE had minimal mucosal involvement. None of the participants with AGEP and DIA had mucosal involvement. (Figure 4.4)

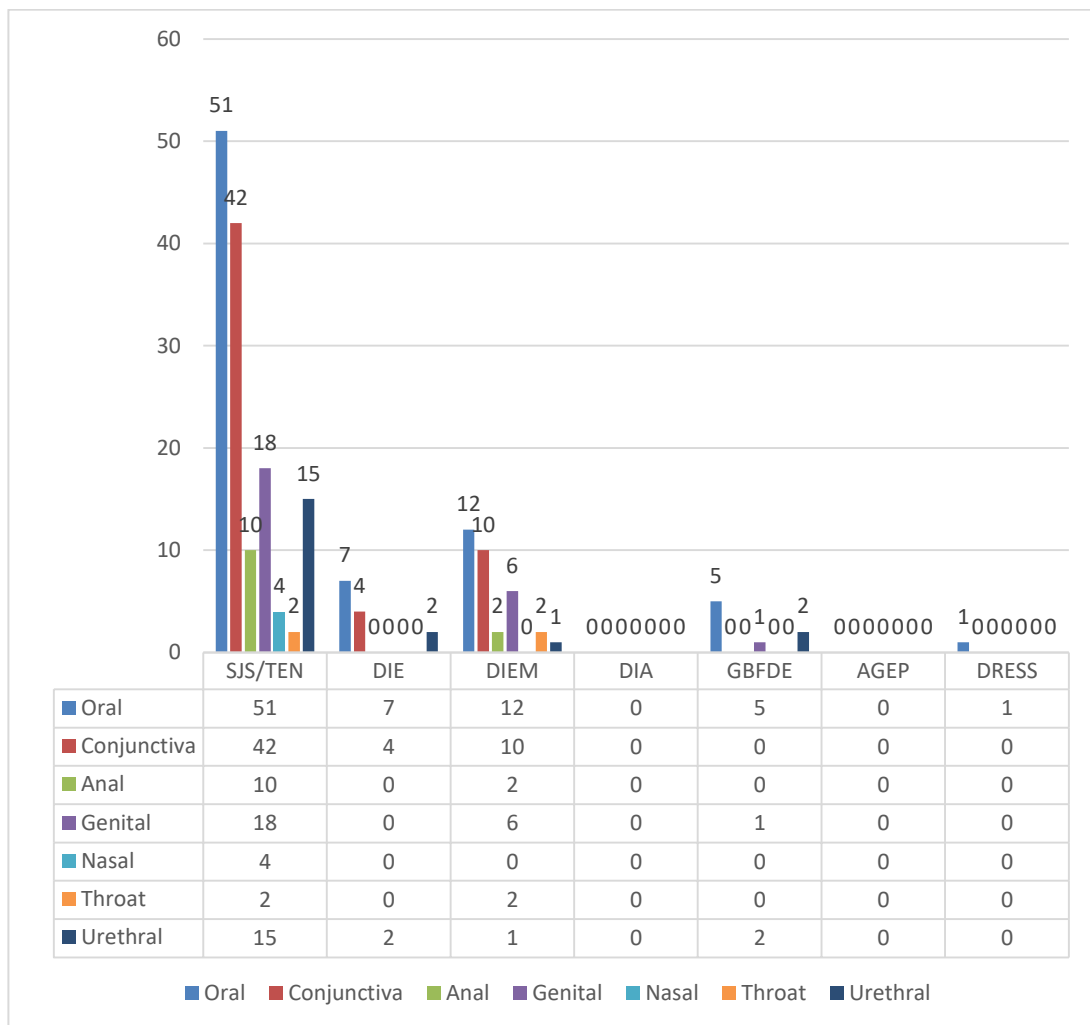


Figure 4.4: Distribution of Mucosal Involvement per SCAR Phenotype

Figure 4.4, the bar chart illustrates the distribution of mucosal sites across different SCAR phenotypes. Mucosal involvement was most extensive in SJS/TEN and DIEM, with multiple sites affected, while minimal or no involvement was observed in other phenotypes. The X-axis represents the SCAR Phenotypes while the Y-axis denotes the number of cases of mucosal involvement for each phenotype.

There was a significant difference in the number of mucosal sites affected across the SCAR phenotypes ($p < 0.0001$) with SJS/TEN affecting more sites than other phenotypes except DIEM ($p = 0.374$). The oral mucosa was the most affected site across all phenotypes,

but its involvement did not significantly differ among the SCAR phenotypes ($p=0.752$). In contrast, conjunctival involvement showed a significant difference across the phenotypes ($p<0.0001$) with SJS/TEN being more affected ($p=0.002$). Furthermore, there was no significant difference in the incidence of genital, urethral, nasal and anal mucosa across SCAR phenotypes ($p > 0.05$), suggesting that these sites are not strongly associated with any specific disease phenotype and occur at similar rates across SCARs. (Table 4.6)

Table 4.6: Distribution of Mucositis among 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

*0.000*¹Pairwise post-hoc analysis showed that number of sites affected were more in SJS/TEN and DIEM. 0.000*²Pairwise post-hoc analysis showed SJS/TEN was more frequently affected.*

Table 4.6 illustrates that mucosal involvement varied significantly across SCAR phenotypes, with SJS/TEN and DIEM demonstrating more extensive multi-site involvement compared to other conditions

4.2.6 Extracutaneous Manifestations

Majority of the study participants ($n=63$, 61.8%) reported additional extracutaneous symptoms, with constitutional symptoms being the most frequently reported, affecting 45% of participants. This included fever, generalised malaise, weakness and loss of appetite. In contrast, gastrointestinal (2%), cardiovascular (1%) and CNS symptoms (1%) were reported less frequently. (Figure 4.5)

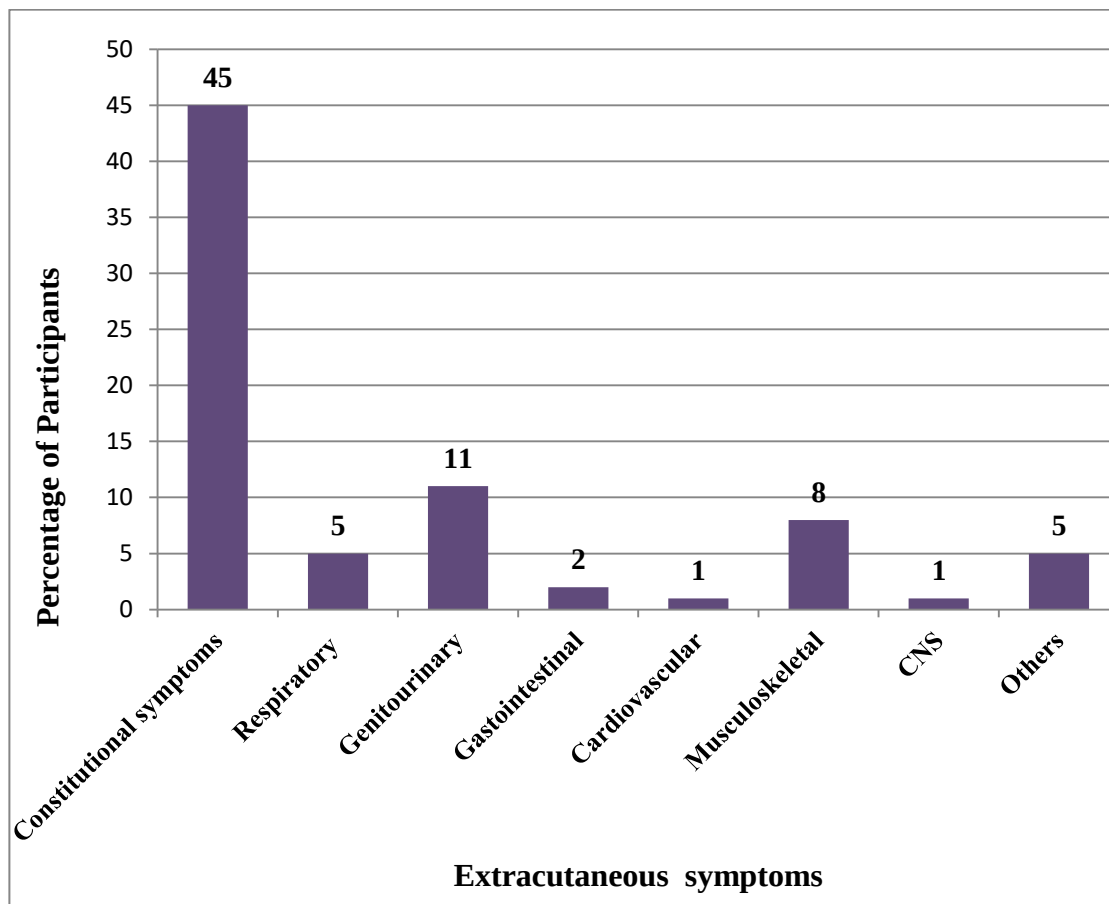


Figure 4.5: Extracutaneous Symptoms of all SCARs

Figure 4.5, the bar graph illustrates that constitutional symptoms were the most frequently reported extracutaneous manifestations, while other systemic symptoms occurred less commonly. The X-axis represents the different extracutaneous symptoms, while the Y-axis indicates the percentage of participants experiencing each symptom.

Among the different disease phenotypes, SJS/TEN exhibited the highest frequency and diversity while GBFDE had a lower frequency (Figure 4.6). However, statistical analysis did not show significant difference in the presence of extracutaneous symptoms across the diseases. (Data not shown)

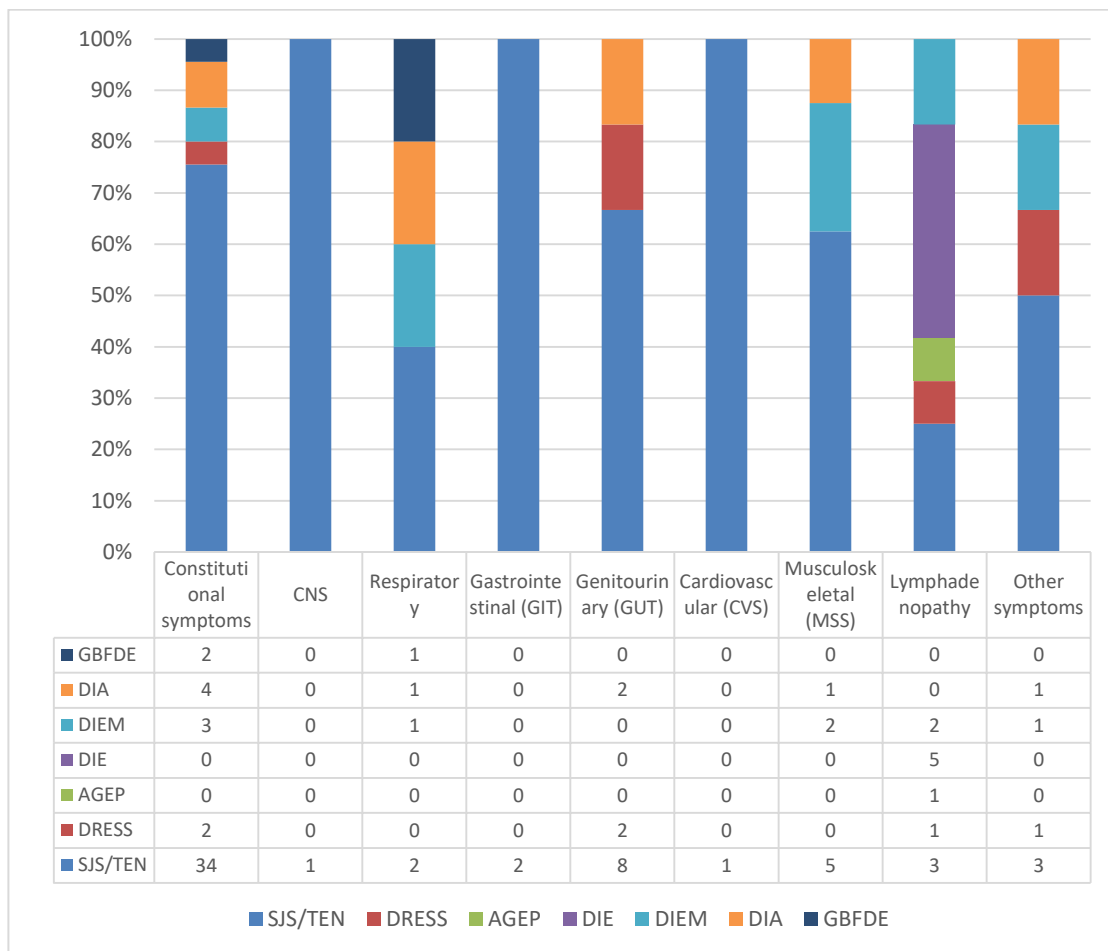


Figure 4.6: Extracutaneous Symptoms per Disease Phenotype

Figure 4.6, the stacked bar chart illustrates the distribution of extracutaneous symptoms across different SCAR phenotypes. SJS/TEN exhibited the greatest diversity of extracutaneous manifestations, whereas other phenotypes demonstrated more limited systemic involvement. The X-axis represents various extracutaneous symptoms while the Y-axis denotes the percentage of cases within each category, where each bar sums to 100% of cases for that specific symptom.

4.2.7 Systemic Involvement per Laboratory Analysis

Systemic involvement was further evaluated through liver and renal function tests. Acute Kidney Injury (AKI), defined according to the Acute Kidney Injury Network (AKIN)

criteria as an increase in serum creatinine to greater than 1.5 times the baseline or an increase of at least 26.5umol/L within 48 hours, was observed in 11.8% (n=12) of the participants. Drug-Induced Liver Injury (DILI), defined as meeting any one of the following criteria: (a) an elevation of ALT ≥ 5 times the upper limit of normal (ULN=40U/L); (b) an elevation of ALP ≥ 2 times the ULN; or (c) an elevation of ALT ≥ 3 times the ULN accompanied by a total bilirubin level exceeding 2 times the ULN(21umol/L), was identified in 8.8% (n=9) of participants. (Figure 4.7).

