

**CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES OF PATIENTS
WITH STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS AT
PIETERSBURG HOSPITAL**

by

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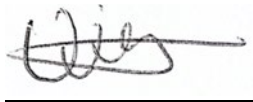
DEDICATION

I dedicate this work to my late father, John Ndinannyi Siala; you have always loved and believed in me. May your soul forever rest in peace. You are dearly missed.

To my mother, Dorothy Livhuwani Siala, who is and has always been the greatest supporter of my dreams. I'm grateful for your undying love that is beyond measure.

DECLARATION

I declare that the “clinical characteristics and treatment outcomes of patients with Stevens-Johnson syndrome/toxic epidermal necrolysis at Pietersburg Hospital” hereby submitted to the University of Limpopo, for the degree of Master of Medicine in Dermatology has not previously been submitted by me for a degree at this or any other university; that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

A handwritten signature in black ink, consisting of stylized, overlapping loops and a long horizontal stroke extending to the right.

Signature

25/10/2024

Date

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Pietersburg Hospital administration staff for their assistance and willingness to retrieve patient records for data collection purposes.

ABSTRACT

Background: Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) are a spectrum of a life threatening illness commonly caused by drugs. There is a paucity of studies on this condition in the country, and to the researcher's knowledge, no study was ever conducted at Pietersburg Hospital, Limpopo Province.

Objectives: To describe the clinical characteristics, evaluate management outcomes and determine associations between demographic factors and clinical characteristics of disease severity and management outcomes of patients with SJS/TEN at Pietersburg Hospital.

Methods: The study was a comprehensive retrospective cross-sectional review of medical records of SJS/TEN patients, who were diagnosed by dermatologists, at Pietersburg Hospital from January 2018 to December 2022. Descriptive statistics and statistical tests were used to analyse the data.

Results: The sample consisted of 43 African patients, 34.9% were male and 65.1% female, with an average age of 39 ± 23 years. Patients with co-morbidities such as HIV, hypertension, and epilepsy accounted for 34.9% of the participants. Antibiotics and antiretrovirals drug groups commonly caused the disease, each accounting for 19% of cases. Allopurinol (14.3%) was identified as the commonest culprit, followed by trimethoprim-sulfamethoxazole (9.3%). Most patients (37.2%) had more than 30% and a SCORTEN score of 2 (34.9%). Older age was significantly associated with diabetes mellitus ($p=0.003$), HIV ($p=0.024$) and hypertension ($p<0.001$). Some SCORTEN parameters were significantly associated with age, which was also significantly associated with sepsis, acute renal failure and hyperkalaemia ($p<0.05$). The mortality rate was 13.9%, with factors such as disease severity, correlating with increased risk.

Conclusion: This study provided a comprehensive review of the clinical characteristics and treatment outcomes of patients with SJS/TEN. The findings underscore the need for prompt diagnosis, identification of causative agents, and tailored therapeutic approaches to improve patient outcomes.

Keywords: Drugs, Mortality, Severe cutaneous adverse reaction, Stevens-Johnson syndrome, Toxic epidermal necrolysis, Severity-of-illness score for toxic epidermal necrolysis, Treatment outcomes (SCORTEN).

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DEFINITION OF CONCEPTS

Stevens-Johnson syndrome is an adverse hypersensitivity reaction that affects the skin and mucous membranes with epidermal detachment lower than 10% of total body surface area (Lerch, Mainetti, Beretta-Piccoli and Harr, 2018).

In this study, it means a mucocutaneous disease resulting from a hypersensitivity reaction with total body surface area of denuded skin lower than 10%.

Stevens-Johnson syndrome/Toxic epidermal necrolysis overlap is a hypersensitivity reaction characterised by acute necrosis of the epidermis and mucous membranes resulting in epidermal denudation between 10 and 30% of the total body surface area (Rozenbajgier, Wójcik-Grudzień, Pawłowska and Ozga-Stachurska, 2022).

In this study, it means mucocutaneous disease resulting from a hypersensitivity reaction with a total body surface area of denuded skin between 10 and 30%.

Toxic epidermal necrolysis is defined as a hypersensitivity adverse reaction with phenotypic clinical presentation similar to that of Stevens-Johnson syndrome characterised by area of denuded skin of more than 30% (Su, Mockenhaupt, Wolkenstein, Dunant, Le Gouvello et al., 2017).

In this study, it means mucocutaneous adverse hypersensitivity reaction, with a total body surface area of denuded skin of more than 30%.

Stevens-Johnson syndrome/Toxic epidermal necrolysis is a singular term used to describe a spectrum of one disease process which entails three entities; Stevens-Johnson syndrome, Stevens-Johnson syndrome/Toxic epidermal necrolysis overlap and Toxic epidermal necrolysis (Coias, Abbas and Cardones, 2019).

In this study, it means a spectrum of Stevens-Johnson syndrome, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap and toxic epidermal necrolysis.

LIST OF ABBREVIATIONS

CRISTEN	Clinical Risk Score for Toxic Epidermal Necrolysis
IVIg	Intravenous Immunoglobulin
DIC	Disseminated Intravascular Coagulation
DILI	Drug-Induced Liver Injury
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
NHLS	National Health Laboratory Service
NSAIDS	Non- Steroidal Anti-Inflammatory Drugs
SCORTEN	Severity-of-illness Score for Toxic Epidermal Necrolysis
SJS	Stevens-Johnson Syndrome
SJS/TEN	Stevens-Johnson Syndrome, Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis overlap and Toxic Epidermal Necrolysis
SJS/TEN overlap	Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis overlap
TBSA	Total Body Surface Area
TEN	Toxic Epidermal Necrolysis
TLD	Tenofovir, Lamivudine and Dolutegravir
TREC	Turfloop Research and Ethics Committee

CHAPTER ONE

INTRODUCTION AND BACKGROUND

1.1. INTRODUCTION

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are uncommon life threatening mucocutaneous adverse reactions (Hama, Sunaga, Ochiai, Kokaze, Watanabe et al., 2023). SJS/TEN is a potentially fatal dermatologic emergency (Farooq, Abbas, Ahmad and Manzoor, 2023). These two conditions are two extremes of a spectrum of a hypersensitivity skin reaction secondary to severe epidermal necrosis (Garg, Buttar, Bhat, Ainur, Priya et al, 2023; Farooq et al., 2023). The prevalence of SJS/TEN is low (van Nispen, Long and Koyfman, 2024). Commonly, the reactions are triggered by drug exposure but may also be triggered by infections (Yang, Hu, Zhang, Huang, Zhang et al., 2018). TEN, also known as Lyell's syndrome, is a more serious and aggressive form of Stevens-Johnson syndrome involving more than 30% of the total body surface area (TBSA) (Dhirawani, Asrani, Taank and Singha, 2019). SJS/TEN is one of the frequent causes of dermatology emergency presentation and resultant hospital admission (Jack, Spence, Nichols, Chong, Williams et al., 2011). The consequence of SJS/TEN include significant morbidity and mortality (Frantz, Huang, Are and Motaparathi, 2021).

The disease spectrum is classified according to the TBSA of epidermal detachment into SJS, Stevens-Johnson syndrome/toxic epidermal necrolysis overlap (SJS/TEN overlap) and TEN (Lucia, Silvia, Paolo, Roberto, Fabio et al., 2019). In SJS, epidermal detachment is lower than 10% of the TBSA, between 10% and 30% is classified as SJS/TEN overlap and more than 30% detachment designated as TEN (Bastuji-Garin, Rzany, Stern, Shear, Naldi et al., 1993). The singular term Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is used to describe this entity (Coias et al., 2019).

The pathophysiology of SJS/TEN is known to be driven by cytotoxic T cells and related effector molecules (Kinoshita, Ogawa, Hama, Ujiie and Hasegawa, 2021), through perforin-granzyme B or Fas-FasL interactions and granulysin (Diana, Rahayu, Wirawan, Dhamayanti, Yuliarto et al., 2020). In most cases, a type IV hypersensitivity reaction to drugs prescribed for acute conditions is thought to underlie the pathophysiology of this disease continuum (Shanbhag, Chodosh, Fathy,

Goverman, Mitchell et al., 2020). Slow acetylation of drugs has been suggested as another pathophysiology of SJS/TEN (Diana, Rahayu, Wirawan, Dhamayanti, Yuliarto et al., 2020). At a microscopic level, epidermal necrolysis resembles mass keratinocyte cell death through apoptosis. Cellular stress, intracellular cytokines and DNA damage are stimuli that can induce apoptosis.

The study profiled the clinical characteristics of patients, evaluated the severity of TEN using SCORTEN and management outcomes of patients. Associations between variables were also determined. This study uncovered the most commonly implicated drugs as well as treatment outcomes, which will influence management protocols. It may also assist in early diagnosis and timeous referral to well-equipped hospitals, and may improve overall care of affected patients.

1.2 RESEARCH PROBLEM

SJS/TEN is commonly caused by drug ingestion in predisposed individuals. However, the researcher, a dermatology registrar at Pietersburg Hospital, observed that some patients gave a history of prior ingestion of traditional herbal medicines and religious preparations prior to the onset of the disease. Okaiyeto and Oguntibeju (2021) found that African herbal medicines were implicated in a minority of cases, and this may well be the case in SJS/TEN patients seen at Pietersburg Hospital. Despite the disease spectrum being associated with high morbidity and mortality (Kridin, Brügggen, Chua, Bygum, Walsh et al., 2021), the researcher has not come across any published studies on SJS/TEN at Pietersburg Hospital and there is a paucity of publications on the spectrum in South Africa in general. In addition, some patients are admitted to Intensive Care Unit (ICU) and managed with utmost care but still demise. Occasionally, a patient presents with limited skin disease, but still succumb to septicaemia.

1.3 PURPOSE OF THE STUDY

1.3.1 Research Aim

The aim of the study was to describe the clinical characteristics and evaluate treatment outcomes of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis.

1.3.2 Research objectives

To describe the clinical characteristics of SJS/TEN in patients at Pietersburg Hospital.

To evaluate the severity of TEN using SCORTEN in patients admitted with SJS/TEN at Pietersburg Hospital.

To characterise management outcomes of patients with SJS/TEN at Pietersburg Hospital.

To determine associations between demographic factors and clinical characteristics, disease severity and management outcomes of patients with SJS/TEN at Pietersburg Hospital.

1.4 RESEARCH QUESTIONS

What are the clinical characteristics of SJS/TEN in patients admitted to Pietersburg Hospital?

What is the severity of TEN using SCORTEN among patients admitted with SJS/TEN at Pietersburg Hospital?

What are the management outcomes of patients with SJS/TEN at Pietersburg Hospital?

What is the association between demographic factors and clinical characteristics, disease severity and management outcomes of patients with SJS/TEN at Pietersburg Hospital?

1.5 RESEARCH METHODOLOGY

1.5.1 Research design

The research was a cross-sectional study, retrospectively analysing hospital records of patients admitted with SJS/TEN at Pietersburg Hospital. Data was collected from hospital records of patients admitted to the hospital from January 2018 to December 2022 was analysed.

1.5.2 Population and Sampling

A census sampling method was applied as all files belonging to patients with a diagnosis of SJS/TEN from 01 January 2018 to 31 December 2022 were used in the study. Census sampling is a systemic representative method that collects and records data from a target population (Blanche, Blanche, Durrheim, and Painter, 2006). Census sampling method considers the entire population as the sample of which it is suitable only when population size is very small. Its accuracy is precise and for this reason, it is considered very suitable for medical research (Nanjundeswaraswamy and Divakar, 2021). From 01 January 2018 to 31 December 2022, a total number of patients with SJS/TEN admitted to Pietersburg hospital was 43 and therefore the sample size was 43.

1.5.3 Data collection

A self-developed data collection sheet was used to collect all the required information. The tool was developed based on literature review and all information was recorded by the researcher. It was composed of three sections, namely, a) Demographic data, b) Clinical data and disease severity and c), Management and complications.

1.5.4 Data analysis

Data was captured into Microsoft Access, extracted into a Microsoft Excel Spreadsheet and then exported to Python Programming Software, where it was analysed. Categorical variables were reported using frequency distribution tables, and for numerical variables, means, standard deviation and range. Where necessary, pie charts, and bar graphs were used. The Chi-squared test or Fisher's exact test was used to determine associations between outcome variable and demographic and clinical variables.

1.5.5 Reliability, validity and objectivity

1.5.5.1 Reliability

Reliability is defined as the researcher's ability to collect and record data accurately (Creswell, 2009). The information in the files was provided by dermatologists who are experts in diagnosis and management of patients with SJS/TEN. The information was extracted by the researcher, who is a registrar in dermatology.

1.5.5.2 Validity

Validity refers to the extent to which a data collection tool measures what it is supposed to measure (Polit and Beck, 2006). The data collection tool used was self-developed based on extensive literature review. All aspects of the topic intended to be measured were included in the measuring instrument. The data collection tool was also reviewed by a consultant dermatologist who is an expert in the field. A pilot study was conducted to enhance validity.