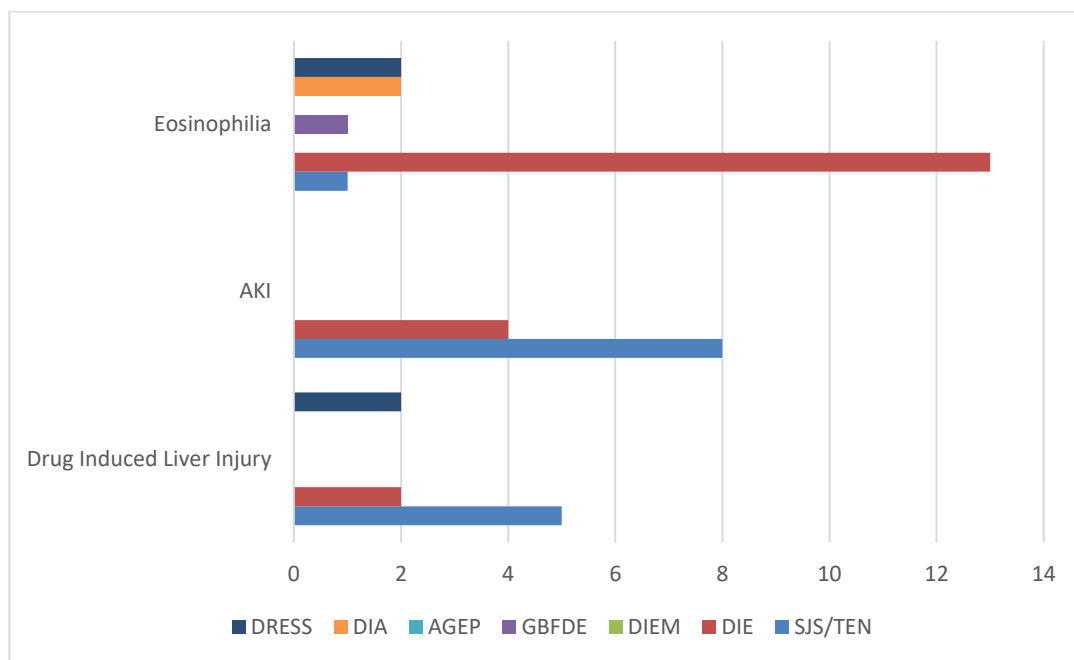


Figure 4.7: Distribution of AKI, DILI and Eosinophilia among Disease Phenotypes

Figure 4.7, the bar chart illustrates that systemic complications varied across SCAR phenotypes, with associations observed for DILI in DRESS and eosinophilia in DIE. The X-axis represents the SCAR phenotypes while the Y-axis represents the number of cases for each systemic complication.

Statistical analysis revealed a significant association between DRESS and DILI ($p=0.00054$), but no association was found between any of the phenotypes and AKI ($p>0.05$). Eosinophil levels varied significantly across SCAR phenotypes ($p < 0.001$), with

DIE showing a strong association with eosinophilia ($p < 0.0001$). In contrast, most patients in the SJS/TEN spectrum, particularly those with TEN, exhibited significantly lower eosinophil counts ($p = 0.0006$) (Data not displayed). Interestingly, these patients had the lowest eosinophil counts in the study.

4.3 Epidemiological Characteristics of Patients with SCARs

4.3.1 Demographic Characteristics of Study Participants

To address Objective 2, which explored the epidemiological characteristics of patients with SCARs, the demographic and clinical profiles of the study participants were analysed.

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 of age. The largest proportion of participants, 31(30.4%), belonged to the paediatric age group (0-12 years), followed by the 19-30 age group ($n=19$, 18.6%). A total of 10 participants (9.8%) were aged above 60 years.

There was a slightly female predominance, with 52 (51.0%) female participants compared to 50 (49%) males, yielding a male to female ratio was 1:1.04. A Mann-Whitney U test was conducted to compare the age distribution between males and females, and the results were not statistically significant ($U=1267.500$, $p=0.878$) indicating that age did not differ significantly between genders. Additionally, a chi-square test was conducted to determine whether gender distribution varied across age groups, but the results were not statistically significant ($p=0.975$). Geographically, most participants, 62 (60.8%) resided in Nairobi, followed by 24 (23.5%) from Central Kenya and 10 (9.8%) from Eastern Kenya. Table 4.7 presents the demographic characteristics of the study participants. The study population was predominantly young, with a mean age of 29.4 years and a slight female predominance

Table 4.7: Demographic Characteristics of all Study Participants (n=102)

Characteristic	Category	Frequency	Percentage (%)	p-value
Age (Mean 29.426, SD 20.5) Median 29.000, IQR=35.0)	0-12	31	30.4	
	13-18	5	4.9	
	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 Residence (Regions)				p=0.975
	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	

4.3.2 Underlying Co-Morbidities among Study Participants

Over half (n=59, 57.8%) {*Retrospective: n=22, Prospective: n= 37*} of the participants had underlying medical conditions, with HIV being the most common (n=17, 23.9%), followed by hypertension (n=11, 15.5%) and psychiatric illnesses (n=10 14.1%). (Table 4.8).

Table 4.8: Co-morbidities among Study Participants

Medical Condition	Frequency	Percentage
HIV	17	23.9%
Hypertension	11	15.5%
Psychiatric disease	10	14.1%
Convulsive disease	9	12.7%
Renal disease	4	5.6%
Autoimmune disorders	3	4.2%
Malignancy	3	4.2%
Other	14	19.7%

Table 4.8 represents the distribution of comorbidities among participants. HIV was the most common comorbidity (23.9%), followed by hypertension and psychiatric disorders.

Among the different disease phenotypes, SJS/TEN and DIE carried the highest comorbidity burden with HIV being the most frequently observed in both disorders. Convulsive disorders were seen more frequently in SJS/TEN, DIEM, DIE and DRESS patients. In contrast, DIA had a low co-morbidity burden while none of the AGEF patients had a recorded comorbidity. (Figure 4.8)

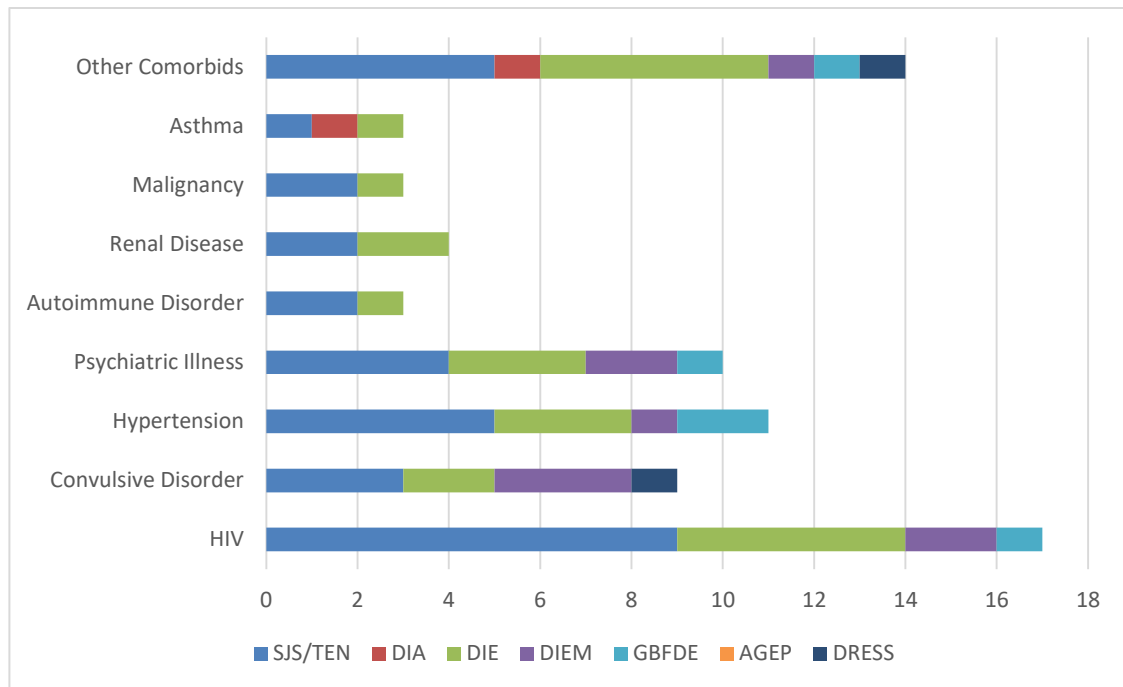


Figure 4.8: Distribution of Comorbidities among the SCAR Phenotypes

Figure 4.8, the horizontal stacked bar chart displays the distribution of various comorbidities across SCAR phenotypes. Comorbidity patterns varied across SCAR phenotypes, with higher burdens observed in SJS/TEN and DIE. The X-axis represents the number of participants with each comorbidity while the Y-axis lists the different comorbidities.

Despite the varying comorbidity burdens across the different SCAR phenotypes, no statistically significant association was found between comorbidities and SCAR

phenotypes in this study ($p>0.05$) Table 4.9 displays the frequency of various medical conditions across SCAR phenotypes.

Table 4.9: Distribution of Co-Morbidities among SCAR Phenotypes

Medical condition	SJS/TEN (n=57)	DRESS (n=2)	AGEP (n=3)	DIE (n=18)	DIEM (n=12)	GBFDE (n=6)	DIA (n=4)	P value
HIV	11(19.3)	0(0)	0(0)	5(27.8)	2(16.7)	1(16.7)	0(0)	0.794
Hypertension	5(8.8)	0(0)	0(0)	3(16.7)	1(8.3)	2(33.3)	0(0)	0.516
Psychiatric disease	4(7.0)	0(0)	0(0)	3(16.7)	1(8.3)	1(16.7)	0(0)	0.816
Convulsive disease	3(5.3)	1(50.0)	0(0)	2(11.1)	3(25.0)	0(0)	0(0)	0.109
Renal disease	2(3.5)	0(0)	0(0)	2(11.1)	0(0)	0(0)	0(0)	0.731
Autoimmune disorders	2(3.5)	0(0)	0(0)	1(5.6)	0(0)	0(0)	0(0)	0.971
Asthma	1(1.8)	0(0)	0(0)	1(5.6)	0(0)	0(0)	1(25.0)	0.222
Other	5(8.8)	1(50.0)	0(0)	5(27.8)	1(8.3)	1(16.7)	1(25.0)	0.562

4.4 Drug-Related Characteristics and Suspected Drug Associations

4.4.1 Drug Classes of Implicated Medications

To address Objective 3, which assessed drug-related characteristics and suspected drug associations, patterns of drug exposure and causality were evaluated. In this study, nearly a quarter of the participants ($n=22$, 21.6%) had multiple drugs administered, resulting in a total of 111 drug exposures. In such cases, drug causality was assessed primarily through expert opinion, considering known associations with SCARs and the temporal relationship between drug exposure and reaction onset. The Naranjo algorithm was applied in selected cases to support causality assessment, but expert opinion remained the primary approach. Drugs taken within six weeks prior to the reaction were considered relevant. The most commonly used drug class was antimicrobials ($n=62$, 55.9% of total drug exposures) followed by the anticonvulsants ($n=15$, 13.5%) and analgesics ($n=14$, 12.6%). Less frequently seen drug classes include anti-psychotics, hormonal drugs, anti-gout and vaccines. (Figure 4.9)

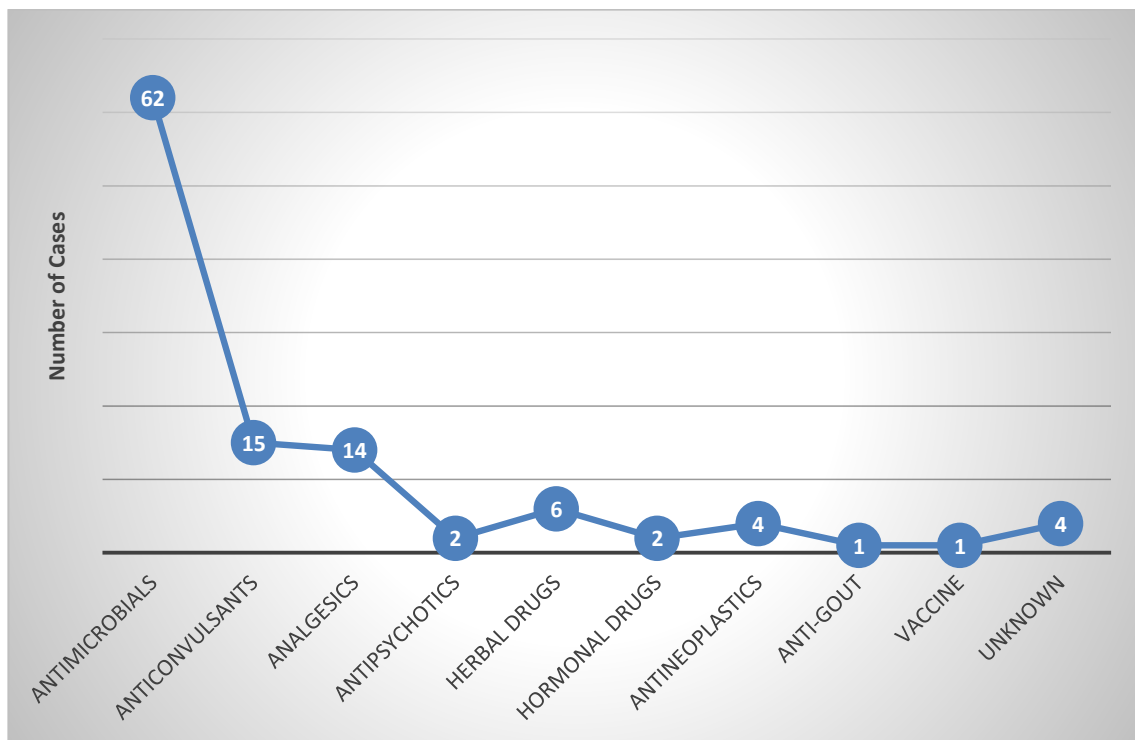


Figure 4.9: Distribution of Drug Classes Implicated in SCARs among Study Participants

In Figure 4.9, the Y-axis represents the number of cases reporting drug use, while the X-axis lists the drug classes associated with SCARs, illustrating their distribution among study participants. Antimicrobials were the most frequently implicated drug class, with other classes contributing less substantially to SCAR occurrence.