1.5.5.3 Objectivity

Objectivity refers to the extent to which biases are eliminated and value free information is gathered (Frambach, van der Vleuten and Durning, 2013). The researcher was objective when collecting data and refrained from manipulating information from patient files.

1.5.6 Bias

Bias refers to an influence that leads to deviation from the truth that may affect the quality of evidence (Pannucci and Wilkins, 2010). The researcher ensured that all information was recorded accurately without deviating from the truth and that all reporting of findings was done precisely by working together with a statistician.

1.6 ETHICAL CONSIDERATIONS

Ethical clearance

Before commencing the research study, ethical clearance certificates were obtained from Turfloop Research Ethics Committee and Limpopo Department of Health.

Permission to conduct the study

The study only commenced after permission was granted by Pietersburg Hospital Clinical Executive Director.

Anonymity and confidentiality

Anonymity and confidentiality of the data collected was preserved at all times. Numbered codes were utilised at all times. No names, surnames nor hospital record numbers were used to identify patients. This ensured that the patient's identity is protected. The information collected was treated as confidential and was kept in a locked cupboard.

Data storage and security

To ensure that scientific data was not interfered with, the collected data was filed in a lever arch file and stored in a secured locked cupboard in the dermatology department, and only the researcher and supervisor had access to the cupboard keys. The electronic captured data was saved in a computer which, only the researcher and the supervisor had a unique password to access the information.

1.7 SIGNIFICANCE OF PROPOSED RESEARCH

This study will provide health professionals with knowledge of the clinical characteristics and associations of SJS/TEN in our hospital setting, and thereby improve patient care. The findings will guide and impact policies, standard operating procedures, treatment guidelines and health promotion strategies. This will also contribute to the body of knowledge on SJS/TEN in the country.

1.8 OUTLINE OF THE STUDY

The study is presented as follows:

Chapter one introduces the study and addresses key concepts, the research problem, purpose of the study, research questions, methodology summary, ethical considerations and significance of the study.

Chapter two entails literature review with major focus on clinical characteristics, SCORTEN and management of patients with SJS/TEN. It also covers literature on associations between demographic factors and clinical characteristics, disease severity and management outcomes of patients with SJS/TEN.

Chapter three encompasses research methodology and design. The research study site, population and sampling, data collection method and data collection instrument are discussed, followed by data analysis and ethical considerations.

Chapter four covers data management and analysis, reports research results presented in tables, graphs and pie charts, and discusses the overview of research findings.

Chapter five reports the focuses on the interpretation of the research findings and recommendations as informed by the findings. The recommendations and study limitations are also alluded to in the chapter.

In Chapter 6, a summary of chapters one through six is provided and conclusions regarding research questions are made.

CHAPTER TWO

LITERATURE REVIEW

2.1 INTRODUCTION

Literature review is a critical evaluation, analysis and synthesis of academic material on a specific topic placed in the researcher's area of interest. The process includes reviewing available information on a topic (Greetham, 2020). Electronic database searches were made online through various search engines such as Google Scholar, ClinicalKey, PubMed and Sciencedirect. Key words used for this literature review included "Stevens-Johnson syndrome", "toxic epidermal necrolysis", "severity-of-illness score for toxic epidermal necrolysis", "severe cutaneous adverse reaction", "clinical characteristics", "treatment outcomes and mortality", and "causative agents".

2.2 PREVALENCE OF SJS/TEN

The global incidence rate of SJS/TEN was estimated to be 0.4-1.3 persons per million yearly in the year 2005 (Fakoya, Omenyi, Anthony, Anthony, Etti et al., 2018). In another study, the worldwide incidence was reported as 0.4 to 6 cases per million persons per year (Tangamornsuksan, Chaikunapruk, Somkrua, Lohitnavy and Tassaneeyakul, 2013). The global incidence of SJS and TEN has also been approximated to be 1–6 and 0.4–1.2 cases per million person years, respectively (Irungu, Nyamu and Opanga, 2017).

In Europe, countries like Germany and France, the incidence varies between 1 to 3 and 1 to 1.4 cases per 1 000 000 inhabitants/year, respectively (Velasco-Tirado, Alonso-Sardón, Cosano-Quero, Romero-Alegría, Sánchez-los, et al., 2018). In Korea, the incidence of SJS and TEN was found to be 3.96-5.03 and 0.94-1.45 per million respectively (Yang, Lee, Kim, Kim and Kim et al., 2016).

In a Brazilian study, 86 patients with SJS/TEN were hospitalised over a period of 15 years, resulting in an average of 5.7 patients per year (Arantes, Reis, Novaes, Carvalho, Göttems et al., 2017). SJS/TEN prevalence in Massachusetts General Hospital between 1983 and 2013 was 375 per million. In a study done in Kenya, it

was found that from June 2006 to June 2016, 115 patients were hospitalised with SJS/TEN (Irungu et al., 2017).

The prevalence of SJS and TEN in Nigeria was 284 cases within 14 years, which amounts to an average frequency of 20 cases per year. A multicentre sub-Saharan African study and a Kenyan study reported a prevalence of 11–16 cases per year. This result further corroborate the extreme rarity or under-reporting of SJS/TEN (Oshikoya, Ogunyinka, Ogar, Abiola Ibrahim et al., 2020). Haitembu, Porter, Basera, Hickmann, Dlamini et al. (2021) aver that the prevalence of SJS/TEN in South Africa and African continent is unknown.

2.3 CLINICAL CHARACTERISTICS OF SJS/TEN

2.3.1 Clinical features

SJS/TEN spectrum consists of life-threatening dermatologic emergency conditions that are frequently induced by drugs and less frequently, by infections (Farooq et al., 2023). Often, SJS/TEN is preceded by prodromal symptoms (Stătescu et al., 2017). The initial presentation includes symptoms such as dysphagia, stinging eyes and fever. Symptoms usually present within 8 weeks of culprit drug ingestion, with most cases appearing between 4 days and 4 weeks of taking the offending drug (Charlton, Harris, Phan, Mewton and Jackson et al., 2020).

The time interval between the onset of symptoms and patient presentation to hospital varies due to various factors (Thakur, Vinay, Kumar, Choudhary, Kumar et al., 2021). A report from Thakur et al. (2021) states that there is no statistically significant difference in delay in hospital presentation, number of mucosa involved, and length of hospital stay between patients who demise and those that survive (Thakur et al., 2021).

Characteristic cutaneous findings are coalescing, dusky red or erythematous macules with purpuric centres, resulting in widespread skin and mucous membrane involvement. Due to extensive necrosis, detachment of the epidermis occurs together with blister formation (Yoo, Kim, Shin and Kim, 2022). Blistering occurs because of accumulation of fluid under the epidermis due to varying degrees of epidermal detachment (Lucia et al., 2019). These skin lesions tend to appear first on

the face and thorax before symmetrical involvement of the rest of the body (Spillers et al., 2023).

Almost all cases of SJS/TEN show mucosal involvement, predominantly the conjunctivae and oral mucosae. Involvement of the oral and genital mucosae is commonly preceded by inflammation and dryness. Subsequently, haemorrhagic erosions occur in these areas, including the nasal cavity, where pseudomembranes are apt to form (Brockow, Ardern-Jones, Mockenhaupt, Aberer, Barbaud et al, 2019). The respiratory, gastrointestinal and genitourinary systems may be affected (Stătescu, Constantin, Morariu and Solovăstru, 2017; Spillers, Luther, Talbot, Ly, Downs et al., 2023).

Nikolsky's sign serves as a very important positive clinical diagnostic tool used in SJS/TEN. It is pathognomonic in various skin disorders such as pemphigus vulgaris, staphylococcal scalded skin syndrome (Arshad and Jawed, 2022). The sign is demonstrated by applying a tangential pressure on the edge of the blister with resultant separation of the superficial epidermis (Spillers et al., 2023). The underlying pathophysiology of Nikolsky's sign in SJS/TEN is necrosis as opposed to acantholysis which is seen in the “true Nikolsky's sign”. It can only be demonstrated in erythematous and affected areas. For this reason, it is sub-characterised as “pseudo Nikolsky's sign” in SJS/TEN (Maity, Banerjee, Sinha, Jha, Ghosh et al., 2020). Epidermal detachment is less than 10% of the TBSA in SJS, 10% to 30% in SJS/TEN overlap and more than 30% in TEN (Bastuji-Garin, Rzany, Stern, Shear, Naldi et al., 1993).

Sepsis is the most common complication and it is associated with increased mortality (Kannenberg, Jordaan, Koegelenberg, Von Groote-Bidlingmaier and Visser, 2012). Eroded areas become secondarily infected with, among others, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Acinetobacter* species.

2.3.2 Evaluation of severity of TEN

To measure the disease severity and predict mortality in TEN patients, a Severity-of-illness Score for Toxic Epidermal Necrolysis (SCORTEN) is performed within the first 24 hours of hospitalisation (Fouchard, Bertocchi, Roujeau, Revuz, Wolkenstein et al.,

2000; Guégan, Bastuji-Garin, Poszepczynska-Guigné, Roujeau, and Revuz, 2006). SCORTEN consists of seven parameters of equal weight, which includes patient age 40 years and above, presence of malignancy, tachycardia 120 beats per minute and above, initial extent of epidermal detachment above 10%, serum glucose above 14 mmol/L, serum urea above 10 mmol/L and bicarbonate level below 20 mmol/L (Seecof et al., 2019) (Table 2.1). No individual SCORTEN parameter is significant in death prediction (Strużyna, Surowiecka, Korzeniowski, Korulczyk, Drozd et al., 2022).

Prognostic factor	Score
Age > 40 years	1
Malignancy	1
Tachycardia >120 b/min	1
TBSA >10%	1
Serum urea > 10mmol/L	1
Serum glucose > 14mmol/L	1
Bicarbonate < 20mmol/L	1
SCORTEN Score	Mortality (%)
0-1	3
2	12
3	35
4	58
≥5	90

Table 2.1 Severity of illness score for toxic epidermal necrolysis (SCORTEN) (Fouchard et al., 2000)

An increase in number of prognostic factors present is directly proportional to the SCORTEN score and mortality rate (Fouchard et al., 2000). Bastuji-Garin et al. showed that mortality is notably higher in patients with a SCORTEN level of two and more (Fouchard et al., 2000). However, a recent study recognised a score over four as a cut-off point for sensitivity and specificity evaluation (Strużyna et al., 2022). These values vary significantly and therefore no consensus has been reached regarding the cut-off point for sensitivity and specificity.

Serial analysis of SCORTEN was found to be better in predicting mortality than analysis performed only on day one (Bansal, Garg, Sardana and Sarkar, 2015). A study to assess accuracy of SCORTEN to predict mortality have shown that its performance is excellent in the first five days of hospital admission and is best on day three (Seecof and Liantonio, 2019).

SCORTEN has proved to be a good predictor of mortality in patients with TEN (Zhang, Lan, Qi, Shuai, Hou et al., 2022). Procalcitonin above 0.67ng/ml and red cell distribution width were further suggested as potential prognostic factors for in-hospital mortality in patients with SJS/TEN. Incorporating the two parameters to SCORTEN has shown to have a better discriminatory and predictive power than SCORTEN alone (Zhang et al., 2022).

A Clinical Risk Score for TEN (CRISTEN) has been developed to predict mortality in patients with SJS/TEN in the early stages based only on clinical findings, whilst other prediction scores such as SCORTEN require blood tests (Hama et al., 2023). CRISTEN is comprised of ten clinical parameters which are age of ≥ 65 years, $\geq 10\%$ TBSA involvement, the use of systemic corticosteroid therapy before the onset of SJS/TEN, the use of antibiotics as culprit drugs, and mucosal damage affecting the buccal, ocular and genital mucosa. Diabetes mellitus, renal impairment, cardiovascular disease, malignant neoplasm, and bacterial infection are included as underlying diseases (Hama et al., 2023).

2.4 RISK FACTORS FOR SJS/TEN

A study has shown that risk factors for developing SJS/TEN include advanced age, human immunodeficiency virus (HIV) infection and female gender (Velasco-Tirado et al., 2018). In a study conducted in Rome, S. Eugenio Hospital, the average age at diagnosis was 44.8 years (range 4-94) (Velasco-Tirado et al., 2018). Chateau et al. found that 32 out of 36 patients were female in a study that was performed in Pietermaritzburg, South Africa (Chateau, Dlova, Dawood and Aldous, 2019). In a Brazilian study, it was also found that the majority of SJS/TEN patients admitted between 1999 and 2014 were female (Arantes et al., 2017).

SJS/TEN occurs in all races (Imatoh and Saito, 2021), however, the Black race predominance has been previously noted (Duplisea, Roberson, Chrisco, Strassle, Williams et al., 2021). Frey et al. (2017) reported that Black and Asian races were at

2-fold risk of SJS/TEN when compared with Whites (Frey, Jossi, Bodmer, Bircher, Jick, et al., 2017). Duplisea et al. (2022) observed a predominance of Black patients reacting to allopurinol and further suggested HLA-B*5801 screening before scripting it for black patients (Duplisea, Ziemer, Laughon and Williams, 2022).