A detailed breakdown of the implicated drug classed is provided in Table 4.10, which categorizes the specific sub-groups within each class.

Table 4.10: Detailed Distribution of Drug Classes and their Frequency among Study Participants Based on Total Drug Exposures (n=111)

Drugs Classes	Number of Cases Reporting Drug Use	Frequency (%)
Antimicrobial	62	55.9%
1. Antibiotics	52	46.9%
a. B-lactams	24	21.6%
b. Sulfonamides	17	15.3%
c. Fluoroquinolones	8	7.2%
d. Tetracyclines	1	0.9%
e. Glycopeptide	1	0.9%
f. Nitroimidazole	5	4.5%
g. Anti-TBs	2	1.8%
2. Antifungals	3	2.7%
a. Azoles	2	1.8%
b. Non-azole	1	0.9%
3. Antivirals	1	0.9%
4. Antimalarials	8	7.2%
5. Others	1	0.9%
Anticonvulsants	15	13.5%
a. Aromatic anticonvulsants	14	12.6%
b. Nonaromatic anticonvulsants	1	0.9%
Antipsychotics	2	1.8%
Analgesics	14	12.6%
a. NSAIDs	11	9.91%
b. Paracetamol	3	2.7%
Hormonal	2	1.8%
Herbal	6	5.54
Antigout	1	0.9%
Antineoplastics	4	3.6%
a. Antimetabolites	4	3.6%
b. Alkylating agents	1	0.9%
Vaccine	1	0.9%
Unknown	4	3.6%

Table 4.10 shows the frequency of the drug classes implicated among the study participants. Antimicrobials were the most frequently implicated drug class, accounting for 55.9% of total drug exposures, followed by anticonvulsants and analgesics.

Among the antimicrobials, antibiotics were the most frequently used, with B-lactam antibiotics and sulfonamides being the dominant sub-groups, together accounting for more than half of all antibiotics used.

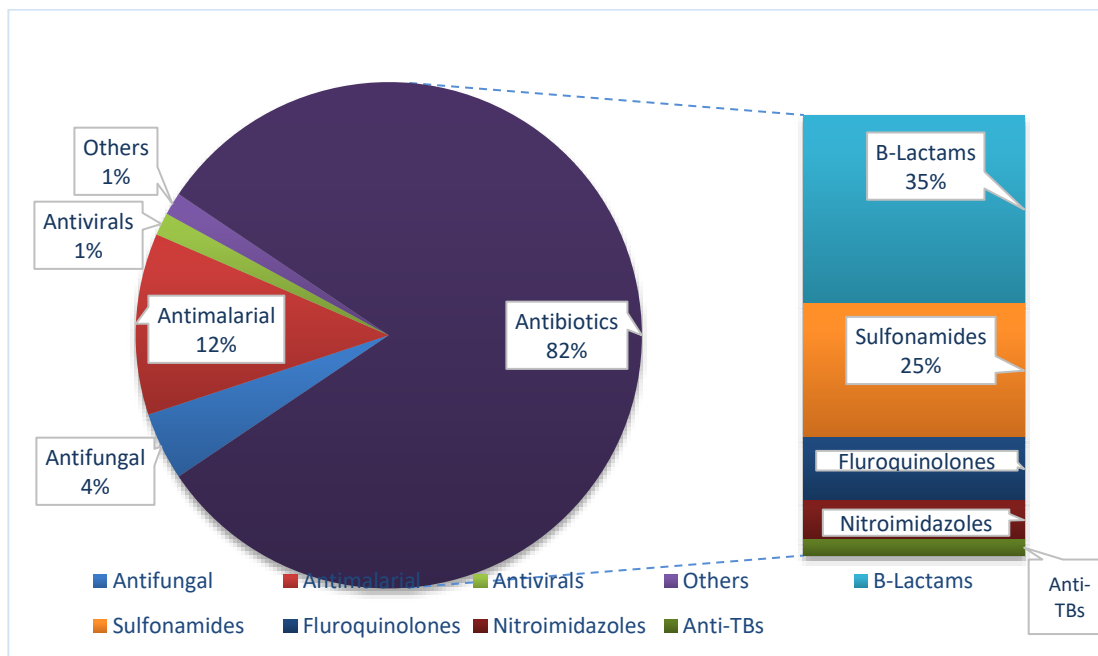


Figure 4.10: Distribution of Antimicrobials and their Sub-Groups

Figure 4.10 illustrates the distribution of antimicrobial drug classes among study participants. The pie chart shows that antibiotics were the most frequently reported (82%) followed by anti-malarial (12%) and anti-fungal (4%). The bar graph provides a breakdown of antibiotic sub-groups, with B-lactams (35%) and sulfonamides (25%) being the most common, followed by fluoroquinolones (12%) and nitroimidazoles (7%).

4.4.2 Distribution of Implicated Drugs across Different SCARs Phenotypes

Antibiotics were the most common drug class across all SCAR phenotypes except DRESS and DIE, where anticonvulsants particularly aromatic anticonvulsants, accounted for 33.3% (n=6) of DIE and 100% (n=2) of DRESS cases. In SJS/TEN, DIEM and GBFDE, B-lactam antibiotics and sulfonamides were the most frequently implicated subgroups, with NSAIDs also contributed significantly. In the less frequent phenotypes, DIA and AGEF, B-lactam antibiotics remained the primary trigger, with hormonal drugs also playing a role in both conditions.

Statistical analysis revealed significant association between specific drug classes and SCARs. Antimicrobials showed a significant variation across SCAR phenotypes ($p=0.001$) with antibiotics demonstrating a significant variation ($p=0.021$). In contrast, analgesics ($p=0.449$), herbal drugs ($p=0.543$) and antineoplastic agents ($p=0.959$) did not show statistically significant variation across the phenotypes (Table 4.11)

Table 4.11: 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	1	
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. Anti-fungals	2	0	0	0	1	0	0	0.087
a. Azole anti-fungals	2	0	0	0	1	0	0	
b. Non-azole antifungals	1	0	0	0	0	0	0	
3. Antivirals	1	0	0	0	0	0	0	
4. Antimalarials	7	1	0	0	0	0	0	
5. Others	1	0	0	0	0	0	0	
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

Table 4.11 shows that the distribution of the implicated drug classes and their sub-groups differed across SCAR phenotypes, particularly for antimicrobials.

Further sub-group analysis revealed that antibiotics were strongly linked to SJS/TEN ($p=0.003$), though no significant associations were found when analysing individual subclasses such as B-lactams or sulfonamides. DIE was significantly associated with antibiotics ($p=0.015$) with further analysis highlighting a specific link to anti-TBs

($p=0.032$). Aromatic anticonvulsants demonstrated strong associations with SJS/TEN ($p=0.012$), DRESS ($p=0.011$) and DIE ($p=0.022$). GBFDE was significantly associated with nitroimidazoles ($p=0.019$) and paracetamol ($p=0.001$). Antipsychotic showed a borderline significant association with SJS/TEN and DIE ($p=0.051$) while antineoplastics did not show any significant associations. (Data not shown)

Notably, the most common drug culprit in this study was cotrimoxazole ($n=16$), followed by ceftriaxone ($n=9$), carbamazepine ($n=7$) and herbal medication ($n=6$). Co-trimoxazole was most frequently observed in cases of SJS/TEN, DIEM and GBFDE while ceftriaxone was mainly reported in SJS/TEN, DIE and DIEM. Carbamazepine was frequently noted in DIE and DIEM. Herbal formulations were identified in cases of SJS/TEN, DIA and DIE. Other notable drugs included ibuprofen (SJS/TEN, DIA and DIE) and paracetamol (primarily seen in AGEP).

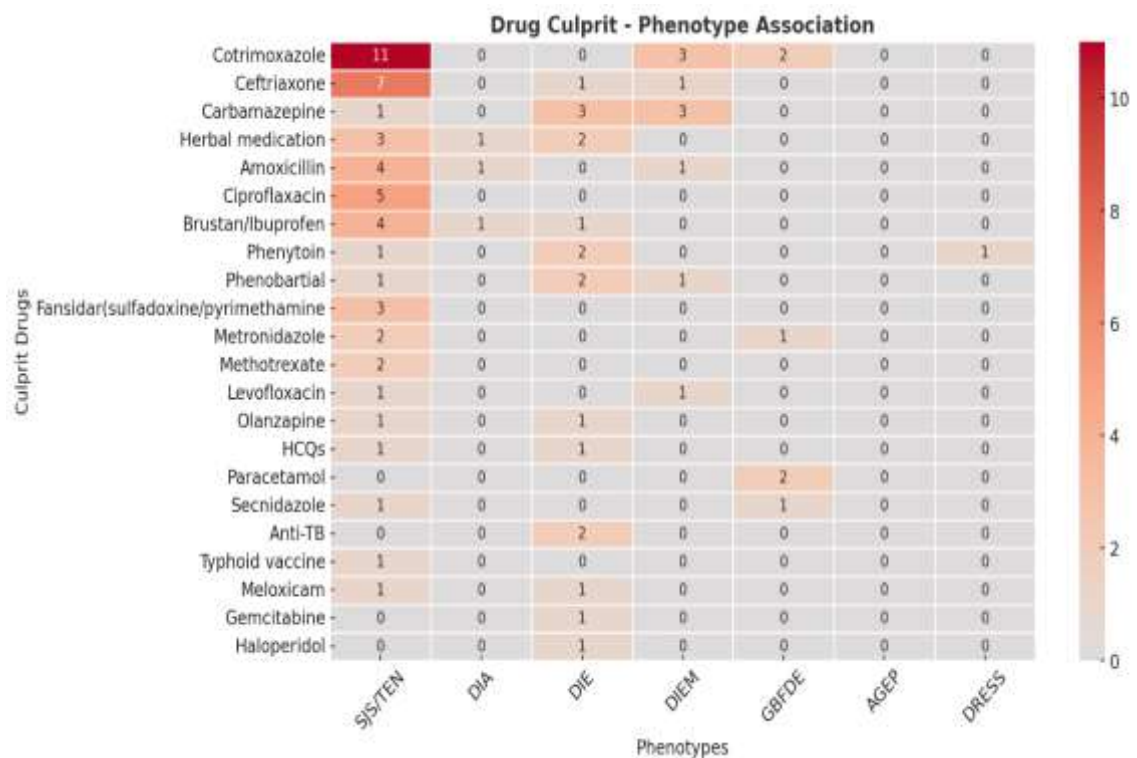


Figure 4.11: Drug Culprit-Phenotype Association

Figure 4.11 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.

4.4.3 Latency Period

The median duration between initiation of the suspected drug and onset of clinical symptoms was 4.0 days (IQR:1-10), with an overall mean of 7.08 days (SD±9.869). (Table 4.12)

Symptoms manifested within a week of drug intake although the latency period varied significantly across disease phenotypes. (Figure 4.12)

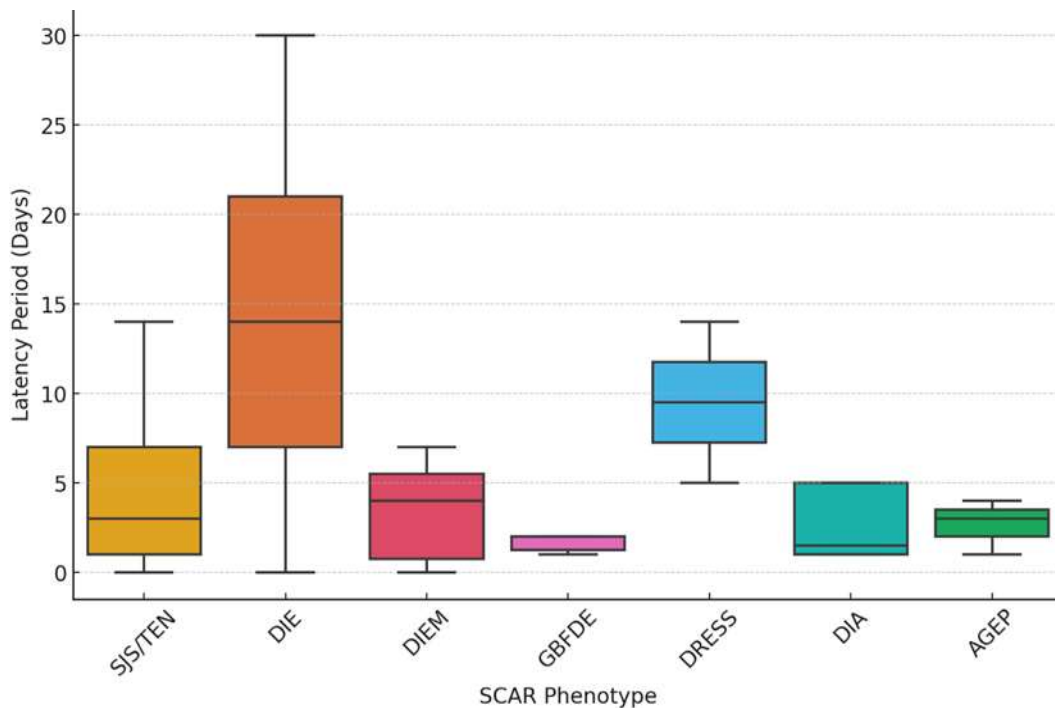


Figure 4.12: Latency Period Distribution across SCAR Phenotypes (Outliers Removed)

In Figure 4.12, the boxplot illustrates the latency period (in days) between drug intake and the onset of SCARs. The median latency period is highest for DIE, indicating a longer reaction time compared to other phenotypes.