Drugs are the commonest cause of SJS/TEN (Stern and Divito, 2017), which mostly present within the first 8 weeks after the introduction of the implicated drug (Alerhand, Cassella, and Koyfman, 2016). The most implicated drug groups include antibiotics, antiepileptics, and nonsteroidal anti-inflammatory drugs (NSAIDs) (Carrasquillo, Santiago-Vazquez, Cardona, Cruz-Manzano and Figueroa, 2019). Trimethoprim-sulfamethoxazole, a sulphonamide, was identified as the frequently offending antibiotic (Carrasquillo et al., 2019; Moosa, 2021).

In South Africa, the commonest causative agents are sulphonamides, anticonvulsants, antiretrovirals (Nevirapine) and antituberculosis drugs (Lehloenya, 2007). Tenofovir alone was reported as the cause of SJS in a patient with acute hepatitis B (Xavier, Athira, Mathew, Basheer, Rahana, 2020). Nonsteroidal anti-inflammatory drugs (NSAIDS) were found to cause a higher TBSA exfoliation and TEN (Yoo et al., 2022). TBSA was notably lower in antiepileptic drug group, and most deaths resulted from antibiotics and allopurinol (Yoo et al., 2022). This signifies a wide list of causative drugs for SJS/TEN.

In some instances, patients are on more than one drug or combination drugs (Noguchi, Takaoka, Hayashi, Tachi and Teramachi, 2020). This poses a difficulty in identifying the definitive culprit drug (Milosavljević, Pejčić and Milosavljević, 2021). Recently, a patch test and/or lymphocyte transformation test have been employed to identify a definite causative drug (Watanabe, Go, Saigusa, Takamura, Watanabe et al., 2021). Published reports suggest that patch testing in SJS/TEN is helpful and safe, with a good positivity rate for various drug groups (Novack, D.E., Braskett, M., Worswick, S.D. and Adler, B.L., 2023).

In a study by Li et al. (2006) in China, traditional Chinese medicines were found to be among the most common cause of SJS/TEN. Yang et al. (2018) reported that Chinese patent medicines were implicated in 5.4% of patients in China, 7.5% of patients in Singapore, 3.6% in Philippines and 2.5% in Malaysia. In 2021, three

cases of SJS following the use of African herbal medicines were reported (Okaiyeto et al., 2021).

Less commonly, infections such as *Mycoplasma pneumonia* and cytomegalovirus cause these conditions (Wetter and Camilleri, 2010). A study done in Kenya reported that infections such as HIV, Herpes simplex virus type 1 (HSV1) and *mycoplasma pneumonia* caused SJS/TEN in 5.2% of the patients (Irungu et al., 2017).

In a South African study conducted in Cape Town, SJS/TEN was found to have a higher incidence in persons infected with HIV (Knight, Muloiwa, Dlamini, and Lehloenya, 2014). Out of 86 patients, 78% (67/86) were infected with HIV and the commonest co-morbidity was *Mycobacterium tuberculosis* infection (Knight et al., 2014). Patients with diabetes mellitus and obesity who develop SJS/TEN are said to have worse outcomes and a higher mortality rate compared to patient who develop SJS/TEN with no co-morbidities (Chandran, Hink, Kahn, and Ozhathil, 2023).

2.5 MANAGEMENT OF SJS/TEN

A multidisciplinary approach is crucial in managing patients with SJS/TEN (Mogole et al., 2016). The initial important step is identifying and stopping the implicated drug (da Silva, Novaes, Göttems and Novaes, 2018). Currently, supportive management is recommended over pharmacotherapy as there is no consensus on efficient pharmacologic therapy to stop the disease progression and reduce mortality (Lehloenya, Isaacs, Nyika, Dhana and Knight, 2021).

Supportive care entails wound care, ophthalmological management, management of other mucosal involvement, nutritional support, hypothermia prevention, fluid resuscitation, infection prevention, pain management and other relevant measures (Brüggen, Le, Walsh, Toussi, de Prost et al., 2021).

Among others, pharmacologic treatments that have been used are systemic corticosteroids, intravenous immunoglobulins (IVIg), cyclosporine, thalidomide and TNF-alpha blockers (Gupta, Martin, Agarwal, D'Souza, Das et al., 2016).

Corticosteroids are efficacious when used in high doses in the early stage of SJS/TEN and in lower doses in the later stages of the disease (Creamer, Walsh, Dziewulski, Exton, Lee et al., 2016). A recent study showed that cyclosporine is the

most efficacious treatment for SJS, and a combination of corticosteroids and IVIg is most effective for SJS/TEN overlap and TEN (Frantz et al., 2021).

In a study by Chateau et al. (2019), HIV-infected patients had a good survival rate (97%) when they were treated with IVIg and systemic corticosteroids whilst Ye et al. (2016) suggested that IVIg combined with corticosteroid does not significantly reduce mortality but could reduce recovery period for SJS and TEN (Ye, Zhang and Zhu, 2016).

2.6 TREATMENT OUTCOMES AND MORTALITY IN SJS/TEN

The estimated worldwide mortality rate is between 5-12% for SJS, 30% for TEN and 33% for SJS/TEN spectrum (Tangamornsuksan et al., 2013). Chantaphakul, Sanon and Klaewsongkram (2015) also found that mortality was higher in TEN than in SJS and SJS/TEN overlap. Amongst others, infection was the major cause of death and morbidity in these patients (Diao, Thapa, Ran, Ran, and Lv, 2020). Mortality rate tends to be higher in patients with co-morbidities and increased age (Mockenhaupt, 2014).

Patients with SJS/TEN have a wide range of complications, which includes but not limited to electrolyte disturbance, drug-induced liver injury, infections, hypoalbuminemia, leucocytosis and leukopenia (Yang, Shou, Li, Zhu, Yang et al., 2020; Thakur, Vinay, Kumar, Choudhary, Kumar et al., 2021; Girish, Hussain and Balkrishna, 2023). Renal and liver function tests may be normal at the time of hospital admission and become abnormal in the course of hospital stay (El-Hamd, El-Dawla and Abd Elmagid, 2017).

A study that was done in Cape Town showed that SJS/TEN-associated mortality was not higher in HIV-infected pregnant women (Knight, Todd, Muloiwa, Matjila and Lehloenya, 2015). Hospital acquired hypernatremia was associated with increased mortality in TEN (Namdar, von Wild, Siemers, Stollwerck, Stang et al., 2010). Arantes et al. (2017) found that the average length of stay in hospital was 10 days, with one patient admitted for over 40 days.

2.7 ASSOCIATIONS BETWEEN DEMOGRAPHIC FACTORS AND CLINICAL CHARACTERISTICS, DISEASE SEVERITY AND MANAGEMENT OUTCOMES

The female gender is associated with longer duration of hospital stay (Duplisea, Ziemer, Laughon and Williams, 2022). A study done by Duplisea et al. (2022) found that female patients had a median length of stay of 21 days compared to 11 days for males.

Irungu et al. (2017) found that there was no association between patient's gender, age and SJS/TEN classes (Irungu et al., 2017). The researcher couldn't find literature reporting other associations between demographic factors and clinical characteristics, disease severity and management outcomes.

CHAPTER THREE

RESEARCH METHODOLOGY

3.1 INTRODUCTION

The primary focus of the preceding chapter was on the theoretical framework of the study and literature review. This chapter will concentrate on, among others, research methodology, research design, sampling methods, data collection, data collection instrument and how the data was collected, summarised and analysed. Ethical issues related to the study are discussed.

3.2 RESEARCH METHOD

A quantitative cross-sectional paradigm was adopted and employed to achieve the research objectives and to answer the research questions of the study. The choice of quantitative study design was influenced by the nature of the research which analyses numerical data. Data was retrospectively collected from the hospital records of patients who were admitted to Pietersburg Hospital from 01 January 2018 to 31 December 2022.

3.3 RESEARCH DESIGN

3.3.1 Study Population and Sampling

3.3.1.1 Study Population and Site

A study population is a portion of the total target population, from which the sample is selected (Johnson, 2018). The target population was all patients with SJS/TEN admitted to Pietersburg Hospital from 01 January 2018 to 31 December 2022.

The study was conducted at Pietersburg Provincial Hospital, which is a state hospital in Polokwane, Limpopo province, South Africa (Figure 3.1). It offers tertiary services to all regional and district hospitals in the Limpopo Province. It has 500 bed capacity and is a training facility for the University of Limpopo. The dermatology department is

one of the clinical departments at the hospital. The department was established as a clinical and training department in 2006 and started training registrars in 2014.



Figure 3.1 Area map of research site

(Kunene, Albers, Lucas, Banwell,

Mathee et al., 2017).

3.3.1.2 Sampling

A census sampling method was used as all files belonging to in-patients with a diagnosis of SJS/TEN from 01 January 2018 to 31 December 2022 were included in the study. A census involves collecting data from every individual or unit in the entire target population rather than from a subset (sample) of the population (Daniel, 2012).

3.3.1.3 Ethical issues related to sampling

Reliability, validity and objectivity

Reliability is defined as the researcher's ability to collect and record data accurately (Creswell, 2009). The information in the files is provided by dermatologists who are experts in diagnosis and management of patients with SJS/TEN. The information was extracted from the medical records by the researcher, who is a registrar in dermatology.

Validity refers to the extent to which observed results of a study can be applied to the manipulated independent variables (Brink, Van der Walt and Van Rensburg, 2012). To ensure the validity of this study, a census sampling method was applied. All patients that were admitted with SJS/TEN meeting the inclusion criteria within the study site and the study period were included in the sample.

Objectivity refers to the extent to which biases are eliminated and value-free information is gathered (Frambach, van der Vleuten & Durning, 2013). The researcher ensured objectivity by including all patients in the sample, leaving out those that did not meet the inclusion criteria.

Bias refers to an influence that leads to deviation from the truth that may affect the quality of evidence (Pannucci and Wilkins, 2010). The researcher used a census sampling method to prevent selection bias.

3.3.1.4 Sample Size

A total of 47 patient medical records was selected from the departmental statistics form. In two patients, the final diagnoses on the medical records was not in keeping with SJS/TEN. In another two patients, the SJS/TEN was already resolving at the time of admission, and the final sample size was 43.

Inclusion Criteria

All records of patients admitted to Pietersburg Hospital with SJS/TEN from 01 January 2018 to 31 December 2022 were included in the study. Only patient records with a definite diagnosis of SJS/TEN confirmed by a dermatologist were utilised.

Exclusion Criteria

All patient records with incomplete information and diagnosed with SJS/TEN before January 2018 and after 31 December 2022, were excluded from the study.

3.3.2 Data collection

3.3.2.1 Data collection approach and method

Data collection is a critical phase in the research process that involves systematically gathering information to answer research questions, test hypotheses, or gain insights

into a specific topic (Jupp and Sapsford, 2006). Information on the target population was obtained from departmental daily statistics files and patient registration forms. The information was used to retrieve hospital files. All files of SJS/TEN patients that fell within the period of the study were retrieved. Patient's hospital records were retrieved from the records department following application for file retrieval. The records were kept safe in a locked cupboard in the dermatology department. Ten files at a time were retrieved and kept for a maximum of 10 days. Files with irrelevant information were taken back to records within a day. The name and hospital number on each file was verified, and the file was given a code. All coded files were double-checked for accuracy to avoid multiple or erroneous entries.

3.3.2.2 Development of data collection instrument

The data collection tool was a self-developed instrument based on extensive literature review. Before the data collection instrument was finalised, it was tested on five patients and was found to be suitable and no challenges were identified.

3.3.2.3 Characteristics of the data collection instrument

The data collection instrument was composed of three sections, namely, A) Demographic data, B) Clinical data and C) Management. Section A recorded demographic data comprising age, gender, pregnancy status and race. Section B recorded data on drug history, past history of allergies, co-morbidities, condition for which the patient was taking the drug, family history of drug reaction, duration between drug ingestion and onset of symptoms, duration of symptoms prior to hospital visit, prodromal symptoms, mucous membrane involvement, severity assessment, SCORTEN parameters and score, blood cultures and outcome. Section C recorded data on management of the patients, length of stay and complications.

3.3.2.4 Data collection process

Data was collected retrospectively on weekdays between 16h45 and 19h00. The researcher gathered information using departmental patient registration forms. From these sources, diagnoses of SJS, SJS/TEN overlap and TEN was searched and noted. Data was entered into a data collection instrument by the researcher. Data collected was double checked by allocated codes, age and sex to exclude

overlapping and repetition of patients. Data was then transferred manually into Microsoft Access by the researcher.

3.3.2.5 Ethical considerations related to data collection

Ethical clearance

Before commencing the research study, an ethical clearance certificate was obtained from the Turfloop Research and Ethics Committee (Annexure B).

Permission to conduct the study

The study commenced after permission was granted by Limpopo Department of Health (Annexure C) and Pietersburg Hospital Clinical Executive Director (Annexure D).

Anonymity and confidentiality

The anonymity and confidentiality of the data collected were preserved at all times. Names, surnames and hospital file numbers were not used and all files were coded to protect the identity of the patients. The information collected was kept in a locked cupboard, and only the researcher and the supervisor had access to the data.

Data storage and security

To ensure that scientific data is not corrupted or misused, the collected data was filed in a lever arch file and stored in a locked cupboard in the dermatology departmental office. Only the researcher and supervisor had access to the cupboard keys where the file was kept. The electronically captured data was saved in a computer and protected with a password.

3.3.3 Data analysis

Data was captured into Microsoft Access and extracted into a Microsoft Excel Spreadsheet and transported into the Python Programming Software where it was analysed. Categorical variables were reported using frequency distribution tables, and for numerical variables, range, means and standard deviation were used. Where necessary data was displayed in pie charts, and bar graphs. The Chi-squared test or Fisher's exact test was used to determine associations between outcome variable and demographic and clinical variables.

3.4 INTERNAL AND EXTERNAL VALIDITY OF THE STUDY

3.4.1 Internal validity

Internal validity is defined by Patino and Ferreira (2018) as the extent to which obtained results are accurate in the studied population and, thus, are not due to methodological errors. Internal validity was ascertained by ensuring that the data collection was done by the researcher who is a dermatology registrar and has vast knowledge in the researched topic. Additionally, a specialist dermatologist who is the researcher's supervisor ensured that the data collection tool was suitable to measure what it purports to measure through extensive experience in dermatology and literature review. A census sampling method was used to avoid selection bias and ensure internal validity.

3.4.2 External validity

External validity is defined as the extent to which a study results can be generalised to similar patients in a different setting (Patino et al., 2018). The patients in this study were all Africans, which does not ascertain external validity in other parts of the world and various race because race and genetic factors influence the occurrence of SJS/TEN.

3.5 CONCLUSION

This chapter described, inter alia, the study design, setting, sampling, data analysis, ethical considerations and validity of the study. The next chapter will present the results of the study.

CHAPTER 4

PRESENTATION AND INTERPRETATION OF THE RESULTS

4.1 INTRODUCTION

This chapter presents the research findings according to the research objectives. Data management and processes involving data analysis will be described first, and presentation of results will begin with the demographic data followed by findings relating to the following research objectives:

To describe the clinical characteristics of SJS/TEN in patients at Pietersburg Hospital.

To evaluate the severity of TEN using SCORTEN in patients admitted with SJS/TEN at Pietersburg Hospital.

To characterise management outcomes of patients with SJS/TEN at Pietersburg Hospital.

To determine associations between demographic factors and clinical characteristics, disease severity and management outcomes of patients with SJS/TEN at Pietersburg Hospital.

4.2 DATA MANAGEMENT AND ANALYSIS

Microsoft Access was used for the creation of a normalised table with defined relationships, ensuring data integrity and efficient organisation. Advanced data analysis tools within Microsoft Access, such as pivot tables, pivot charts, and calculated fields, were harnessed to extract meaningful information and gain insights from the collected data. The implementation of security measures, including user-level permissions, password protection, and encryption, was highlighted as critical for safeguarding the confidentiality and integrity of stored information. Chi-squared or Fisher's Exact test was used to test for associations. The level of statistical significance was set at a p-value < 0.05.

4.3 RESEARCH RESULTS

4.3.1 Demographic characteristics of participants

The demographic characteristics are presented in Figures 4.1, 4.2 and 4.3. The variables reported on are age, gender and pregnancy status. A total of 43 files were reviewed.

Age

The average age in years of study subjects was 39 ± 23 with the youngest being 23 days and the oldest 82 years old. The majority of patients were in the 21-40 (15/43; 35%) class (Figure 4.1), followed by 41-60 class (12/43, 28%). Patients aged 0-20 were 19% (8/43) and patients older than 60 years were 19% (8/43).

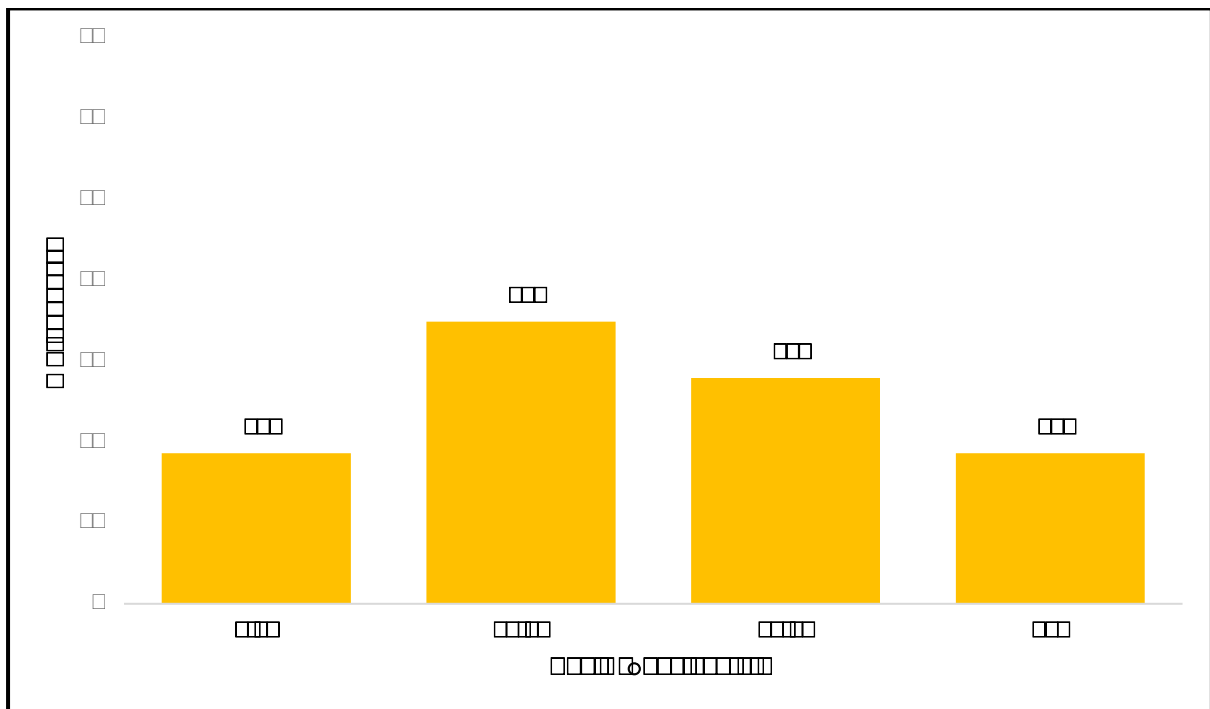


Figure 4.1: Age distribution

Gender

Most patients were female (Figure 4.2) with a prevalence of 65.1% (28/43) compared to males (15/43; 34.9%).

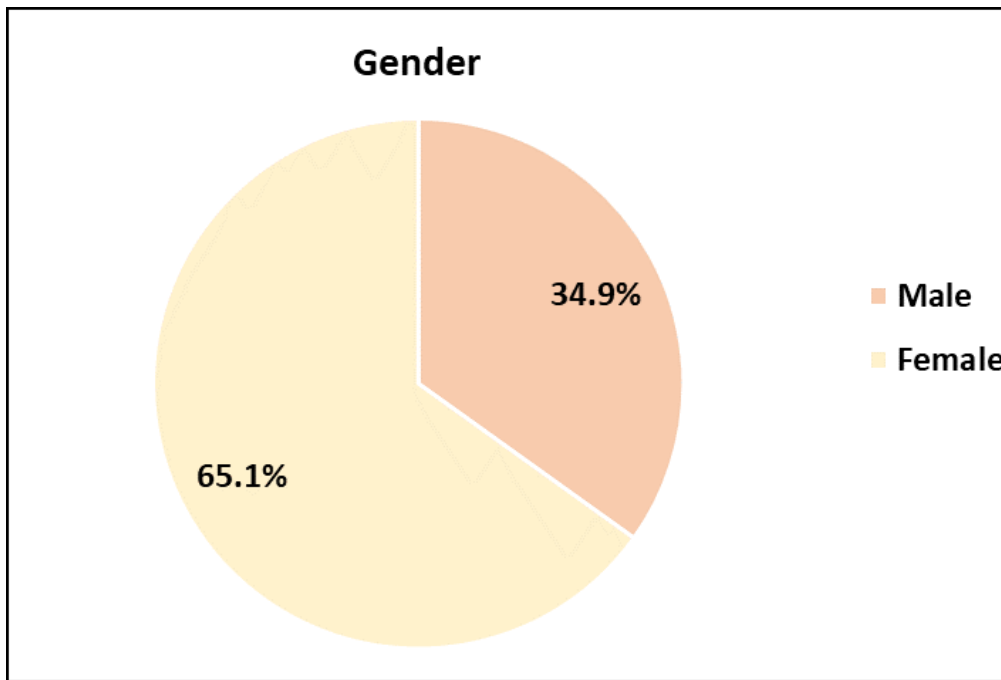


Figure 4.2 Gender distribution

Pregnancy status

Of the female patients, 3.6% (1/28) were pregnant (Figure 4.3).

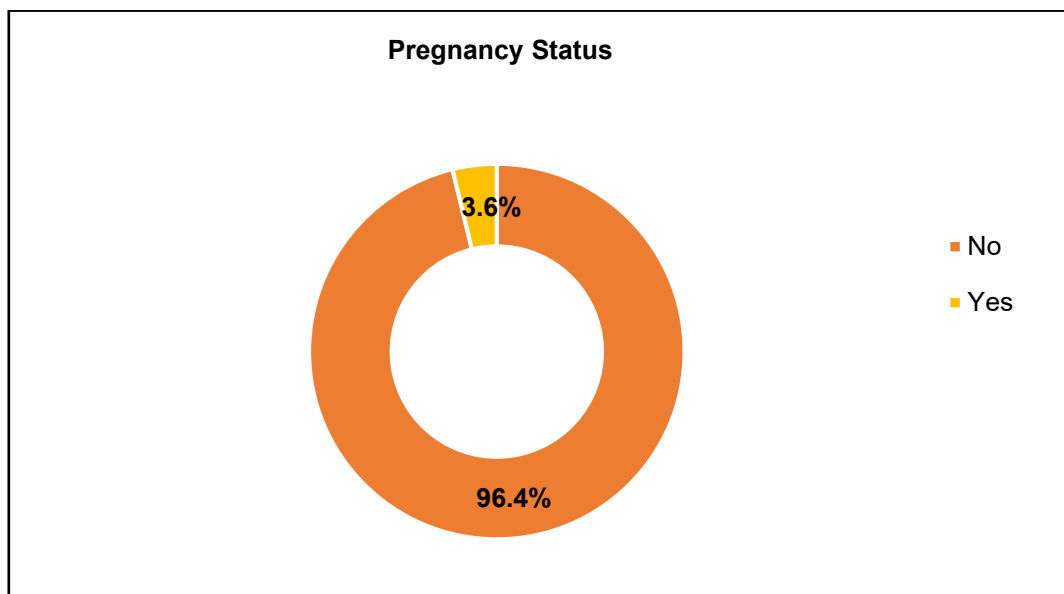


Figure 4.3 Pregnancy status of females (n=28)

4.3.2 Objectives

4.3.2.1 Objective 1: To describe the clinical characteristics of SJS/TEN in patients admitted to Pietersburg Hospital

Drug history

A commonly implicated drug class was found in 90.5% (39/43) patients, and in a minority of cases (4/43, 9.5%), the drug was unknown. Antibiotics and antiretrovirals each accounted for 19% (8/43) of the reactions. Antigout drug class was implicated in 14.0 % (6/43) of the cases. Results show that 16.3% (7/43) of patients had multiple possible agents from different drug classes. Of those with multiple possible agents, 57.1% (4/7) were exposed to antibiotics and antiretrovirals (Figure 4.4).



Figure 4.4 Drug classes implicated in SJS/TEN

Among individual drug causes, the highest percentage of cases fell under the category "unknown" (20.9%, 9/43) (Figure 4.5). Allopurinol was the most commonly implicated drug, comprising 14.0% (6/43) of cases, followed by trimethoprim-sulfamethoxazole (11.6%, 5/43) and nevirapine (7%, 3/43). Of note, herbal preparations such as aloe and grape seed oil were found among possible implicated agents causing SJS/TEN in 4.7% (2/43) of the patients.

A notable percentage of patients (20.9%, 9/43) took a combination of drugs before the onset of SJS/TEN comprising trimethoprim-sulfamethoxazole and nevirapine

(4.7%, 2/43), trimethoprim-sulfamethoxazole and Tenofovir/Lamivudine/Dolutegravir (TLD) (4.7%, 2/43), Grandpa and grape seed oil (2.3%, 1/43), enalapril and amlodipine (2.3%, 1/43), sodium valproate and carbamazepine (2.3%, 1/43).

Several individual drugs like sodium valproate, Trifen, Grandpa, methotrexate, diclofenac, abacavir, carbamazepine, aloe, trivage, rifampicin, amoxicillin, and Tribuss, each accounted for 2.3% of cases.