A Kruskal-Wallis test revealed a statistically significant difference in latency period across SCAR phenotypes ($H=21.41$, $p=0.0015$), indicating that at least one SCAR phenotype had a significantly different latency period from the others. Further pairwise comparisons using Mann-Whitney U tests showed a significant difference between DIE and SJS/TEN ($p<0.0001$) with DIE exhibiting a longer latency period. Several phenotypes including DRESS ($n=2$), AGEP ($n=3$), GBFDE ($n=6$) and DIA ($n=4$) had small sample sizes. This limitation may have reduced the statistical power of the test. (Table 4.12)

Table 4.12: Latency Period among SCAR Phenotypes

Disease Phenotype	Median(Q1-Q3)	Mean (SD)	P value
Overall participants (n=99)	4.00(1-10)	7.08 ±9.869	0.0015* (Kruskal-Wallis, H=21.41)
SJS/TEN (n=55)	3(1-7)	5.04 ± 4.91	
DIE (n=17)	14.5(7-21)	18.41 ± 17.59	
DIEM (n=12)	4(0.75-5.5)	4.75± 5.72	
GBFDE (n=6)	2(1.25-2)	1.50 ± 0.83	
DIA (n=4)	1.5(1-5)	4.50 ± 6.35	
AGEP (n=3)	3(2-3.5)	2.67 ± 1.52	
DRESS(n=2)	9.5(7.25-11.75)	9.5 ± 6.36	

Table 4.12 shows the 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.

4.4.4 Indication for Drug Use and Prescription Mode

Acute illness, defined as disease with a duration less than 6 weeks, was the primary indication for drug use in 66 patients (67.3%) (Figure 4.13). In 75.2% ($n=76$) of all patients, the medication was prescribed by a health care practitioner. (Figure 4). Figure 4.13 illustrates the primary indications for drug use among patients, showing that majority

(67.3%) were treated for acute illness while 32.7% used medication for chronic conditions. Figure 4.14 shows the mode of drug acquisition. Most drugs (75.2%) were prescribed by a health-care practitioner while 22.8% were obtained over the counter with no prescription.

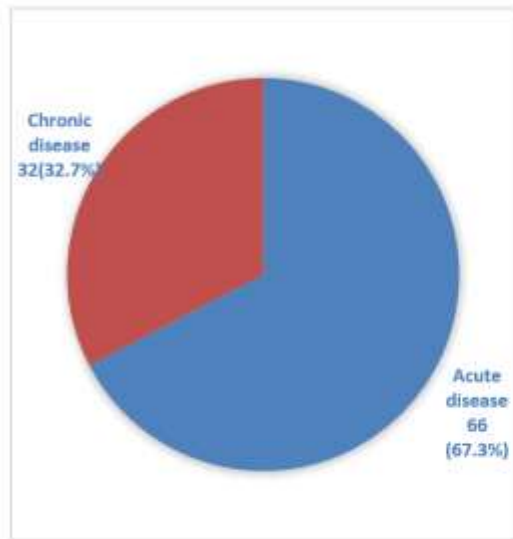


Figure 4.13: Indication for Use

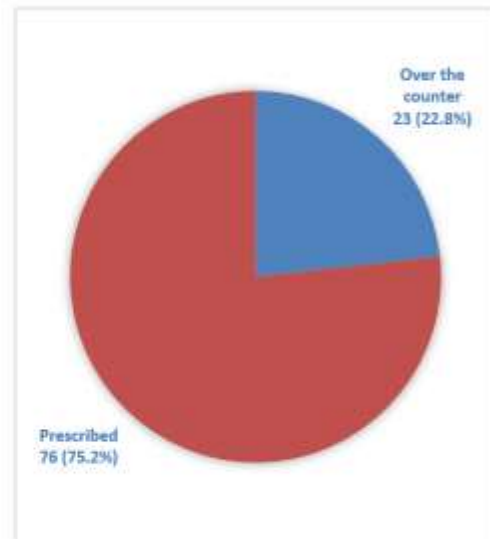


Figure 4.14: Mode of Acquisition

The majority of the patients with GBFDE, SJS/TEN, DIA and DIEM took the medication for an acute disease while patients with DIE and DRESS had been on long-term treatment for chronic conditions. This difference in drug indication among the SCAR phenotypes was statistically significant ($p < 0.05$). In contrast, the mode of drug acquisition did not significantly differ between conditions ($p = 0.492$). Table 4.13 Drug indication differed across SCAR phenotypes, with acute use predominating in SJS/TEN and chronic use more common in DIE and DRESS.

Table 4.13: Drug Use Patterns (Indication and Acquisition) and their Associations with SCAR Phenotypes

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

4.4.5 Drug Allergy History

More than a third of the participants (n=37, 36.3%) reported a history of drug allergies (Figure).

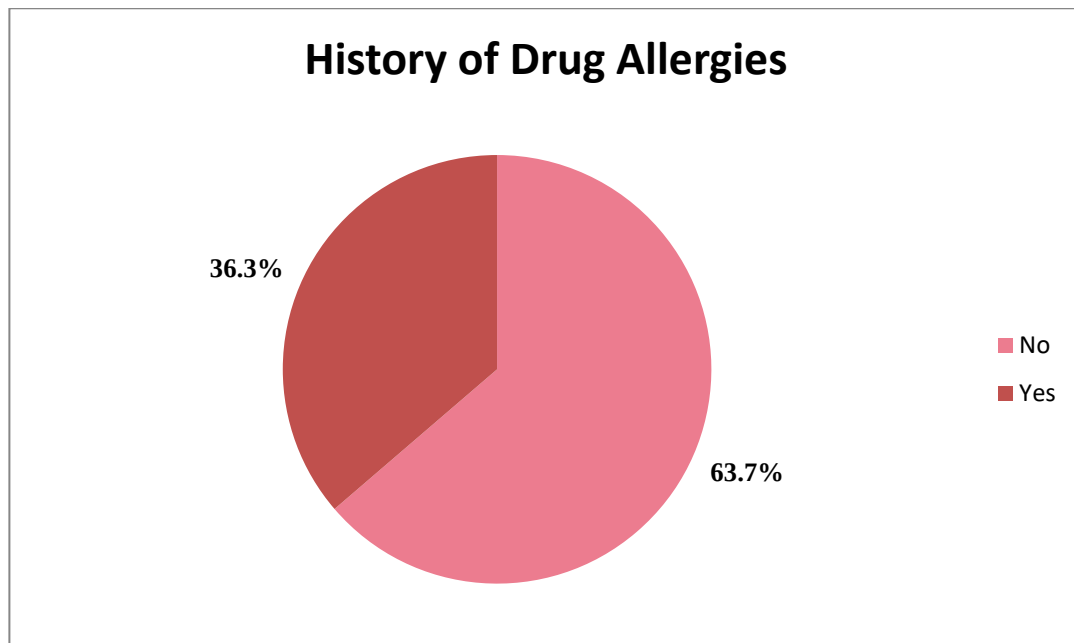


Figure 4.15: History of Drug Allergies

In Figure 4.15, the bar graph illustrates the distribution of patients based on their drug allergies. The X-axis represents the history of drug allergies while the Y-axis indicates the

percentage of study participants. The majority (63.7%) reported no prior allergies, while 36.3% had a documented history of drug allergies.

A significant proportion of these participants (n=22) were from the SJS/TEN group. Notably, all patients with GBFDE had reacted to a drug before while none of the patients with AGEP reported a prior drug allergy. Statistical analysis revealed a significant difference (p=0.012) in the history of past drug reactions among the seven phenotypes. **(Error! Reference source not found.)** Post-hoc analysis identified that GBFDE showed significant association (p=0.0036) with past reactions (data not shown).

Table 4.14: Association between Drug History and SCAR Phenotypes

Drug allergy history	SJS/TEN	DIE	DIEM	DRESS	AGEP	GBFDE	DIA	P-value
Positive history of drug reaction	22	4	4	1	0	6	0	0.012

Table 4.14: A prior history of drug reactions was significantly associated with SCAR phenotype, particularly in GBFDE where all patients reported previous reactions.

4.5 In-Hospital Mortality of Study Participants

The overall in-hospital mortality rate among the patients in this study is 16.8%. (Figure). Outcomes were recorded only during the hospitalization period and no follow-up was conducted after discharge. By the end of the study, outcomes had been recorded for all retrospective patients (n=62) and for 39 of the 40 prospective patients (total, n=101). One prospective patient remained hospitalized at the time of study completion was not categorized under final outcomes.

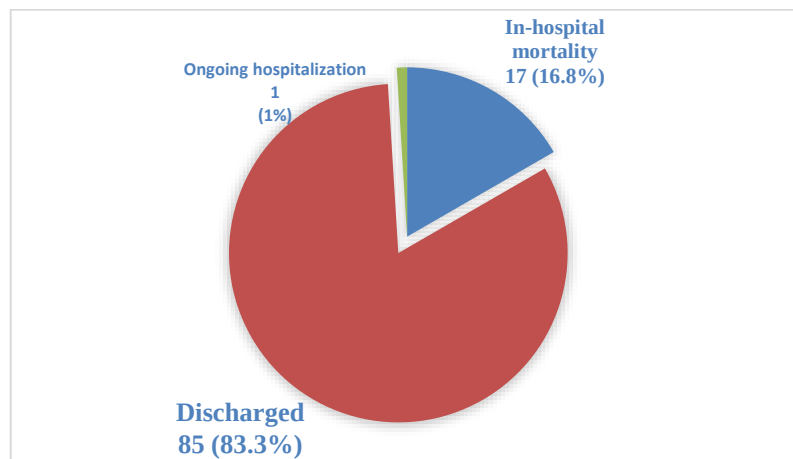


Figure 4.16: Outcome of Study Participants

Figure 4.16 illustrates the outcomes of study participants at the time of study completion. Most patients (83.3%) were discharged while 16.8% (n=17) experienced in-hospital mortality.

Among the phenotypes, SJS/TEN had the highest mortality, with a case fatality rate of 21.05% while DRESS, DIA and AGEP had no recorded fatalities. However, these differences were not statistically significant (p=0.785) (Table 4.15)

Table 4.15: Outcomes of Study Participants

	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 (80)*	4(100)	
In-hospital mortality	12(21.1)	0(0)	0(0)	3(16.7)	1(8.3)	1(20)	0(0)	
Case Fatality Rate (%)	21.05	0.00	0.00	16.67%	8.33%	20%	0.00	

Table 4.15 summarizes the outcomes of patients with SCAR phenotypes, categorized as either discharge (alive) or in-hospital mortality (dead) *One patient excluded due to on-going admission.

The findings of this study indicate that elevated creatinine ($>172\mu\text{mol/L}$, defined as AKI) was significantly associated with in-hospital mortality in SCAR patients ($p=0.003$, OR = 7.18, 95% CI= 2.02 – 25.53). This association remained significant even after adjusting for renal disease ($p = 0.002$), suggesting that acute kidney injury (AKI) plays a critical role in SCAR-related mortality, rather than chronic disease. Univariate logistic regression also showed that age was significantly associated with mortality ($p=0.015$, OR = 1.003 per year), indicating that the risk of mortality increases with age. However, in the multivariate model, only AKI remained significant ($p=0.029$), while age lost significance ($p=0.058$), suggesting AKI is a stronger predictor of mortality than age alone. (Appendix X)

CHAPTER FIVE

DISCUSSION

Severe Cutaneous Adverse Drug Reactions (SCARs) encompass a group of rare but potentially life-threatening drug-induced reactions with diverse clinical presentations and many drugs have been implicated as causative agents.