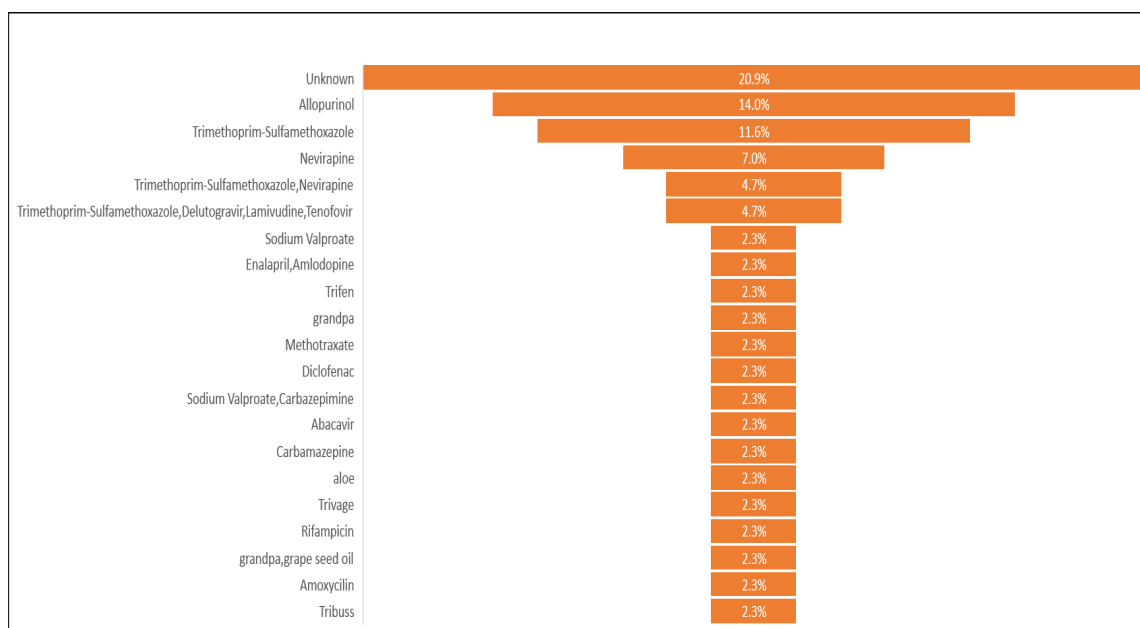


Figure 4.5 Drugs implicated in SJS/TEN

Past history of allergies/drug reactions

Most patients (93%, 40/43) did not have a past history of drug reactions, whilst 7% (3/43) had previous history of drug reactions (Figure 4.6).

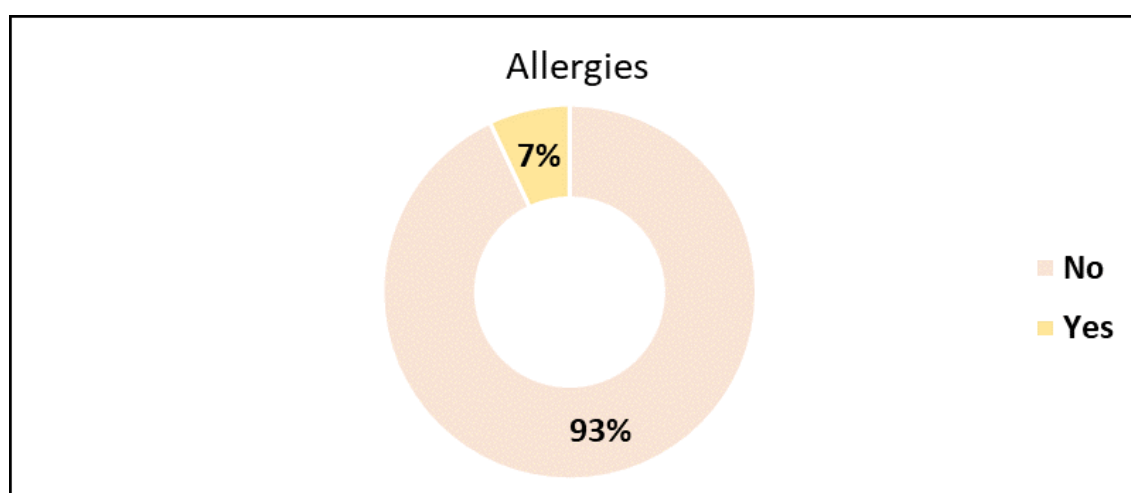


Figure 4.6 History of drug allergy

Co-morbidities

A total of 86% (37/43) of the patients had co-morbidities and 14% (6/43) were without co-morbidities (Table 4.1). Various (14) co-morbidities were found, with 32.6% (14/43) of the patients having more than one condition. HIV was the commonest co-morbidity in the cohort (34.9%, 15/43). Hypertension, diabetes mellitus and epilepsy each had a frequency of 4.7% (2/43 each).

Table 4.1 Frequency distribution of co-morbidities

Comorbidity	n (%)
None	6(14)
HIV	15(34.9)
Hypertension	2(4.7)
Epilepsy	2(4.7)
Hypertension, Gout	2(4.7)
HIV, Epilepsy	2(4.7)
HIV exposure	1(2.3)
HIV, Osteoarthritis	1(2.3)
HIV, Tuberculosis	1(2.3)
HIV, Epilepsy, Bipolar mood disorder	1(2.3)
HIV, Gout, Hypertension	1(2.3)
Epilepsy, Obesity	1(2.3)
Epilepsy, Hypertension	1(2.3)
Diabetes mellitus, Hypertension	1(2.3)
Diabetes mellitus, Hypertension, Dyslipidaemia	1(2.3)
Diabetes mellitus, Hypertension, Osteoarthritis	1(2.3)
Distal radial fracture	1(2.3)
B-cell acute lymphoblastic leukemia	1(2.3)
Clear cell renal carcinoma	1(2.3)

Condition for which the patient was taking the drug

The most common condition for which the patient was taking the causative drug was HIV (n=9, 20.9%) followed by pharyngitis (n=6, 14%) and gout (n=4, 9.3%) (Table 4.2). Some patients (9.3%, 4/43) did not have a history of drug ingestion. A few patients had taken the drug for HIV prophylaxis (n=1, 2.3%), PCP prophylaxis (n=2, 4.7%) and 4.7% (n=2) were taking HIV treatment and PCP prophylaxis concurrently.

Table 4.2 Condition for which the patient was taking the drug

Condition	n (%)
HIV	9(20.9)
Pharyngitis	6(14)
Gout	4(9.3)
Not applicable	4(9.3)
Not Provided	3(7)
Influenza	2(4.7)
Epilepsy	2(4.7)
HIV prophylaxis	1(2.3)
PCP prophylaxis	2(4.7)
HIV, PCP prophylaxis	2(4.7)
Tuberculosis	1(2.3)
Osteoarthritis	1(2.3)
Hypertension	1(2.3)
Distal radial fracture	1(2.3)
Painful feet	1(2.3)
Constipation	1(2.3)
Headache	1(2.3)
B-cell acute lymphoblastic leukemia	1(2.3)

Family History

There was no family history of SJS/TEN in 74.4% (32/43). Data was not provided in 23.3% (10/43) of patients and was unknown in 2.3% (Figure 4.7).

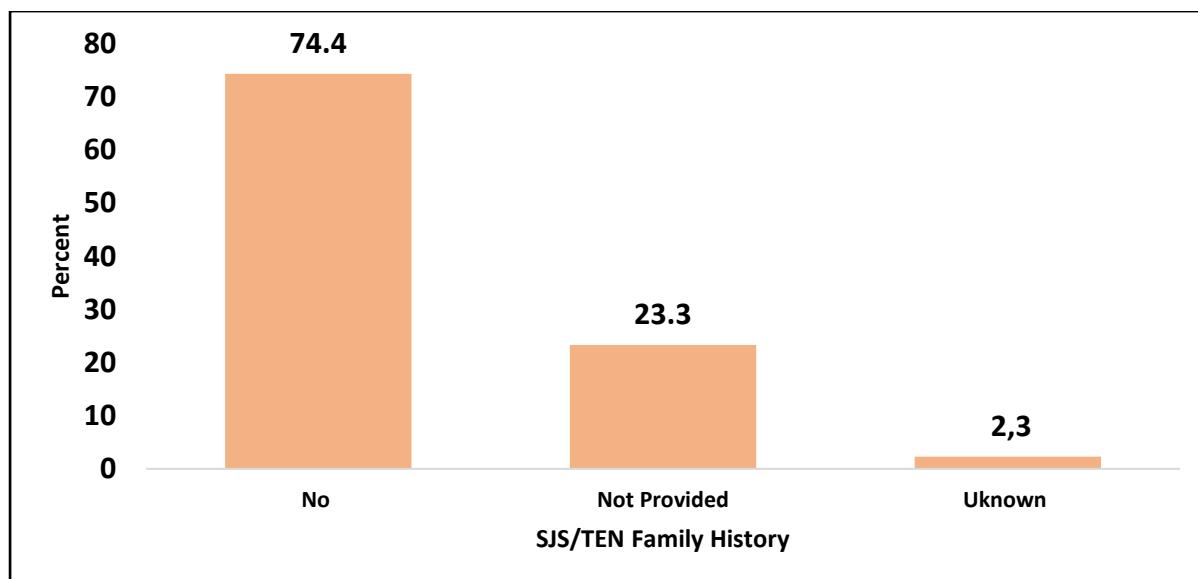


Figure 4.7 Family history of SJS/TEN

Reaction time/duration between drug ingestion and onset of symptoms

In 18.6% of cases (8/43) the reaction time was longer than 28 days (Table 4.3). It was 0 to 3 days in 16.3% (n=7), 4 to 7 days in 16.3% (7/43), and 8 to 14 days in 16.3% (7/43), with 11.6% (5/43) developing symptoms at 15 to 28 days. The reaction time was unknown in 9.3% (4/43) of patients (Table 4.3).

Table 4.3 Reaction time/duration between drug ingestion and onset of symptoms

REACTION TIME (DAYS)	n (%)
0-3	7(16.3)
4-7	7(16.3)
8-14	7(16.3)
15-28	5(11.6)
>28	8(18.6)
Not Provided	5(11.6)
Not Applicable	4(9.3)

Duration of symptoms prior to hospital visit

Most patients had a duration of symptoms beyond 72 hours (69.8%, 30/43) before presenting to Pietersburg Hospital. A minority (11.6%, 5/43) of patients presented

within 24-48 hours whilst 18.6% (8/43) presented within 49 to 72 hours. No patients presented to hospital in less than 24 hours from the onset of symptoms (Table 4.4).

Table 4.4 Duration of symptoms prior to hospital visit

Duration (hours)	n (%)
<24	0
24-48	5(11.6)
49-72	8(18.6)
>72	30(69.8)

Prodromal symptoms

In the study cohort, prodromal symptoms were mostly not provided (n=22, 51.2%) followed by no symptoms (n=6, 14.0%). The most commonly reported prodromal symptom was fever (n=8, 18.6%) followed by odynophagia (n=6, 14%), stinging eyes (n=4, 9.3%) and asthenia (n=3, 7.0%) (Table 4.5).

Table 4.5 Prodromal Symptoms

Prodromal symptom	n (%)
None	6(14.0)
Not Provided	22(51.2)
Fever	8(18.6)
Odynophagia	6(14)
Stinging eyes	4(9.3)
Asthenia	3(7.0)
Dysuria	2(4.7)

Mucous membrane involvement

All patients (100%, 43/43) in the study had mucous membrane involvement (Table 4.6).

Table 4.6: Mucous membrane involvement

Mucous membrane involvement	n (%)
No	0
Yes	43(100)

Total body surface area of skin detachment

Table 4.7 shows that 37.2% (n=16) of patients had TEN (TBSA of detachment >30%), 32.6% (n=14) had SJS/TEN overlap (TBSA of detachment=10-30%) and 30.2% (n=13) had SJS (TBSA of detachment <10%).

Table 4.7 TBSA of detachment (N=43)

Skin detachment	n (%)
SJS (TBSA of detachment <10%)	13(30.2)
SJS/TEN Overlap (TBSA of detachment= 10-30%)	14(32.6)
TEN (TBSA of detachment >30%)	16(37.2)

Blood cultures

Blood culture tests were done in 20 (46.5%) patients, and 50% were positive. The most commonly isolated pathogen was coagulase negative *Staphylococcus spp* (40%) of which in 10% it was isolated alone and in 30% it was mixed with other pathogens. *Escherichia coli*, *Bacillus spp.* *Acinetobacter spp.*, *Enterococcus faecium* and *Enterococcus faecalis* each comprised 10% of the cultured organisms.

Mixed infections consisting of coagulase negative *Staphylococcus aureus* and *Staphylococcus epidermidis* (10%), coagulase negative *Staphylococcus aureus* and Gram-positive cocci (10%), coagulase negative *Staphylococcus aureus* and *Acinetobacter baumannii* (10%) and *Staphylococcus aureus* mixed with *Acinetobacter baumannii* (10%) accounted for 40% of cases.

4.3.2.2 Objective 2: To evaluate the severity of TEN using SCORTEN among patients with SJS/TEN at Pietersburg Hospital

SCORTEN parameters

The TBSA of detachment was more than 10% in 69.8% (30/43), and 46.5% (20/43) were over the age of 40 years (Table 4.8). Patients who had a tachycardia of more than 120 beats/minute amounted to 30.2% (13/43) and 29.3% (N=41, n=12) had an elevated blood urea of more than 10mmol/L. Serum bicarbonate levels were less than 20mmol/L in 37.5% (N=24, n=9), and 5.1% (N=39, n=2) had glucose levels of over 14mmol/L. Malignancy was observed in 2 patients (4.7%) and the SCORTEN parameters were normal in 11.6% (5/43) of patients.

Table 4.8: Frequency distribution of SCORTEN parameters

SCORTEN	n (N, %)
TBSA >10%	30(43, 69.8)
Age ≥40	20(43, 46.5)
Tachycardia >120/min	13(43, 30.2)
Urea >10mmol/L	12(41, 29.3)
Serum bicarbonate <20mmol/L	9(24, 37.5)
Malignancy	2(43, 4.7)
Glucose >14mmol/L	2(39, 5.1)
None	5(43, 11.6)

SJS/TEN and SCORTEN parameters

Table 4.9 indicates the distribution of SCORTEN parameters across SJS/TEN. Age ≥ 40 was prevalent across SJS/TEN spectrum (n=20, 46.5%) with the highest occurrence in the SJS/TEN overlap group (n=9, 20.9%). The presence of malignancy was equally distributed (2.3%, 1/43) in the SJS and SJS/TEN Overlap group. Tachycardia ≥120/min was more common in the TEN group (18.6%, 8/43) compared to the SJS (4.7%, 2/43) and SJS/TEN overlap (7.0%, 3/43) groups. Blood urea nitrogen of >10 mmol/L was equally distributed across all severities (9.8%, 4/41). Glucose >14mmol/L was equally present in the SJS/TEN Overlap and TEN group (2.6%, 1/39). Serum bicarbonate level <20mmol/L was more common in the TEN

group (16.7%, 4/24) compared to SJS (12.5%, 3/24) and SJS/TEN overlap (8.3%, 2/24).

Table 4.9 SCORTEN parameters across SJS/TEN classes

Parameter	SJS	SJS/TEN Overlap	TEN
	n(%)	n(%)	n(%)
Normal	5(11.6)	0	0
Age ≥40 (N=43)	6(14.0)	9(20.9)	5(11.6)
Malignancy (N=43)	1(2.3)	1(2.3)	0
Tachycardia ≥120/min (N=43)	2(4.7)	3(7.0)	8(18.6)
TBSA of skin detachment >10% (N=43)	0	14(32.6)	16(37.2)
Serum urea > 10 mmol/L (N=41)	4(9.8)	4(9.8)	4(9.8)
Glucose >14mmol/L (N=39)	0	1(2.6)	1(2.6)

Severity according to SCORTEN

The SCORTEN scores ranged from 0 to 5, and most patients had a score of 2 (36.4%, 8/22). A score of 3 was present in 27.3% (6/22) of the patients and SCORTEN score of 4 was present in 13.6 % (3/22) of the patients (Table 4.10). SCORTEN scores of 4 and 5 were present in 13.6% (3/22) and 4.5% (1/22) of patients, respectively.

Table 4.10 SCORTEN score

SCORTEN SCORE	n (%)
SCORTEN 0	2(9.1)
SCORTEN 1	2(9.1)
SCORTEN 2	8(36.4)
SCORTEN 3	6(27.3)
SCORTEN 4	3(13.6)
SCORTEN 5	1(4.5)
SCORTEN 6	0

4.3.2.3 Objective 3: To characterise management outcomes of patients with SJS/TEN at Pietersburg Hospital

Management

All patients received supportive therapy. Most patients were treated with systemic antibiotics (81.4%, 35/43). A total of 11 patients (25.6%) received systemic steroids (oral prednisone). Only one (2.3%) patient received cyclosporine A, similarly only one (2.3%) patient received IVIg (Table 4.11). Some patients (n=5, 11.6%) received supportive care alone.

Table 4.11 Management

Management	n (%)
Supportive care	43(100)
Oral/IV Antibiotics	35(81.4)
Systemic steroids	11(25.6)
Cyclosporine A	1(2.3)
Intravenous immunoglobulins	1(2.3)

Outcomes of management

Length of stay

The majority of patients were hospitalised for 3 to 7 days (37.2%, 16/43), followed by those that were hospitalised for 8-14 days (27.9%, 12/43) and 15-28 days (27.9%, 12/43). Only 4.7% (2/43) stayed for >28 days (Table 4.12).

Table 4.12 Length of stay

Length of hospitalisation (days)	n (%)
<3	1(2.3)
3-7	16(37.2)
8-14	12(27.9)
15-28	12(27.9)
>28	2(4.7)

When the length of stay was categorised into three groups, the majority of inpatients were admitted for less than 8 days (39.5%, 17/43), followed by patients that were admitted for more than 14 days (32.6%, 14/43). A total of 27.9 % (12/43) patients were admitted for 8 to 14 days. (Figure 4.8).

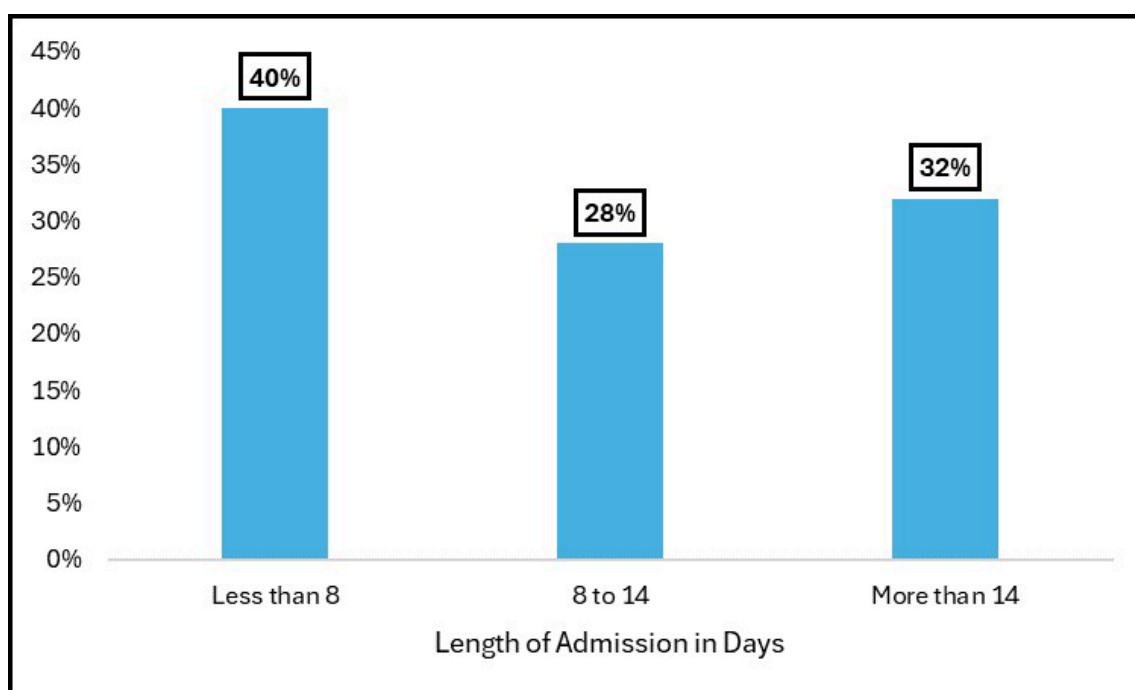


Figure 4.8 Length of admission

Complications

Table 4.13 displays the frequency of various complications among patients. The most prevalent were hypoalbuminemia (n=31, 72.1%) and hyponatremia (n=22, 51.2%), followed by sepsis (n=18, 41.9%), hypokalaemia (n=11, 25.6%), acute renal failure (n=7, 16.3%) and anaemia (n=7, 16.3%). Other complications included hyperkalaemia (n= 11, 25.6%), acute liver injury (n=3.7%), synechiae (n=1, 2.3%), hypernatremia (n=1, 2.3%) and eosinophilia (n=12.3%). There were no complications in 9.3% (n=4) of patients.

Table 4.13: Frequency distribution of complications

Complication	n (%)
Hyponatremia	22(51.2)
Hypokalaemia	11(25.6)
Hypoalbuminemia	31(72.1)
Hypernatremia	1(2.3)
Hyperkalaemia	11(25.6)
Anaemia	7(16.3)
Sepsis	18(41.9)
Lower respiratory tract infection	2(4.7)
Acute Renal Failure	7(16.3)
Acute Liver Injury	3(7)
Eosinophilia	1(2.3)
Synechiae	1(2.3)
None	4(9.3)
Symblepharon	0
Corneal scarring	0
Phimosis	0

Mortality

The SJS/TEN mortality rate was 14% (n=6) and 86.1% (37/43) patients survived. Table 4.14 displays the characteristics of patients who demised. There was an equal

proportion of males (50%, 3/6) and females (50%, 3/6) in the patients that demised. The majority of them were diagnosed with TEN (n=4, 66.7%). One patient had a SCORTEN score of 5 with a predicted mortality of 90%.

Table 4.14: Characteristics of patients that demised

Age	Gender	Severity	Implicated Drug	SCORTEN score	Predicted Mortality	Treatment	Complication
29	Male	TEN	Unknown	1	3%	Supportive Systemic Steroids Antibiotics	Sepsis Hypernatremia Hypoalbuminemia Drug-induced Liver Injury
69	Male	TEN	Allopurinol	4	58%	Supportive Antibiotics	Sepsis Acute Renal Failure Hyperkalaemia Hypoalbuminemia
58	Female	SJS/TEN Overlap	Trimethoprim Sulfamethoxazole Dolutegravir/Lamivudine /Tenofovir	5	90%	Supportive Systemic Steroids Antibiotics	Sepsis Acute Renal Failure Hypokalaemia Hyponatremia Hypoalbuminemia
30	Female	TEN	Unknown	2	12%	Supportive Antibiotics	Sepsis Lower respiratory tract infection Hyperkalaemia

							Hypernatremia
							Hypoalbuminemia
50	Male	TEN	Trimethoprim Sulfamethoxazole Dolutegravir/Lamivudine /Tenofovir	3	35%	Supportive Antibiotics	Sepsis Hypoalbuminemia
44	Female	SJS	Highly Active Antiretroviral Therapy (HAART)	3	35%	Supportive Antibiotics	Acute Renal Failure Hyperkalaemia Hypoalbuminemia Anemia

4.3.1.4 Objective 4: To determine association between demographic factors and clinical characteristics, disease severity and management outcomes of patients with SJS/TEN at Pietersburg Hospital

Association between pregnancy status and variables was not analysed, as only one (3.6%) female patient was pregnant in the study.

Association between demographic factors and clinical characteristics

Drug history

Table 4.15 presents associations between drug classes and gender. Drug classes were not statistically significantly associated with gender ($p=0.370$).

Table 4.15: Associations between drug classes and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (N=28)	Male (N=15)	P-value
Drug classes			0.370
Analgesics	0 (0.0%)	2 (13.3%)	
Analgesics, Antipyretics	1 (3.6%)	0 (0.0%)	
Analgesics, Herbal	1 (3.6%)	0 (0.0%)	
Immunomodulators	1 (3.6%)	0 (0.0%)	
Antibiotics	3 (10.7%)	5 (33.3%)	
Antibiotics, Antiretrovirals	3 (10.7%)	1 (6.7%)	
Antiepileptics	3 (10.7%)	0 (0.0%)	
Antigout	5 (17.9%)	1 (6.7)	
Antihypertensives	1 (3.6%)	0 (0.0%)	
Antibiotics, Analgesics	0 (0.0%)	1 (6.7%)	
Antiretrovirals	5 (17.9%)	3 (20.0%)	
Antituberculosis	1 (3.6%)	0 (0.0%)	
Herbal	1 (3.6%)	0 (0.0%)	
None	1 (3.6%)	0 (0.0%)	
Unknown	2 (7.1%)	2 (13.3%)	

Table 4.16 presents the association between age and drug classes. Age categories were not statistically significantly associated with drug classes ($p=0.222$).

Table 4.16: Associations between drug classes and age

Variables	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Drug classes					0.222
Analgesics	0 (0.0%)	0 (0.0%)	1 (8.3%)	1 (12.5%)	
Analgesics, Antipyretics	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Analgesic, Herbal	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Immunomodulators	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Antibiotics	3 (37.5%)	3 (20.0%)	2 (16.7%)	0 (0.0%)	
Antibiotics, Antiretrovirals	0 (0.0%)	2 (13.3%)	2 (16.7%)	0 (0.0%)	
Antiepileptics	1 (12.5%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	
Antigout	0 (0.0%)	0 (0.0%)	1 (8.3%)	5 (62.5%)	
Antihypertensives	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Antibiotics, Analgesics	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Antiretrovirals	2(25%)	5 (33.3%)	1 (8.3%)	0 (0.0%)	
Antituberculosis	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Herbal	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
None	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Unknown	0 (0.0%)	2 (13.3%)	1 (8.3%)	1 (12.5%)	

Our study found no association between culprit drug names and gender (p=0.240) (Table 4.17).