5.1 Clinical Phenotypes and Clinical Features of SCARs

The SJS/TEN spectrum was the most common SCAR phenotype, accounting for over half of all cases. This finding is consistent with reports from Jamaica (Guzman & Paliza, 2018). In contrast, DRESS was the least common, accounting for 2.0% of the study participants. This differs from findings in other regions such as Korea, where DRESS occurs at a frequency comparable to SJS/TEN (48.5% vs 51.5% of SCAR cases, respectively) (Kang et al., 2021). Given the known role of genetic susceptibility in SCARs, these differences may reflect variations in genetic background, prescribing patterns and healthcare access. Distinct clinical patterns were observed across SCAR phenotypes. Compared to previous studies, patients with SJS/TEN in this study were younger, with a mean age of SJS/TEN patients was lower at 27.5 years compared to 49.0 years in a United States cohort and 53.4 years in the EuroSCAR study (Micheletti et al., 2018). SJS/TEN demonstrated a wide age distribution and was characterized by extensive mucosal involvement affecting multiple sites, consistent with previous reports. (McNish et al., 2024) Drug-Induced Erythroderma (DIE) was the second most common phenotype, accounting for 17% of cases. Patients with DIE were also younger than previously reported, with a mean age of 41 years compared to 67 years in other studies by Kliniec et al. (Kliniec et al., 2024) DIE was strongly associated with eosinophilia, affecting 72.2% of patients, consistent with findings by Khaled et al. (Khaled et al., 2010) Among the thirteen patients with eosinophilia, five presented with moderate eosinophilia ($1.5-5.0 \times 10^9/L$) while one had severe eosinophilia ($>5.0 \times 10^9/L$). Two of these patients also had organ involvement and of these, one had been exposed to an anticonvulsant and one had

used allopurinol, both known culprits of DRESS. Since erythroderma is a typical presentation of DRESS, it is plausible that these patients may have had DRESS but were not evaluated according to the RegiSCAR criteria. The relatively low frequency of DRESS in this study may be attributed to its protean cutaneous manifestations and the suboptimal use of diagnostic criteria. Among patients with Generalized Bullous Fixed Drug Eruption (GBFDE), mucositis was more frequent in our cohort, occurring in 83.3% of cases compared to 66.7% reported in Lee et. al.'s study (C.-H. Lee et al., 2012). Half of the affected patients had involvement of two or more mucosal sites, aligning with previous observations (Lipowicz et al., 2013) Drug-Induced Erythema Multiforme(DIEM) predominantly affected younger individuals, with 66.7% of patients below 30years, consistent with previous studies. Mucositis was severe in most patients, with 91.6% of DIEM participants exhibiting involvement of two or more mucosal sites, a pattern consistently reported in the literature(Panthalla et al., 2019). Acute Generalized Exanthematous Pustulosis (AGEP) was observed primarily in younger patients, with a mean age of 16.3 years, and demonstrated a female predominance similar to findings from the EuroSCAR study. (Mockenhaupt et al., n.d.) The youngest patient was 6 months old, the overall youngest in this study with a diagnosis of AGEP. While rare, paediatric AGEP has been described, typically linked to infections rather than drug exposures. However, in drug induced cases, antibiotics are the main triggers, as seen in this patient. Antibiotic exposure during intercurrent infection has been proposed as a trigger of AGEP, underscoring the need for formal allergy testing post-recovery(E. Y. Lee & Koh, 2021). No mucosal involvement was observed, which is lower compared to previous reports. Additionally, no organ involvement was noted, also lower than prior studies(Creadore et al., 2022). The AGEP scoring system confirmed the diagnosis in one case. Generalised pustular psoriasis, was ruled out, based on the lack of psoriasis history, sudden drug-induced onset and absence of a drug known to trigger pustular psoriasis. Furthermore, skin biopsies were performed in two patients, both revealing findings consistent with AGEP. The low DIA frequency (3.9%) likely reflects the study's referral hospital setting, limiting its representativeness of the broader Kenyan DIA landscape. Unlike previous studies, DIA in this study primarily affected the paediatric group (mean age: 8.5years). However, the

observed female predominance aligns with prior findings, although the cause remains unclear.(Hanschmann et al., 2023) Systemic involvement and haematological abnormalities are common in SCAR patients as evidenced by the presence of *Acute Kidney Injury* (AKI) and *Drug-Induced Liver Injury* (DILI), observed in 11.8% and 8.8% of the participants respectively. Both AKI and DILI were more frequent in SJS/TEN patients and all DRESS cases exhibited DILI, consistent with known disease characteristics.(Calle et al., 2023)

5.2 Epidemiological Characteristics of SCAR Patients

In this study, SCAR patients were significantly younger compared to those in the EuroSCAR study (mean age of 27.5 years vs 53.4 years) (Mockenhaupt, 2017) and the RegiSCAR study (mean age of 26.0 vs 48years for DRESS) [24]. While SCARs have been previously reported are rare in the paediatric population, 30.4% (n=31) of the participants were below 12years. This may be attributed to the referral nature of the study hospital, where younger patients with severe cases are more likely to be admitted (Singh et al., 2021). There was a slight female predominance in patients with SCARs, although gender distribution did not significantly differ across phenotypes (Guzman & Paliza, 2018). Most participants resided in Nairobi, where the study was conducted. This geographical skew may reflect referral patterns, potentially underrepresenting cases from other areas. Comorbidities were common in this cohort, with HIV being the most frequently observed condition. This finding is consistent with studies from sub-Saharan Africa, including a South African cohort where HIV prevalence among SCAR patients ranged from 55.1% to 75.8%, and tuberculosis was also a common comorbidity. (Konyana et al., 2024) In contrast, studies from Europe and the United States report lower HIV prevalence among SCAR patients. (Mockenhaupt et al., n.d.). Among patients with SJS/TEN, HIV was the most common co-morbidity. Its prevalence was lower than findings from a multicentric study in four Sub-Saharan African countries but higher than recorded in European countries and the United States. (Mockenhaupt, 2017; Saka et al., 2013).

5.3 Drug-Related Characteristics and Suspected Drug Associations

Antibiotics were the most frequently implicated drug group, consistent with findings from a previous study in a predominantly black population. In contrast, a study from Korea identified the xanthine oxidase inhibitor allopurinol as the most common culprit, which was identified in only one case in our study[36][95].

Latency periods varied across SCAR phenotypes. SJS/TEN demonstrated a shorter latency period (mean 5.04 days) compared to previous reports (Mockenhaupt, 2017) while DIE had the longest latency (mean 18.41 days), consistent with delayed hypersensitivity reactions(Kliniec et al., 2024). GBFDE showed the shortest latency (mean 1.5 days), reflecting a recall response mechanism (Brahimi et al., 2010). DRESS exhibited an intermediate latency (mean 9.5 days), shorter than 22-day mean reported in the RegiSCAR but longer compared to SJS/TEN and AGEP as previously reported(Mockenhaupt, 2017). In AGEP patients, variations in the latency period have been reported, with antibiotic-induced AGEP having a shorter latency of 1 day. In our study, the mean latency period was 2.67 days. Notably, none of the AGEP patients had a documented prior reaction, making this the rapid onset despite a lack of sensitization unexplainable(Mockenhaupt, 2017).

The patients with a reported history of drug reactions or allergy was higher in this study (36.3%) than previously reported, suggesting a lack of awareness regarding the avoidance of culprit drugs. Repeated exposure to the same or structurally similar drugs may lead to more severe reactions or even fatal outcomes. (Pudukadan & Thappa, 2004) Among patients with GBFDE, all patients had a history of previous reactions, higher than previously reported in the literature (C.-H. Lee et al., 2012; Lipowicz et al., 2013).In this study, the primary indication for drug use was acute diseases (defined as a condition lasting less than 6 weeks), a finding that differs from previous studies(Mokhtari et al., 2014). This may be attributed to the frequent use of medication, particularly antibiotics, for the treatment of upper respiratory tract infections, which tend to be more common among children - who comprised one-third of SCAR patients in our study.

Drug associations varied across phenotypes. In SJS/TEN patients, the sulfonamide, co-trimoxazole was the most commonly implicated drug, followed by ceftriaxone, a B-lactam antibiotic, as reported by Michelletti et al. (Micheletti et al., 2018) While allopurinol was the most common agent in the EuroSCAR study, it was not implicated in any SJS/TEN case in our study (Mockenhaupt et al., n.d.). Among SJS/TEN patients with HIV, nevirapine was implicated in only one case, lower than reported from SJS/TEN cases among PLHIV(Saka et al., 2013). This could be explained by the infrequent use of nevirapine as first line HAART among adults in our setting.

Among patients with Drug-Induced Erythroderma (DIE), an association between anti-TBs ($p=0.032$) and aromatic anticonvulsants ($p=0.022$) and DIE was identified where carbamazepine was the most common culprit, as previously reported by Miyashiro et al. (Miyashiro & Sanches, 2020) A study in Nigeria found that erythroderma in HIV patients was primarily caused by anti-retroviral medication and sulfonamides while Zhu et. al. identified antivirals followed by anti-TBs as the major culprits in HIV patients. In contrast, in this study, anticonvulsants and anti-TBs were the most common causes of DIE among the HIV-positive population(Salami et al., 2012; Zhu et al., 2021).

A French multicentric study identified NSAIDs and paracetamol as the most common causative agents of Fixed Drug Eruptions (FDE). In contrast, our study found a significant association between GBFDE and nitroimidazoles($p=0.0027$) and paracetamol($p=0.009$). However, the association between drug class and patient age, as reported in the French study, was not observed in our dataset(Brahimi et al., 2010).

Three drug classes - sulfonamides, NSAIDs and aromatic anticonvulsants - were implicated with equal frequency, but none demonstrated statistically significant association with Drug-Induced Erythema Multiforme (DIEM). Our findings align with Panthalla et al. who identified sulfonamides as the most common causative agents. (Panthalla et al., 2019)

Both Creadore et al. and the EuroSCAR identified B-lactams as the most common Acute Generalized Exanthematous Pustulosis (AGEP) triggers. While antifungals, especially terbinafine, are well documented AGEP triggers, one patient in this study reacted to ketoconazole. Another developed AGEP after using hormonal contraceptives, a unique finding not previously reported.

Among DRESS patients, an association with aromatic anticonvulsants and DILI was found in our study, further reinforcing the established links between DRESS and anticonvulsant use and DILI (Devarbhavi & Raj, 2019; Kardaun et al., 2013).

Among Drug-Induced Anaphylaxis (DIA) cases, antibiotics and analgesics were the leading triggers, each implicated in one case and asthma, a known anaphylaxis risk factor was present in one patient (Hanschmann et al., 2023; Regateiro et al., 2020). Additionally, a progestin-only contraceptive, a rare trigger of anaphylaxis was identified in another patient, suggesting that hormonal influence on anaphylaxis may be more complex than previously thought (Foer et al., 2016).

5.4 Conclusion

This study provides critical insights into the epidemiological, clinical, and drug causality patterns of SCARs in a Kenyan referral hospital, highlighting key differences from global studies while reinforcing established findings from other regions. SCAR patients in this study were significantly younger than previously reported, with a notable proportion being paediatric cases, suggesting a heightened burden among younger populations. This age distribution may be influenced by referral patterns and the frequent use of antibiotics for acute infections, a major precipitant of SCARs in this study. While the slight female predominance aligns with global trends, variations were observed across SCAR phenotypes. SJS/TEN emerged as the most prevalent phenotype while DRESS was the least common phenotype. Distinct patterns of drug causality were evident, with antibiotics emerging as the leading drug group where sulfonamides and B-lactams played a significant role. In SJS/TEN, DIEM, GBFDE, B-lactams and sulfonamides were the most

frequently implicated subgroups, with NSAID also contributing significantly. In the less frequent phenotypes such as DIA and AGEF, B-lactams remained the primary trigger, with hormonal drugs also playing a role. Aromatic anticonvulsants were particularly associated with cases of DIE and DRESS. Among specific drugs, cotrimoxazole, ceftriaxone and carbamazepine were the three most frequently implicated. Organ involvement was a key finding, with acute kidney injury (AKI) and *Drug-Induced Liver Injury* (DILI) occurring more frequently in SJS/TEN cases. The high prevalence of previous drug reactions (36.3%) underscores a lack of awareness regarding drug avoidance, increasing the risk of recurrent severe reactions. Although comorbidities were common, no significant association was found between underlying conditions and SCAR-related mortality. HIV was the most prevalent comorbidity, but its impact on SCAR severity remains unclear. Unlike global trends where SCARs predominantly affect older adults with chronic conditions, this study found that most cases resulted from drug exposures for acute illness rather than chronic conditions. These findings reinforce the urgent need for improved pharmacovigilance, improved patient education and stricter drug avoidance measures to reduce the risk of recurrence. Additionally, further research into genetic and immunological risk factors is essential to enhance early detection, refine risk-stratification and develop targeted prevention strategies for SCAR patients in Kenya.

5.5 Study Strengths

This study provides comprehensive clinical and epidemiological data, offering a detailed characterization of SCAR phenotypes in a Kenyan population. By incorporating both retrospective and retrospective data, it ensures a well-rounded analysis of SCAR trends over time. The use of robust statistical methods enhances the validity of associations between SCAR phenotypes, drug exposure and clinical outcomes. Notably, this is the first study on the clinical profile of all SCAR phenotypes in the region, making a pioneering contribution to dermatological and pharmacovigilance research in the region.

5.6 Study Limitations

The retrospective design of part of the study introduced inherent limitations, including reliance on existing medical records, which varied in completeness and accuracy. Missing data in this arm affected the completeness of certain variables, potentially introducing information bias. As described in the methodology, available case analysis was used to minimize this impact, but some degree of bias remains a limitation. Files with substantial missing data were excluded to maintain data quality, while missing information in other files were systematically documented in each section of the data collection tool.

Additionally, in the prospective arm, some patients were too ill to participate, which limited enrolment and reduced the breadth of clinical data collected. Where possible, proxies provided consent on behalf of these patients. Paper-based tools posed risks of data loss, mitigated by secure storage in locked cabinets with restricted access.

The study was conducted in single referral hospital, which may not fully represent SCAR patterns across Kenya. The geographic distribution of participants, with a predominance from Nairobi and surrounding regions, reflects referral patterns to Kenyatta National Hospital and may introduce selection and referral bias.

The sample size for certain SCAR phenotypes was small, limiting the strength of inferential analysis for these subgroups. This restricted the ability to draw strong conclusions for these subgroups.

Finally, the use of a hybrid study design may have introduced variability between the two arms. While a standardized data collection tool was used to enhance consistency, no formal comparative analysis was conducted between the two arms. This absence of direct comparison limits the ability to evaluate potential differences between the two groups that could influence the overall findings.

5.7 Study Results Dissemination Plan

The results of this study will be disseminated through multiple channels. First, the findings will be presented to the Department of Dermatology at KNH to provide practical insights that can enhance clinical practices. A summary of the results will also be archived in the online repository of the Department of Internal Medicine at JKUAT, ensuring that the findings are accessible to academic and healthcare professionals. Additionally, a report of the study findings will be shared with the KNH-UON ERC team to fulfil reporting requirements. The study results will be presented at relevant conferences and seminars to engage with the broader medical community and provide information on the findings of the study. Finally, an abstract summarising the findings will be prepared for submission to peer-reviewed dermatology journals for potential publication, aiming to contribute to the scientific literature on SCARs.

5.8 Recommendations

Kenyan healthcare facilities should strengthen pharmacovigilance systems by implementing mandatory SCAR reporting and ensuring that cases of SCARs are promptly identified and documented. This will not only prevent the escalation of reactions but also prevent misinterpretation of prodromal symptoms as separate illness, which often leads to the addition of unnecessary medications that may worsen the reactions. To enhance drug safety, safer prescribing practices should be enforced, especially for antimicrobials, while over-the-counter sales of high-risk medications should be restricted to prevent misuse. Promoting antimicrobial stewardship can further curb inappropriate drug use. Finally, patient education on drug allergy awareness must be prioritized, as repeated exposure to offending drugs can lead to more severe or fatal reactions.