Table 4.17: Associations between individual drugs and gender

Variables	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Drug names			0.240
Abacavir	0 (0.0%)	1 (6.7%)	
Aloe	1 (3.6%)	0 (0.0%)	
Allopurinol	5 (17.9%)	1 (6.7%)	
Amoxicillin	1 (3.6%)	0 (0.0%)	
Carbamazepine	1 (3.6%)	0 (0.0%)	
Diclofenac	0 (0.0%)	1 (6.7%)	
Enalapril, Amlodipine	1 (3.6%)	0 (0.0%)	
Grandpa	0 (0.0%)	1 (6.7%)	
Grandpa, Black Seed Oil	1 (3.6%)	0 (0.0%)	
Methotrexate	1 (3.6%)	0 (0.0%)	
Not Applicable	3 (10.7%)	0 (0.0%)	
Not Specified	2 (7.1%)	1 (6.7%)	
Nevirapine	2 (7.1%)	1 (6.7%)	
Rifampicin	1 (3.6%)	0 (0.0%)	
Sodium valproate	1 (3.6%)	0 (0.0%)	
Sodium valproate, Carbamazepine	1 (3.6%)	0 (0.0%)	
Tribuss	0 (0.0%)	1 (6.7%)	
Trimethoprim Sulfamethoxazole	2 (7.1%)	3 (20.0%)	
Trimethoprim Sulfamethoxazole, Ibuprofen	0 (0.0%)	1 (6.7%)	
Trimethoprim Sulfamethoxazole, Nevirapine	2 (7.1%)	0 (0.0%)	
Trifen	1 (3.6%)	0 (0.0%)	
Trivage	1 (3.6%)	0 (0.0%)	
Trimethoprim Sulfamethoxazole, Tenofovir/Lamivudine/Dolutegravir	1 (3.6%)	1 (6.7%)	
Unknown	0 (0.0%)	3 (20.0%)	

This study found no association between culprit drug names and age ($p=0.312$).
(Table 4.18)

Table 4.18: Associations between individual drugs and age

Variables	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Drug names					0.312
Abacavir	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Aloe	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Allopurinol	0 (0.0%)	0 (0.0%)	1 (8.3%)	5 (62.5%)	
Amoxycillin	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Carbamazepine	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Diclofenac	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Enalapril, Amlodipine	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Grandpa	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Grandpa_Black Seed Oil	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Methotrexate	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Not Applicable	0 (0.0%)	1 (6.76%)	1 (8.3%)	1 (12.5%)	
Not Specified	0 (0.0%)	2 (13.3%)	1 (8.3%)	0 (0.0%)	
Nevirapine	1 (12.5%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	
Rifampicin	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Sodium valproate	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Sodium valproate, Carbamazepine	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Tribuss	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Trimethoprim Sulfamethoxazole	2 (25%)	1 (6.67%)	2 (16.7%)	0 (0.0%)	
Trimethoprim Sulfamethoxazole, Ibuprofen	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Trimethoprim Sulfamethoxazole, Nevirapine	0 (0.0%)	2 (13.3%)	0 (0.0%)	0 (0.0%)	
Trifen	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Trivage	0 (0.0%)	1 (6.67%)	0 (0.0%)	0 (0.0%)	
Trimethoprim Sulfamethoxazole, Tenofovir/Lamivudine/Dolutegravir	0 (0.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	
Unknown	0 (0.0%)	2 (13.3%)	1 (8.3%)	0 (0.0%)	

Past history of allergies

Table 4.19 show associations between past history of allergies and gender. No statistically significant associations were found ($p=0.231$).

Table 4.19: Association between past history of allergies and gender

Variables	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Past history of allergies			0.231
No	27 (96.4%)	13 (86.7%)	
Yes	1 (3.6%)	2 (13.3%)	

Table 4.20 show associations between past history of allergies and age. No statistically significant associations were found ($p=0.391$).

Table 4.20: Association between past history of allergies and Age

Variables	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Past history of allergies					0.391
No	7 (87.5%)	15 (100%)	10 (83.3)	8 (100.0%)	
Yes	1 (12.5%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	

Co-morbidities

There was no significant association between gender and co-morbidities ($p>0.05$) (Table 4.21).

Table 4.21: Association between co-morbidities gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (N=28)	Male (N=15)	P-value
Diabetes mellitus	2 (7.1%)	1 (6.7%)	0.953
Distal Radial Fracture	1 (3.5%)	0 (0.0%)	0.459
Epilepsy	4 (14.3%)	3 (20%)	0.629
Gout	2 (7.1%)	1 (6.7%)	0.953
HIV	14 (50%)	9 (60%)	0.531
Hypertension	6 (21.4%)	3 (20%)	0.913
Clear cell renal carcinoma	0 (0.0%)	1 (6.7%)	0.623
B-cell acute lymphoblastic leukaemia	1 (3.5%)	0 (0.0%)	0.459
Obesity	1 (3.5%)	0 (0.0%)	0.459
Tuberculosis	1 (3.5%)	1 (6.7%)	0.646
Osteoarthritis	2 (7.1%)	0 (0.0%)	0.289
HIV exposure	1 (3.5%)	0 (0.0%)	0.459
Bipolar mood disorder	1 (3.5%)	0 (0.0%)	0.459
Dyslipidemia	0 (0.0%)	1 (6.7%)	0.623

In terms of co-morbidities, age was significantly associated with diabetes mellitus, HIV and hypertension ($p=0.003$, $p=0.024$ and $p<0.001$ respectively). Diabetes mellitus was only among patients over 60 years of age. High percentage (73.3%, 11/15) of patients with HIV was among patients aged 21 to 40 and those with hypertension (87.5%, 7/8) were mostly over 60 years of age (Table 4.22).

Table 4.22: Association between co-morbidities and age

Variable	AGE (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Diabetes mellitus	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (37.5%)	0.003
Distal Radial Fracture	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0.450
Epilepsy	1 (12.5%)	3 (20%)	3 (8.3%)	0 (0.0%)	0.482
Gout	0 (0.0%)	0 (0.0%)	1 (8.3%)	2 (25%)	0.124
HIV	3 (37.5%)	11 (73.3%)	8 (66.7%)	1 (12.5%)	0.024
Hypertension	0 (0.0%)	0 (0.0%)	2 (16.7%)	7 (87.5%)	<0.001
Clear renal cell carcinoma	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.214
B-cell acute lymphoblastic leukaemia	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.214
Obesity	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0.450
Tuberculosis	1 (12.5%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	0.457
Osteoarthritis	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (12.5%)	0.527
HIV exposure	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.214
Bipolar Mood disorder	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0.462
Dyslipidemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0.214

Condition for which the patient was taking the drug

Table 4.23 presents associations between condition for which the patient was taking the drug and gender. There was no statistically significant association between condition for which the patient was taking the drug and gender ($p=0.789$).

Table 4.23: Association between condition for which the patient was taking the drug and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Condition for which the patient was taking the drug			0.789
Constipation	1 (3.6%)	0 (0.0%)	
Distal radial fracture	1 (3.6%)	0 (0.0%)	
Epilepsy	2 (7.1%)	0 (0.0%)	
Gout	3 (10.7%)	1 (6.7%)	
Headache	0 (0.0%)	1 (6.7%)	
HIV	6 (21.4%)	3 (20%)	
HIV prophylaxis	1 (3.6%)	0 (0.0%)	
HIV, PCP prophylaxis	1 (3.6%)	1 (6.7%)	
Hypertension	1 (3.6%)	0 (0.0%)	
Influenza	1 (3.6%)	1 (6.7%)	
Malignancy: B-cell acute lymphoblastic leukaemia	1 (3.6%)	0 (0.0%)	
Not applicable	3 (10.7%)	1 (6.7%)	
Not provided	2 (7.1%)	1 (6.7%)	
Osteoarthritis	1 (3.6%)	0 (0.0%)	
Painful feet	0 (0.0%)	1 (6.7%)	
PCP prophylaxis	1 (3.6%)	1 (6.7%)	
Pharyngitis	2 (7.1%)	4 (26.7%)	
<i>Mycobacterium tuberculosis</i> infection	1 (3.6%)	0 (0.0%)	

Table 4.24 presents association between condition for which the patient was taking the drug and age. There was a statistically significant association between condition for which the patient was taking the drug and age ($p=0.002$). Most patients in the 21 to 40 age group were taking a drug for HIV (7/15, 46.7%).

Table 4.24: Association between condition for which the patient was taking the drug and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Condition for which the patient was taking the drug					0.002
Constipation	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	
Distal radial fracture	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Epilepsy	1 (12.5%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	
Gout	0 (0.0%)	0 (0.0%)	1 (8.3 %)	3 (37.3%)	
Headache	0 (0.0%)	0 (0.0%)	1 (8.3 %)	0 (0.0%)	
HIV	1 (12.5%)	7 (46.7%)	1 (8.3%)	0 (0.0%)	
HIV prophylaxis	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
HIV, PCP prophylaxis	0 (0.0%)	0 (0.0%)	2 (16.7%)	0 (0.0%)	
Hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Influenza	1 (12.5%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	
Malignancy: B-cell acute lymphoblastic leukaemia	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Not applicable	0 (0.0%)	2 (16.7%)	1 (8.3%)	1 (12.5%)	
Not provided	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (25%)	
Osteoarthritis	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Painful feet	0 (0.0%)	0 (0.0%)	1 (8.3 %)	0 (0.0%)	
PCP prophylaxis	1 (12.5%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	
Pharyngitis	2 (25%)	2 (16.7%)	2 (16.7%)	0 (0.0%)	
Tuberculosis	0 (0.0%)	0 (0.0%)	1 (8.3%)	0 (0.0%)	

Family history

Table 4.25 presents association between family history of drug reaction and gender. Both female and male gender, did not report a positive family history of drug reaction (p=0.138).

Table 4.25: Association between family history of drug reaction and gender

Variables	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Family history of drug reaction			0.138
No	23 (82.1%)	9 (60.0%)	
Not provided	4 (14.3%)	6 (40.0%)	
Unknown	1 (3.6%)	0 (0.0%)	

Table 4.26 presents association between family history of drug reaction and age. There was no statistically significant association between age and family history of drug reaction ($p=0.314$).

Table 4.26: Association between family history of drug reaction and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Family history of drug reaction					0.314
No	7 (87.5%)	11 (73.3%)	7 (58.3%)	7 (87.5%)	
Not provided	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	
Unknown	1 (12.5%)	4 (26.7%)	5 (41.7%)	0 (0.0%)	

Reaction time

Table 4.27 presents association between reaction time and gender. There was no significant association between gender and reaction time ($p=0.157$).

Table 4.27: Association between reaction time and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Reaction time			0.157
0-3	3 (10.7%)	4 (26.7%)	
4-7	5 (17.9%)	2 (13.3%)	
8-14	4 (14.3%)	3 (20%)	
15-28	5 (17.6%)	0 (0.0%)	
>28	7 (25%)	1 (6.7%)	
Not provided	1 (3.6)	4 (26.7%)	
Not applicable	3 (10.7%)	1 (6.7%)	

Table 4.28 presents association between reaction time and age. There was no statistically significant association between age and reaction time ($p=0.060$).

Table 4.28: Association between reaction time and age

Variables	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Reaction time					0.060
0-3	4 (50%)	2 (13.3%)	1 (8.3%)	0 (0.0%)	
4-7	2 (25%)	1 (6.7%)	3 (25%)	1 (12.5%)	
8-14	0 (0.0%)	3 (20.0%)	1 (8.3%)	3 (37.5%)	
15-28	1 (12.5%)	0 (0.0%)	3 (25%)	1 (12.5%)	
>28	1 (12.5%)	4 (26.7%)	2 (16.7%)	1 (12.5%)	
Not provided	0 (0.0%)	3 (20.0%)	1 (8.3%)	1 (12.5%)	
Not applicable	0 (0.0%)	2 (13.3%)	1 (8.3%)	1 (12.5%)	

Duration of symptoms prior hospital visit

Table 4.29 presents association between duration of symptoms prior hospital visit and gender. No statistically significant association was found between duration of symptoms prior hospital visit and gender ($p=0.889$).

Table 4.29: Association between duration of symptoms prior hospital visit and gender

Variable	Gender (N=28)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Duration of symptom prior hospital visit			0.889
<24	0 (0.0%)	0 (0.0%)	
24-48	4 (14.3%)	1 (6.7%)	
49-72	5 (17.9%)	3 (20%)	
>72	19 (67.9%)	11 (73.3%)	

Table 4.30 presents association between duration of symptoms prior hospital visit and age. No statistically significant association was found between duration of symptoms prior hospital visit and age ($p=0.760$).