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APPENDICES

Appendix I: Data Collection Tool

Title: CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF SEVERE CUTANEOUS ADVERSE DRUG REACTIONS AT THE KENYATTA NATIONAL HOSPITAL.

Study Participant Number:

A. DEMOGRAPHIC DATA

1. What was the date of admission?
2. Age: years.....months (decimals for age 6 and below)
3. Gender: Male (1) /Female (2)
4. Where do you reside: Central (1), Coast ((2), Eastern (3), Nairobi (4), North-Eastern (5), Nyanza (6), Rift Valley (7), Western (8)
5. Which ethnic community do you identify with?
6. Missing data:

B. CLINICAL PRESENTATION

1. What was the time interval (in days) from the initiation of suspected culprit drug(s) to onset of cutaneous symptoms.....days
2. Were there any prodromal symptoms? Yes/ No
 - i. If Yes, indicate the type
 1. Respiratory symptoms: Yes (1)/ No (2)
 2. Gastrointestinal symptoms: Yes (1)/ No (2)
 3. Fever: Yes (1)/ No (2)
 4. Central and peripheral nervous symptoms: Yes (1)/ No (2)
 5. Musculoskeletal symptoms: Yes (1)/ No (2)
 6. Cardiac symptoms: Yes (1)/ No (2)
 7. Others.....

3. What is the clinical phenotype:
 - i. SJS , SJS/TEN overlap, TEN: Yes (1)/ No (2)
 1. If Yes, indicate type:
 - a. SJS (1), SJS/TEN overlap (2), TEN (3)
 - ii. DRESS: Yes (1)/ No (2)
 1. If yes, was the RegiSCAR criteria used (Appendix 4)?
 - a. Yes (1). What was the score.....
 - b. No (2)
 - iii. AGEP: Yes (1)/ No (2)
 1. If yes, was the AGEP validation score used (Appendix 5)?
 - a. Yes (1). What was the score?
 - b. No (2)
 - iv. Drug-induced exfoliative erythroderma (DIE): Yes (1)/ No (1)
 - v. Drug induced erythema multiforme major (DIEM): Yes (1)/ No (2)
 - vi. Drug induced anaphylaxis (DIA): Yes (1)/ No (2)
 1. If yes, was the WAO criteria used (Appendix 6)?
 - a. Yes (1)
 - b. No (2)
4. Muco-cutaneous symptoms:
 - i. What is the percentage of body surface area affected: %
 - ii. What are the specific cutaneous manifestations: macules (1), papules (2), vesicles (3), bullae (4), erosions (5), plaques (6), other (7):
 - iii. Mucositis: Yes (1) /No (2)
 1. If Yes, indicate site:
 - a. Oral mucosa (1)
 - b. Conjunctiva (2)
 - c. Urethral mucosa (3)
 - d. Vaginal mucosa (4)
 - e. Anal mucosa (5)
 - f. Other (6): (indicate site)

5. Associated symptoms:
 - i. Fever: Yes (1) / No (2)
 - ii. Pruritus: Yes (1) / No (2)
 - iii. Joint pain: Yes (1) / No (2)
 - iv. Others:
6. Associated signs:
 - i. Lymphadenopathy: Yes (1)/ No (2)
 - ii. Organomegaly: Yes (1)/ No (2)
 - iii. Others:
- 7. Missing data.....**

C. DRUG INFORMATION

1. What was the suspected culprit drug(s) based on:
 - i. Expert opinion:
 - ii. Algorithm (Appendix 2 and 3)
2. What is the drug class of the suspected culprit drug?
 - i. Antimicrobials (1)
 - ii. Anticonvulsants (2)
 - iii. Anti-neoplastics (3)
 - iv. Analgesics (4)
 - v. Antipsychotics (5)
 - vi. Anticoagulants (6)
 - vii. Anti-hypertensive (7)
 - viii. Anti-glycaemic (8)
 - ix. Hormonal medications (9)
 - x. Immunosuppressive drugs (10)
 - xi. Others (11)
 1. Indicate drug class.....
3. Was the medication prescribed or over-the-counter?
 - i. Prescribed (1)

- ii. OTC (2)
- 4. What was the indication for which the suspected drug was taken?
 - i. Acute disease < 6 weeks duration (1)
 - ii. Chronic disease >6 weeks duration (2)
- 5. Past history of drug allergies or adverse reactions:
 - i. Yes (1)
 - ii. No (2)
- 6. Missing data.....

D. MEDICAL HISTORY

- 1. Underlying medical conditions:
 - i. Autoimmune diseases (1),
 - ii. HIV/AIDS (2),
 - iii. Malignancies (3),
 - iv. Convulsive disorders (4),
 - v. Psychiatric illnesses (5),
 - vi. Type 2 diabetes (6),
 - vii. Hypertension (7),
 - viii. Renal disease (8),
 - ix. Hepatic disease (9),
 - x. Other (10)
- 2. Missing data.....

E. LABORATORY TESTS

- 1. Complete blood count (CBC)
 - i. White cell count on admission:
 - 1. Total count..... x $10^9/L$ (Normal 4-10 x $10^9/L$)
 - 2. Total eosinophil count..... x $10^9/L$ (Normal 0.02-0.10 x $10^9/L$)
 - a. Normal (1)
 - b. Low (2)

- c. Elevated (3)
 - 3. Total neutrophil count..... x 10⁹/L (Normal 2-7 x10⁹/L)
 - a. Normal (1)
 - b. Low (2)
 - c. Elevated (3)
 - ii. Haemoglobin level..... g/dL (Normal 12-15g/dL)
 - 1. Normal (1)
 - 2. Low (2)
 - 3. Elevated (3)
 - iii. Total platelet count..... x 10⁹/L (Normal 150-450 x 10⁹/L)
 - 1. Normal (1)
 - 2. Low (2)
 - 3. Elevated (3)
- 2. Liver Function tests(LFTs)
 - i. Alanine aminotransferase (ALT)..... U/L (10-40U/L)
 - ii. Aspartate aminotransferase (AST)..... U/L (10-40U/L)
 - iii. Total bilirubin..... Umol/L (4.30-21Umol/L)
- 3. Renal function tests
 - i. Serum creatinine..... Umol/L (60-130Umol/L)
 - ii. Blood urea nitrogen:.....mmol/L (1.7-8.3mmol/L)
- 4. Serological tests
 - i. Herpes simplex virus (HSV) IgM:
 - 1. Indicate if done Yes (1), No (2)
 - 2. If yes, Positive (1), Negative (2)
 - ii. HIV screening: Positive (1), Negative (2)
 - iii. HbsAg (Hepatitis B Surface Antigen): Positive (1), Negative (2)
 - iv. Hepatitis C Antibody test: Positive (1), Negative (2)
- 5. Missing data.....

F: OUTCOME

1. Discharged..... (1)
2. In-hospital mortality..... (2)
3. On going hospitalization..... (3)

Appendix II: Naranjo Algorithm

Interrogation	Yes	No	Do not know
Are there previous confirmed reports of reaction?	+1	0	0
Did the adverse event appear after the drug was administered?	+2	-1	0
Did the adverse reaction improve following discontinuation of the medication or administration of a specific antagonist?	+1	0	0
Were there other plausible causes for the reaction?	-1	+2	0
Did the adverse reaction recur upon administration of placebo?	-1	+1	0
Was the drug found in the blood or other fluids in toxic concentrations?	+1	0	0
Did the reaction worsen with increasing dosage? Or did it improve with dosage reduction?	+1	0	0
Did the adverse reaction recur upon re-administration of the drug?	+2	-1	0
Has the patient experienced a similar reaction to the medication or a related agent in the past?	+2	0	0
Was the adverse event supported by other objective evidence?	+1	0	0

Total score:

Interpretation: Score ≤ 0 , probability doubtful, 1- 4; possible, 5-8; likely/probable, ≥ 9 ; definite probability

Appendix III: Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN)

Criteria	Possible score
Time elapsed between initial drug intake and onset of reaction (index day)	-3 to +3
Presence of drug in the body on the index day	0 to -3
Prechallenge/rechallenge outcome with the suspected drug	-2 to +4
Outcome of rechallenge	0 to -2
Drug reputation for causing SJS/TEN	-1 to +3
Other potential etiological alternatives	-1, if applicable

Total score:

Interpretation: ≥ 6 : very probable, 4-5: probable, 2-3: possible, 0-1: unlikely and ≤ 0 : very unlikely

Appendix IV: RegiSCAR Criteria for DRESS

Score	-1	0	1	2
Fever $\geq 38.5^{\circ}\text{C}$	No/U	Yes		
Lymphadenopathy		No/U	Yes	
Eosinophilia - Eosinophil count - Eosinophil count, if leukocytes $< 4.0 \times 10^9 \text{ L}^{-1}$			0.7- $1.499 \times 10^9 \text{ L}^{-1}$ 10 % - 19.9%	$\geq 1.5 \times 10^9 \text{ L}^{-1}$ $\geq 20\%$
Atypical lymphocytes		No/U	Yes	
Skin involvement - Skin rash extent (%TBSA) - Skin rash suggesting DRESS - Biopsy suggesting DRESS	No No	No/U U Yes/U	>50% Yes	
Organ involvement - Liver - Kidney - Muscle/heart - Pancreas - Other organs		No/U No/U No/U No/U No/U	Yes Yes Yes Yes Yes	
Resolution ≥ 15 days	No/U	Yes		
Evaluation of other potential causes - Antinuclear antibody - Blood cultures - Hepatitis A/B/C serology - Chlamydia/mycoplasma serology - If none positive and ≥ 3 of the above negative		Yes		

Total score:

U: unclassifiable or unknown.

Interpretation: Score <2: no case, 2-3: possible case, 4-5: probable case, >5: definite case.

Appendix V: AGEP validation Score for AGEP Cases

Morphology	
Presence of pustules	
- Typical	+2
- Compatible	+1
- Insufficient	0
Presence of erythema	
- Typical	+2
- Compatible	+1
- Insufficient	0
Distribution pattern	
- Typical	+2
- Compatible	+1
- Insufficient	0
Post-pustular desquamation	
- Yes	+1
Absent/insufficient	0
Course	
Mucosal involvement	
- Present	-2
- Absent	0
Acute Onset (≤ 10 days)	
- Present	0
- Absent	-2
Resolution ≤ 15 days	
- Present	0
- Absent	-4
Fever $\geq 38^{\circ}\text{C}$	
- Present	+1
- Absent	0
PMN $\geq 7000/\text{mm}^3$	
- Present	+1
- Absent	0
Histology	
- Other disease	
- Not Representative/No Histology	-10
- Presence of exocytosis of PMN	0
- Presence of subcorneal and/or intra-epidermal non-spongiform or NOS pustule(s) with papillary edema or subcorneal and/or intra-epidermal spongiform or NOS pustule(s) without papillary edema	+1 +2
- Presence of spongiform subcorneal and/or intra-epidermal pustule(s) with papillary edema	+3

Total score:

Interpretation: ≤ 0 : no AGEP, 1-4: possible, 5-7: probable, 8-12: definite

Appendix VI: The World Allergy Organisation's Criteria for the Diagnosis of Anaphylaxis

Anaphylaxis is highly probable when any one of the following 2 sets of criteria is met:
1. An abrupt onset of symptoms (minutes to several hours) characterised by concurrent involvement of the skin, mucous membranes or both
AND AT LEAST ONE of the following:
a) Respiratory compromise (for example dyspnoea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
b) Decreased blood pressure or associated symptoms or end-organ dysfunction such as hypotonia (collapse), syncope, incontinence
c) Severe gastrointestinal symptoms (for example severe crampy abdominal pain, repetitive vomiting) particularly following exposure to non-food allergens.
2. Sudden onset of hypotension or bronchospasms or laryngeal involvement after exposure to a known or highly likely allergen for that individual (occurring within minutes to hours), even in the absence of typical skin manifestations.

Appendix VII: Informed Consent Form for Adults

Informed Consent Form in English

Title: CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF SEVERE CUTANEOUS ADVERSE DRUG REACTIONS AT THE KENYATTA NATIONAL HOSPITAL

Principal investigator: Dr Caroline Mutio

Affiliation: Dermatology Resident at Jomo Kenyatta University of Agriculture and Technology/Kenyatta National Hospital

Introduction:

My name is Dr Caroline Mutio. I am currently pursuing my postgraduate studies at the Jomo Kenyatta University of Agriculture and Technology (JKUAT). As part of my studies, I am required to undertake research. I am researching the Clinical and Epidemiological characteristics of severe cutaneous adverse drug reactions for patients admitted at the Kenyatta National Hospital and you are invited to participate in the study. Before you agree to participate, it is important that you understand the purpose, procedures, potential risks and benefits of the study. Kindly take your time to read this consent form and feel free to ask any questions before making your decision.

Researcher's statement

As the principal investigator of this study, I am committed to conducting this research in an ethical manner that ensures your rights, dignity and well-being are protected during this study. I assure you that your participation is voluntary and you have the right to withdraw at any time without any consequences and that your withdrawal will not impact your medical care. All data collected will be kept confidential and your identity will be made anonymous.

Purpose of the Study:

The aim of the study is to investigate the clinical phenotypes and epidemiological features of all severe cutaneous adverse drug reactions among patients admitted at the Kenyatta National Hospital. Severe adverse drug reactions are those reactions that result in hospitalisation and are caused by drugs. By collecting and analysing this information, we aim to understand the clinical characteristics of these reactions as well as the drugs that are mostly associated with these severe reactions with the aim of developing strategies to prevent such reactions in the future.

Study Procedures:

Should you agree to participate in the prospective arm of the study, you will be requested to provide information about your medical history, give a history on drug exposure and provide information on the clinical symptoms related to severe cutaneous adverse drug reactions. Additionally, a full physical examination will be performed. The entire data collection process is expected to take approximately 20 to 30 minutes. Your participation is voluntary and you have a right to withdraw at any time without consequences. Your decision to withdraw at any point will not result in refusal of treatment or any consequence.

Risks and Benefits:

There is minimal risk associated with participation in this study and this includes discomfort during the interviews or physical examination. We will however take measures to minimize these risks and ensure comfort. There are no direct benefits to you for participating in the study. However, your participation may contribute to advancements in medical knowledge and improve patient care of other patients affected by SCARs in the future.

Confidentiality:

All information collected during this study will be kept confidential and your identity will be protected and any data shared with researcher will be made anonymous to ensure privacy. Your participation in the study will not affect your medical care in any way.

Contact Information:

If you have any questions or would like more information, feel free to contact:

Dr Caroline Mutio:

Mobile number: +254 701 220 110

Email address: mutiocarol41@gmail.com

Dr Hannah Wanyika: Mobile number: +254 705 501 600

Email address: drwanyika14@gmail.com

[illegible]

KNH-UoN ERC: Email address: uonknh_erc@uonbi.ac.ke
Phone number: (254-020)2726300

Consent:

Subject's statement: I voluntarily agree to participate in the study. I understand that participation in the study does not entail any financial benefits. I have had a chance to ask questions and I have been informed that the information obtained will be treated with utmost confidentiality.

If I have questions about my rights as a research subject or complaints about the study, I have been provided with the phone number of the Ethical Review Committee (ERC) at Kenyatta National Hospital which is (254-020)2726300. I have not been coerced into

precipitating in the study and the nature, benefits, risks have been explained to me. I am aware I can withdraw from the study at any time without penalty or any consequence to my medical care.

Participant's name:

Participant's Signature (or guardian/medical proxy):

Date:

Researcher's statement: I hereby certify that I have explained in detail the nature and purpose, procedures, risks and benefits of the research study to the volunteer.

Investigator's Signature:

Date:

Principal Investigator: Dr Caroline Mutio, +254 701 xxx x10

Informed Consent Form (Swahili)

Jina la Utafiti: TABIA ZA KLINIKIA-EPIDEMIOLOJIA ZA MADHARA MAKALI YA DAWA KATIKA NGOZI KATIKA HOSPITALI YA TAIFA YA KENYATTA

Mtafiti Mkuu: Dkt. Caroline Mutio

Mahusiano: Mwanafunzi wa Dermatology katika Chuo Kikuu cha Kilimo na Teknolojia cha Jomo Kenyatta/Hospitali ya Taifa ya Kenyatta

Utangulizi:

Jina langu ni Dkt. Caroline Mutio. Kwa sasa, ninasomea masomo ya shahada ya uzamili katika Chuo Kikuu cha Kilimo na Teknolojia cha Jomo Kenyatta (JKUAT). Sehemu ya masomo yangu ni kufanya utafiti. Ninafanya utafiti kuhusu Tabia za Kliniki na Epidemiolojia za madhara makali ya dawa kwenye ngozi kwa wagonjwa walioingizwa

katika Hospitali ya Taifa ya Kenyatta. Unaalikwa kushiriki katika utafiti kuhusu madhara makali ya dawa kwenye ngozi unaofanywa katika Hospitali ya Taifa ya Kenyatta. Kabla ya kukubali kushiriki, ni muhimu uelewe lengo, taratibu, hatari, na faida za utafiti. Tafadhali tumia muda wako kusoma fomu hii ya idhini na usisite kuuliza maswali yoyote kabla ya kufanya uamuzi wako.

Tamko la Mtafiti

Kama mtafiti mkuu wa utafiti huu, ningependa kufanya utafiti huu kwa njia inayofaa na ambayo inakakikisha kwamba haki yako inalindwa wakati wa utafiti huu. Nakuhakikishia kwamba ushiriki wako ni wa hiari na una haki ya kujiondoa wakati wowote bila athari yoyote na kujiondoa kwako hakutaathiri huduma zako za matibabu. Taafira yote itakayokusanywa itahifadhiwa kwa siri na utambulisho wako utabaki kuwa siri.

Lengo la Utafiti:

Lengo la utafiti huu ni kuchunguza vipengele vya kliniki na epidemiolojia vya madhara makali ya dawa kwenye ngozi miongoni mwa wagonjwa waliolazwa katika Hospitali ya Taifa ya Kenyatta. Madhara makali ya dawa ni yale yanayosababisha hospitalini na husababishwa na dawa. Kwa kukusanya na kuchambua habari hii, tunalenga kuelewa sifa za madhara haya na kuboresha mikakati ya matibabu na kuzuia.

Taratibu za Utafiti

Ikiwa utakubali kushiriki katika sehemu ya sasa ya utafiti, utaulizwa kutoa habari kuhusu historia yako ya matibabu, kutoa historia ya mfiduo wa dawa, na kutoa habari kuhusu dalili za kliniki zinazohusiana na madhara makali ya dawa kwenye ngozi. Aidha, uchunguzi kamili wa kimwili utafanywa. Ukusanyaji wa data unatarajiwa kuchukua takriban dakika 20 hadi 30. Ushiriki wako ni wa hiari na una haki ya kujiondoa wakati wowote bila athari yoyote. Uamuzi wako wa kujiondia wakati wowote hautasababisha kukataliwa kwa matibabu au athari yoyote ile.

Hatari na Faida

Kuna hatari ndogo zinazohusiana na kushiriki katika utafiti huu na hii ni pamoja na kutokwa na taarifa wakati wa mahojiano au uchunguzi wa kimwili. Hata hivyo, tutachukua hatua za kupunguza hatari hizi na kuhakikisha faraja yako. Hakuna faida moja kwa moja kwako kwa kushiriki katika utafiti. Hata hivyo, ushiriki wako unaweza kuchangia maendeleo ya maarifa ya matibabu na kuboresha huduma kwa wagonjwa wengine walioathiriwa na SCARs siku za usoni.

Usiri

Taarifa zote zilizokusanywa wakati wa utafiti huu zitahifadhiwa kwa usiri kabisa na utambulisho wako utalindwa. Ushiriki wako katika utafiti hautaathiri huduma yako ya matibabu kwa njia yoyote.

Taarifa za Mawasiliano

Ikiwa una maswali au ungependa habari zaidi, tafadhali wasiliana na:

Dkt. Caroline Mutio: Nambari ya Simu: +254 701 220 110

Anwani ya barua pepe: mutiocarol41@gmail.com

Dkt. Hannah Wanyika: Nambari ya simu: +254 705 501 600

Anwani ya barua pepe: drwanyika14@gmail.com

Dkt. P. Namasaka: Nambari ya simu: +254 721 689 085

Anwani ya barua pepe: pnamasaka@gmail.com

KNH-UoN ERC: Anwani ya barua pepe: uonknh_erc@uonbi.ac.ke

Nambari ya simu: (254-020)2726300

Idhini:

Tamko la mhusika: Nakubali kwa hiari yangu kushiriki katika utafiti huu. Naelewa kuwa kushiriki kwangu hauna manufaa ya kifedha. Nimepata fursa ya kuuliza maswali na nimejulishwa kwamba taarifa itakayokusanywa itashughulikiwa kwa usiri mkubwa. Ikiwa nina maswali kuhusu haki zangu kama mhusika wa utafiti au malalamiko kuhusu utafiti huu, nimepewa mabari ya simu ya Kamati ya Mapitia ya Maadili katika hospitali kuu ya Kenyatta ambayo ni (254-020)2726300. Kuhisika kwangu si wa kulazimishwa na asili, manufaa na hatari za utafiti huu zimeelezwa kwangu. Nafahamu kwamba naweza kujiondoa katika utafiti huu wakati wowote bila adhabu au athari yoyote kwa huduma zangu za matibabu.

Jina la mhusika:

Sahihi ya mhusika (ama mlezi/mwakilishi wa matibabu):

Terehe:

Tamko la mtafiti: Ninathibitisha kuwa nimeeleza kwa undani asili, taratibu, hatari na manufaa ya utafiti huu kwa msalishaji.

Sahihi ya mtafiti:

Terehe:

Mtafiti mkuu: Dkt. Caroline Mutio, +254 701 220 110

Appendix VIII: Informed Consent for Minors

Parental Informed Consent (English)

Title: CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF SEVERE CUTANEOUS ADVERSE DRUG REACTIONS AT THE KENYATTA NATIONAL HOSPITAL

Principal Investigator: Dr. Caroline Mutio

Affiliation: Dermatology Resident at Jomo Kenyatta University of Agriculture and Technology/Kenyatta National Hospital

Introduction

My name is Dr. Caroline Mutio, and I am currently pursuing my postgraduate studies at the Jomo Kenyatta University of Agriculture and Technology (JKUAT). As part of my studies, I am required to undertake research. I am researching the Clinical and Epidemiological characteristics of severe cutaneous adverse drug reactions for patients admitted at the Kenyatta National Hospital, and your child is invited to participate in the study. Before you consent to your child's participation, it is crucial that you understand the purpose, procedures, potential risks, and benefits of the study. Please take your time to read this consent form and feel free to ask any questions before making your decision.

Researcher's Statement

As the principal investigator of this study, I am committed to conducting this research in an ethical manner that ensures that the rights, dignity and well-being of your child are protected during this study. I assure you that your participation and that of your child is voluntary and you have the right to withdraw at any time without any consequences. Your withdrawal or that of your child will not impact his or her medical care. All data collected will be kept confidential and the identity of your child will be made anonymous.

Purpose of the Study

The aim of the study is to investigate the clinical phenotypes and epidemiological features of all severe cutaneous adverse drug reactions among patients admitted at the Kenyatta National Hospital. Severe adverse drug reactions are those reactions that result in hospitalisation and are caused by drugs. By collecting and analysing this information, we aim to understand the clinical characteristics of these reactions as well as the drugs that are mostly associated with these severe reactions, with the aim of developing strategies to prevent such reactions in the future.

Study Procedures

Should you consent to your child's participation in the prospective arm of the study, your child will be requested to provide information about their medical history, give a history on drug exposure, and provide information on the clinical symptoms related to severe cutaneous adverse drug reactions. Additionally, a full physical examination will be performed. The entire data collection process is expected to take approximately 20 to 30 minutes. Participation is voluntary, and you and your child have the right to withdraw at any time without consequences. Your decision to withdraw at any point will not result in refusal of treatment or any consequence for your child.

Risks and Benefits

There is minimal risk associated with participation in this study, including discomfort during the interviews or physical examination. We will, however, take measures to minimize these risks and ensure comfort. There are no direct benefits to your child for participating in the study. However, their participation may contribute to advancements in medical knowledge and improve patient care of other patients affected by SCARs in the future.

Confidentiality

All information collected during this study will be kept confidential, and your child's identity will be protected. Any data shared with researchers will be made anonymous to ensure privacy. Participation in the study will not affect your child's medical care in any way.

Contact Information

If you have any questions or would like more information, feel free to contact:

Dr Caroline Mutio:

Mobile number: 0701220110

Email address: mutiocarol41@gmail.com

Dr Hannah Wanyika: Mobile number: 0705501600

Email address: drwanyika14@gmail.com

Dr P. Namasaka : Mobile number 0721689085

Email address: pnamasaka@gmail.com

KNH-UoN ERC: Email address: uonknh_erc@uonbi.ac.ke
Phone number: (254-020)2726300

Consent:

Parental/Guardian statement: I am the parent/guardian of the minor participant and I voluntarily agree to allow my child to participate in the study. I understand that participation in the study does not entail any financial benefits. I have had the opportunity to ask questions and I have been informed that the information obtained will be treated with utmost confidentiality.

If I have questions about my child's rights as a research subject or any complaints about the study, I have been provided with the phone number of the Ethical Review Committee (ERC) at Kenyatta National Hospital which is (254-020)2726300. Neither my child nor I have been coerced into precipitating in the study and the nature, benefits, risks have been explained to me. I am aware that my child can withdraw from the study at any time without penalty or any consequence to their medical care.

Parent/Guardian's name:

Parent/Guardian's Signature:

Date:

Researcher's statement: I hereby certify that I have explained in detail the nature and purpose, procedures, risks and benefits of the research study to the volunteer.

Investigator's Signature:

Date:

Principal Investigator: Dr Caroline Mutio, 0701220110

Parental Informed Consent (Swahili)

Jina la utafiti: TABIA ZA KLINIKIA-EPIDEMIOLOJIA ZA MADHARA MAKALI YA DAWA KATIKA NGOZI KATIKA HOSPITALI YA TAIFA YA KENYATTA

Mtafiti Mkuu: Dk. Caroline Mutio

Mahusiano: Mwanafunzi wa Dermatology katika Chuo Kikuu cha Kilimo na Teknolojia ya Jomo Kenyatta/Kenyatta National Hospital

Utangulizi:

Jina langu ni Dk. Caroline Mutio, na kwa sasa ninasomea masomo ya shahada ya uzamili katika Chuo Kikuu cha Kilimo na Teknolojia ya Jomo Kenyatta (JKUAT). Kama sehemu ya masomo yangu, ninahitajika kufanya utafiti. Ninachunguza sifa za kliniki na epidemiolojia ya majibu makali ya ngozi kwa wagonjwa wanaoadimishwa katika Hospitali ya Kitaifa ya Kenyatta, na mtoto wako anaalikwa kushiriki katika utafiti huu. Kabla ya kutoa idhini ya mtoto wako kushiriki, ni muhimu uelewe lengo, taratibu, hatari, na faida za utafiti huu. Tafadhali chukua muda wako kusoma fomu hii ya idhini na uhisi huru kuuliza maswali kabla ya kufanya maamuzi.

Taarifa ya Mtafiti

Kama mtafiti mkuu wa utafiti huu, ningependa kufanya utafiti huu kwa njia inayofaa na ambayo inakakikisha kwamba haki ya mtoto wako inalindwa wakati wa utafiti huu. Nakuhakikishia kwamba ushiriki wako na mtoto wako ni wa hiari na una haki ya kujiondoa wakati wowote bila athari yoyote na kujiondoa kwako hakutaathiri huduma zako za matibabu kwa mtoto wako. Taafira yote itakayokusanywa itahifadhiwa kwa siri na utambulisho wa mtoto wako utabaki kuwa siri.

Lengo la Utafiti

Lengo la utafiti ni kuchunguza sifa za kliniki na epidemiolojia ya majibu makali ya ngozi kwa wagonjwa wanaoadimishwa katika Hospitali ya Kitaifa ya Kenyatta. Majibu makali ya dawa ni yale yanayosababisha kuadimishwa hospitalini na husababishwa na dawa. Kwa kukusanya na kuchambua habari hii, lengo letu ni kuelewa sifa za kliniki za majibu haya pamoja na dawa ambazo mara nyingi zinahusishwa na majibu haya makali, kwa lengo la kuendeleza mikakati ya kuzuia majibu kama haya katika siku zijazo.

Taratibu za Utafiti

Ukiidhinisha ushiriki wa mtoto wako katika mkono wa upeo wa utafiti huu, mtoto wako ataulizwa kutoa habari kuhusu historia yake ya matibabu, kutoa historia ya utumiaji wa dawa, na kutoa habari kuhusu dalili za kliniki zinazohusiana na majibu makali ya ngozi kwa dawa. Aidha, ukaguzi kamili wa mwili utafanywa. Ukusanyaji wa data unatarajiwa kuchukua takriban dakika 20 hadi 30. Ushiriki ni wa hiari, na wewe na mtoto wako mna haki ya kujiondoa wakati wowote bila ya madhara. Uamuzi wako au mtoto wako kujiondia wakati wowote hautasababisha kukataliwa kwa matibabu kwa mtoto wako au athari yoyote ile.

Hatari na Faida:

Kuna hatari ndogo zinazohusiana na ushiriki katika utafiti huu, ikiwa ni pamoja na usumbufu wakati wa mahojiano au ukaguzi wa mwili. Hata hivyo, tutachukua hatua za kupunguza hatari hizi na kuhakikisha faraja. Hakuna faida moja kwa moja kwa mtoto wako kwa kushiriki katika utafiti huu. Hata hivyo, ushiriki wao unaweza kuchangia katika maendeleo ya maarifa ya kitabibu na kuboresha huduma kwa wagonjwa wengine wanaoathiriwa na majibu makali ya ngozi katika siku zijazo.

Usiri:

Taarifa zote zilizokusanywa wakati wa utafiti huu zitahifadhiwa kwa siri, na utambulisho wa mtoto wako utalindwa. Data yoyote itakayoshirikiwa na watafiti itafanywa kuwa isiyo na utambulisho ili kuhakikisha faragha. Ushiriki katika utafiti hautaathiri huduma ya matibabu ya mtoto wako kwa njia yoyote.

Mawasiliano:

Ikiwa una maswali au unataka habari zaidi, tafadhali wasiliana na:

Dkt. Caroline Mutio: Nambari ya Simu: 0701220110

Anwani ya barua pepe: mutiocarol41@gmail.com

Dkt. Hannah Wanyika: Nambari ya simu: 0705501600

Anwani ya barua pepe: drwanyika14@gmail.com

Dkt. P. Namasaka: Nambari ya simu: 0721689085

Anwani ya barua pepe: pnamasaka@gmail.com

KNH-UoN ERC: Anwani ya barua pepe: uonknh_erc@uonbi.ac.ke

Nambari ya simu: (254-020)2726300

Idhini

Tamko la mzazi/mlezi: Mimi ni mzazi/mlezi wa mshiriki mdogo and nakubali kumruhusu mtoto wangu kushiriki katika utafiti huu. Ninaelewa kwamba kushiriki kwake hakutaleta faida zozote za kifedha. Nimepata nafasi ya kuuliza maswali na nimejulishwa kwamba taarifa itakayopatikana itatunzwa kwa usiri mkubwa.

Ikiwa nina swali kuhusu haki za mtoto wangu kama mshiriki wa utafiti au malalamiko yoyote kuhusu utafiti huu, nimepewa nambari ya simu ya Kamati ya Mapitia ya Maadili katika hospitaki kuu ya Kenyatta ambayo ni (254-020)2726300. Kuhisika kwa mtoto wangu si wa kulazimishwa na asili, manufaa na hatari za utafiti huu zimeelezwa kwangu. Nafahamu kwamba mtoto wangu anaweza kujiondoa katika utafiti huu wakati wowote bila adhabu au athari yoyote kwa huduma yake ya matibabu.

Jina la mzazi/mlezi:

Sahihi ya mzazi/mlezi:

Terehe:

Tamko la mtafiti: Ninathibitisha kuwa nimeeleza kwa undani asili, taratibu, hatari na manufaa ya utafiti huu kwa mzazi/mlezi.

Sahihi ya mtafiti:

Terehe:

Mtafiti mkuu: Dkt Caroline Mutio, 0701220110

Appendix IX: Assent Forms for Minors

Assent Form for Minors in English

Title: CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF SEVERE CUTANEOUS ADVERSE DRUG REACTIONS AT THE KENYATTA NATIONAL HOSPITAL

Principal Investigator: Dr. Caroline Mutio

Affiliation: Dermatology Resident at Jomo Kenyatta University of Agriculture and Technology/Kenyatta National Hospital

Introduction

My name is Dr. Caroline Mutio, and I am a student at Jomo Kenyatta University of Agriculture and Technology (JKUAT). As part of my studies, I am doing a study on skin reactions that are caused by medicines for patients at Kenyatta National Hospital and I would like to invite you to join this study. Before you decide, I would like to explain what the study is about, what you will need to do and any risks and benefits. Please read this form and feel free to ask any questions you might have.

Why are we doing this study?

We would like to learn about serious skin reactions caused by medicines because these reactions are very serious that patients need to be admitted to hospital. By understanding the reactions, we hope to prevent them in the future.

What will you do in the study?

If you agree to join, we will ask you about any medicines you have taken and your symptoms. We will also check your whole body for skin rashes and this will take 20 to 30

minutes. Please remember that if you do not want to continue, you can stop at any time and this will not affect your medical care.

Are there any risks or benefits?

There is a small risk that you will feel some discomfort during the examination of the body for skin rashes. We will do our best to make sure you are comfortable. There are no direct benefits to you but the information you provide may help improve care for other patients with similar diseases in the future.

Will your information be kept private?

Yes, everything you tell us will be kept private. We will not share your name with anyone.

Contact Information

If you have any questions, you or your parents can contact:

Dr Caroline Mutio: Mobile number: 0701220110

Email address: mutiocarol41@gmail.com

Dr Hannah Wanyika: Mobile number: 0705501600

Email address: drwanyika14@gmail.com

Dr P. Namasaka : Mobile number 0721689085

Email address: pnamasaka@gmail.com

KNH-UoN ERC:

Email address: uonknh_erc@uonbi.ac.ke

Phone number: (254-020)2726300

Assent

If you agree to join the study, please sign below. Remember, you can stop at any time.
Participant's statement: I understand what the study is about and I know that I can stop at any time without any problems. I agree to be part of this study.

Participant's name:

Participant's signature or name initials.....Date.....

Researcher's statement: I have explained the study in detail to the participant.

Investigator's signature:**Date.....**

Principal Investigator: Dr Caroline Mutio, 0701220110

Assent Form for Minors(Swahili)

Jina la utafiti: TABIA ZA KLINIKIA-EPIDEMIOLOJIA ZA MADHARA MAKALI
YA DAWA KATIKA NGOZI KATIKA HOSPITALI YA TAIFA YA KENYATTA

Mtafiti Mkuu: Dk. Caroline Mutio

Mahusiano: Mwanafunzi wa Dermatology katika Chuo Kikuu cha Kilimo na
Teknolojia ya Jomo Kenyatta/Kenyatta National Hospital

Utangulizi

Jina langu ni Dkt Caroline Mutio na mimi ni mwanafunzi katika chuo kikuu cha JKUAT. Nafanya utafiti kuhusu athari za Ngozi zinazotokana na dawa katika hospitali kuu ya Kenyatta. Ningependa kukualika kujuunga na utafiti huu. Kwanza, ningependa kuelezea utafiti huu unahusu nini, unachohitajika kufanya, hatari na manufaa ya utafiti huu. Tafadhali soma fomu hii na jiskie huru kuuliza maswali yoyote uliyo nayo.

Kwa nini tunafanya utafiti?

Tungependa kujua athari mbaya za ngozi zinazotokana na dawa kwa sababu athari hizi ni mbaya sana na wagonjwa wanahitaji kulazwa hospitali. Kwa kuelewa athari hizi, tunaweza kuzuia kwa magonjwa wengine.

Utahitajika kufanya nini katika utafiti?

Kama utakubali kujiunga, tutakuuliza kuhusu dawa yoyote ambayo umetumia na dalili zako. Tutaangalia mwili wako pia ili tuweze kuona vidonda vya ngozi na hii itachukua dakika 20 hadi 30. Tafadhali kumbuka kwamba kama haugenda kuendelea unaweza kusimama wakati wowote na haitaathiri matibabu yako.

Je, kuna manufaa au hatari yote?

Wakati ya kuangalia vidonda mwilini, kuna uwezekano kuwa hautaskia vizuri kwa mfano baridi mwilini lakini tutatia bidi ili tuhakikishe kwamba uko sawa. Hakuna manufaa yoyote ya moja kwa moja kwako lakini taarifa utakazotoa itaweza kusaidia kuboresha huduma kwa wagonjwa wengine ambao wakona ugonjwa kama unayougua.

Je, tutaambia watu wengine kuhusu habari utakayotupa?

Hapana. Taafira yote utakayotupa tutaweka kwa siri na hatutaambia mtu yeyote kwamba ulishiriki.

Kama una swali yoyote, wewe au mzazi wako mnaweza kuwasiliana na:

Dkt. Caroline Mutio: Nambari ya Simu: 0701220110

Anwani ya barua pepe: mutiocarol41@gmail.com

Dkt. Hannah Wanyika: Nambari ya simu: 0705501600

Anwani ya barua pepe: drwanyika14@gmail.com

Dkt. P. Namasaka:

Nambari ya simu: 0721689085

Anwani ya barua pepe: pnamasaka@gmail.com

KNH-UoN ERC:

Anwani ya barua pepe: uonknh_erc@uonbi.ac.ke

Nambari ya simu: (254-020)2726300

Idhini

Kama umekubali kujiunga na utafiti huu, tafadhali andika jina lako hapo chini na kumbuka kwamba unaweza kusimama wakati wowote.

Taafira ya mshiriki: Nimeelewa utafiti huu ni kuhusu nini na nimekubali kujiunga.

Jina la mshiriki:

Saini ya mshiriki au mwanzo za jina:.....**Tarehe:**.....

Taarifa ya mtafiti: Nimeeleza utafiti kwa undani kwa mshiriki

Saini ya mtafiti :..... **Tarehe:**

Mtafiti mkuu: Dkt Caroline Mutio, 0701220110

Appendix X: Supplemental Tables Section

Table 5 0.1: Logistic Regression Analysis of Predictors of Mortality among SCAR Patients

Variable	Univariate P-value	Univariate OR	Univariate 95% CI Lower	Univariate 95% CI Upper	Multivariate P-value	Multivariate OR	Multivariate 95% CI Lower	Multivariate 95% CI Upper
Age (per year increase)	0.015	1.033	1.006	1.059	0.058	1.027	0.998	1.056
Serum Creatinine $\geq$ 172 (AKI) (Ref: <172 μ mol/L)	0.003	7.18	2.02	25.53	0.029	5.08	1.63	15.87

Appendix XI: Ethical Approval

 UNIVERSITY OF NAIROBI FACULTY OF HEALTH SCIENCES P O BOX 19676 Code 00202 Telephone: 254-20 2726300	 KENYATTA NATIONAL HOSPITAL P O BOX 20723 Code 00202 Tel: 725300-9 Ext 44355, 44102 Fax: 725272 Telegrams: MEDSUP, Nairobi
Ref: KNH-ERC/A/293	15 th August, 2024
Dr. Caroline Mutio Reg. No HSM/351-1242/2022 Dermatology Unit Dept. of Internal Medicine School of Medicine <u>J.K.U.A.T</u>	
Dear Dr. Mutio,	
ETHICAL APPROVAL-RESEARCH PROPOSAL: CLINICO-EPIDEMIOLOGICAL CHARACTERISTICS OF SEVERE CUTANEOUS ADVERSE DRUG REACTIONS AT THE KENYATTA NATIONAL HOSPITAL (P421/05/2024)	
This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is P421/05/2024. The approval period is 15 th August 2024 – 14 th August 2025.	
This approval is subject to compliance with the following requirements:	
i. Only approved documents including (informed consents, study instruments, MTA) will be used. ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC. iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification. iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours. v. Clearance for export of biological specimens must be obtained from relevant institutions. vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal. vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.	
Protect to discover	

Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) <https://research-portal.nacosti.go.ke> and also obtain other clearances needed.

Yours sincerely,



PROF. BEATRICE K.M. AMUGUNE
SECRETARY, KNH- UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
 The Senior Director, CS, KNH
 The Chairperson, KNH- UoN ERC
 The Assistant Director, Health Information Dept., KNH
 The Chair, Dept. of Internal Medicine, J.K.U.A.T
 Supervisors: Dr. Hannah Wanyika, Consultant Dermatologist, KNH
 Dr. Philemon Mwella Namasaka, Dept. of Internal Medicine, J.K.U.A.T