Table 4.30: Association between duration of symptoms prior hospital visit and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n= 8)	P-value
Duration of symptom prior hospital visit					0.760
<24	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
24-48	1 (12.5%)	2 (13.3%)	0 (0.0%)	2 (25%)	
49-72	2 (25%)	3 (20%)	2 (16.7%)	1 (12.5%)	
>72	5 (62.5%)	10 (66.7%)	10 (83.3%)	5 (62.5%)	

Prodromal symptoms

Table 4.31 presents association between prodromal symptoms and gender. No statistically significant association was found between prodromal symptoms and gender ($p=0.266$).

Table 4.31: Association between prodromal symptoms and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Prodromal symptoms			0.266
Fever	6 (21.4%)	2 (13.3%)	
Asthenia	3 (10.7%)	0 (0.0%)	
Stinging eyes	3 (10.7%)	1 (6.7%)	
None	4 (14.3%)	2 (13.3%)	
Not provided	14 (50%)	8 (53.3%)	
Odynophagia	4 (14.3%)	2 (13.3%)	
Dysuria	0 (0.0%)	2 (13.3%)	

Table 4.32 presents association between prodromal symptoms and age. No statistically significant association was found between prodromal symptoms and age ($p=0.328$).

Table 4.32: Association between prodromal symptoms and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n= 8)	21-40 (n=15)	41-60 (n=12)	>60 (n= 8)	P-value
Prodromal symptoms					0.328
Fever	3 (37.5%)	1 (6.7%)	2 (16.7%)	2 (25%)	
Asthenia	0 (0.0%)	1 (6.7%)	2 (16.7%)	0 (0.0%)	
Stinging eyes	2 (25%)	1 (6.7%)	0 (0.0%)	1 (12.5%)	
None	0 (0.0%)	3 (20%)	1 (8.3%)	2 (25%)	
Not provided	5 (62.5%)	9 (60%)	6 (50%)	2 (25%)	
Odynophagia	0 (0.0%)	1 (6.7%)	2 (16.7%)	3 (37.5%)	
Dysuria	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (25%)	

Mucous membrane involvement

In our study, all patients had mucous membrane involvement irrespective of gender and age. There was no statistically significant association between mucous membrane involvement and gender ($p=1.00$) (Table 4.33) as well as mucous membrane involvement and age ($p=100$) (Table 4.34).

Table 4.33: Association between mucous membrane involvement and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Mucous membrane involvement			
Yes	28 (100.0%)	15 (100.0%)	1.00

Table 4.34: Association between mucous membrane involvement and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n= 8)	21-40 (n= 15)	41-60 (n= 12)	>60 (n= 8)	P-value
Mucous membrane involvement					
Yes	8 (100%)	15 (100%)	12 (100%)	8 (100%)	1.00

SJS/TEN severity

The provided results in Table 4.35 detail association between SJS/TEN severity and gender. No statistically significant association was found ($p=0.832$).

Table 4.35: Associations between SJS/TEN severity and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Severity			0.832
SJS	8 (28.6%)	5 (33.3%)	
SJS/TEN	10 (35.7%)	4 (26.7%)	
TEN	10 (35.7%)	6 (40.0%)	

The provided results in Table 4.36 detail association between SJS/TEN severity and age. No statistically significant association was found ($p=0.194$).

Table 4.36: Associations between SJS/TEN severity and age

Variables	Age Category (N=43)				Fisher's Exact Test
	0-20 (n= 8)	21-40 (n= 15)	41-60 (n= 12)	>60 (n=8)	P-value
Severity					0.194
SJS	2 (25%)	5 (33.3%)	4 (33.3%)	2 (25%)	
SJS/TEN	3 (37.5%)	3 (20%)	5 (41.7%)	4 (37.5%)	
TEN	3 (37.5%)	7 (46.7%)	3 (25%)	2 (25%)	

Blood cultures

Table 4.37 presents associations between blood cultures and gender. The blood culture results did not show a statistically significant association with gender (p=0.311).

Table 4.37: Associations between blood cultures and gender

Variable	Gender (N=20)		Fisher's Exact Test
	Female (n=12)	Male (n=8)	P-value
Blood cultures			0.311
<i>Acinetobacter baumannii</i>	1 (8.3%)	0 (0.0%)	
<i>Bacillus species</i>	0 (0.0%)	1 (12.5%)	
<i>Coagulase negative staphylococcus aureus</i>	1 (8.3%)	0 (0.0%)	
<i>Coagulase negative staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	1 (8.3%)	0 (0.0%)	
<i>Coagulase negative staphylococcus aureus</i> <i>Acinetobacter baumannii</i>	1 (8.3%)	0 (0.0%)	
<i>Enterococcus faecalis</i>	1 (8.3%)	0 (0.0%)	
<i>Enterococcus faecium</i>	1 (8.3%)	0 (0.0%)	
<i>Escherichia coli</i>	1 (8.3%)	0 (0.0%)	
<i>Gram positive cocci, Coagulase negative</i> <i>staphylococcus aureus</i>	0 (0.0%)	1 (12.5%)	
<i>Staphylococcus aureus, Acinetobacter</i> <i>baumannii</i>	1 (8.3%)	0 (0.0%)	
Negative	4 (33.3%)	6 (75%)	

Table 4.38 presents associations between blood cultures and age. The blood culture results did not show a statistically significant association with age (p=0.299).

Table 4.38: Associations between blood cultures and age

Variable	Age Category (N=20)				Fisher's Exact Test
	0-20 (n=6)	21-40 (n=6)	41-60 (n=5)	>60 (n=3)	P-value
Blood cultures					0.299
<i>Acinetobacter baumannii</i>	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	
<i>Bacillus species</i>	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
<i>Coagulase negative staphylococcus aureus</i>	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
<i>Coagulase negative staphylococcus aureus, staphylococcus epidermidis</i>	0 (0.0%)	0 (0.0%)	1 (20%)	0 (0.0%)	
<i>Coagulase negative staphylococcus aureus, acinetobacter baumannii</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	
<i>Enterococcus faecalis</i>	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	
<i>Enterococcus faecium</i>	0 (0.0%)	0 (0.0%)	1 (20%)	0 (0.0%)	
<i>Escherichia coli</i>	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	
<i>Gram positive cocci-coagulase negative staphylococcus aureus</i>	0 (0.0%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	
<i>Staphylococcus aureus-acinetobacter baumannii</i>	1 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Negative	3 (50%)	3 (50%)	3 (60%)	1 (33.3%)	

Association between demographic factors and SCORTEN parameters

SCORTEN parameters

Table 4.39 presents association between SCORTEN parameters and gender. There was no significant association between gender and SCORTEN parameters ($p>0.05$).

Table 4.39: Association between SCORTEN parameters and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Age > 40			0.531
Yes	14 (50%)	6 (40%)	
No	14 (50%)	9 (60%)	
	Gender (N=43)		
	Female (n=28)	Male (n=15)	
Tachycardia >120 b/min			0.077
Yes	11 (39.3%)	2 (13.3%)	
No	17 (60.7%)	13 (86.7%)	
	Gender (N=43)		
	Female (n=28)	Male (n=15)	
TBSA >10%			0.746
Yes	20 (71.4%)	10 (66.7%)	
No	8 (28.6%)	5 (33.3%)	
	Gender (N=41)		
	Female (n=27)	Male (n=14)	
Urea > 10mmol/L			0.894
Yes	8 (30%)	4 (28.6%)	
No	19 (70%)	10 (71.4%)	
	Gender (N=39)		
	Female (n=27)	Male (n=12)	
Glucose > 14mmol/L			0.289
Yes	2 (7.4%)	0 (0.0%)	
No	25 (92.6%)	12 (100%)	
	Gender (N= 24)		
	Female (n=18)	Male (n=6)	
Serum bicarbonate <20mmol/L			0.092
Yes	8 (44.4%)	01 (16.7%)	
No	10 (55.6%)	05 (83.3%)	
	Gender (N=43)		
	Female (n=28)	Male (n=15)	
Malignancy			0.646
Yes	1 (3.6%)	1 (6.7%)	
No	27 (96.4%)	14 (93.3%)	

Our study found that the parameters age ≥ 40 , tachycardia ≥ 120 b/min, urea > 10 mmol/L and the presence of malignancy were significantly associated with age ($p < 0.05$). Tachycardia and malignancy was most prevalent in patients aged 0-20. Age ≥ 40 and urea > 10 mmol/L was most prevalent in those aged 41-60 and above 60 years (Table 4.40).

Table 4.40: Association between SCORTEN parameters and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n= 8)	P-value
Age ≥ 40 (N=43)					0.001
Yes	0 (0.0%)	1 (6.7)	12 (100%)	8 (100%)	
No	8 (100%)	14 (93.3%)	0 (0.0%)	0 (0.0%)	
	Age Category (N=43)				
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n= 8)	
Tachycardia >120 b/min					0.018
Yes	6 (75%)	4 (26.7%)	1 (8.3%)	2 (25%)	
No	2 (25%)	11 (73.3%)	11 (91.6%)	6 (75%)	
	Age Category (N=43)				
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n= 8)	
TBSA >10%					0.746
Yes	6 (75%)	10 (66.7%)	8 (66.7%)	6 (75%)	
No	2 (25%)	5 (33.3%)	4 (33.3%)	2 (25%)	
	Age Category (N=41)				
	0-20 (n=8)	21-40 (n=14)	41-60 (n=11)	>60 (n=8)	
Urea > 10mmol/L					<0.001
Yes	0 (0.0%)	1 (7.1%)	4 (36.4%)	7 (87.5%)	
No	8 (100%)	13 (92.9%)	7 (63.6%)	1 (12.5%)	
	Age Category (N=39)				
	0-20 (n=8)	21-40 (n=12)	41-60 (n=12)	>60 (n=7)	
Glucose > 14mmol/L					0.107
No	0 (0.0%)	0 (0.0%)	1 (8.3%)	1 (14.3%)	
	8 (100%)	12 (100%)	11 (91.7%)	7 (85.7%)	
	Age Category (N= 24)				
	0-20 (n=6)	21-40 (n=6)	41-60 (n=7)	>60 (n=5)	
Serum bicarbonate <20mmol/L					0.319
Yes	2 (33.3%)	1 (16.7%)	3 (42.9%)	3 (60%)	
No	4 (66.7%)	5 (83.3%)	5 (57.1%)	2 (40%)	
	Age Category (N=43)				
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	
Malignancy					0.027
Yes	2 (25%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
No	6 (75%)	15 (100%)	12 (100%)	8 (100%)	

Predicted mortality

Table 4.41 presents association between predicted mortality and gender. No statistically significant association was found ($p=0.761$).

Table 4.41: Association between predicted mortality and gender

Variable	Gender (N=22)		Fisher's Exact Test
	Female (n=17)	Male (n=5)	P-value
Predicted Mortality			0.761
3%	3 (17.6%)	2 (40.0%)	
12%	7 (41.2%)	1 (20.0%)	
35%	4 (23.5%)	1 (20.0%)	
58%	2 (11.8%)	1 (20.0%)	
90%	1 (5.9%)	0 (0.0%)	

The provided results in Table 4.42 detail association between predicted mortality and age. No statistically significant association was found ($p=0.322$).

Table 4.42: Association between predicted mortality and age

Variables	Age Category (N=22)				Fisher's Exact Test
	0-20 (n=6)	21-40 (n=5)	41-60 (n=6)	>60 (n=5)	P-value
Predicted Mortality					0.322
3%	1 (16.7%)	3 (60%)	1 (16.7%)	0 (0.0%)	
12%	3 (50%)	1 (20%)	2 (33.3%)	2 (40%)	
35%	2 (33.3%)	1 (20%)	2 (33.3%)	0 (0.0%)	
58%	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (60%)	
90%	0 (0.0%)	0 (0.0%)	1 (16.7%)	0 (0.0%)	

Association between demographic factors and management and management outcomes

Management

Management did not show a statistically significant association with gender ($p > 0.05$, Table 4.43).

Table 4.43: Association between management and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Management			
Cyclosporine A	1 (3.6%)	0 (0.0%)	0.459
IVIg	1 (3.6%)	0 (0.0%)	0.459
Antibiotics	25 (89.3%)	10 (66.7%)	0.069
Steroids	9 (32.1%)	10 (66.7%)	0.089
Supportive care	28 (100%)	15 (100%)	1.00

Table 4.44 presents association between management and age. No statistically significant association was found ($p > 0.05$).

Table 4.44: Association between management and age

Variables	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Management					
Cyclosporine A	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0.591
IVIg	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.591
Antibiotics	8 (100%)	10 (66.7%)	11 (91.7%)	6 (75%)	0.170
Steroids	1 (12.5%)	5 (33.3%)	3 (25%)	2 (25%)	0.754
Supportive care	8 (100%)	15 (100%)	12 (100%)	8 (100%)	1.00

Mortality

Mortality did not exhibit a statistically significant association with gender ($p > 0.05$, Table 4.45).

Table 4.45: Association between mortality and gender

Variable	Gender (N=43)	Fisher's
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			Exact Test
	Female (n=28)	Male (n=15)	P-value
Mortality			0.402
Survived	25 (89%)	12 (80%)	
Demised	3 (11%)	3 (20%)	

Mortality did not exhibit a statistically significant association with age ($p>0.05$, Table 4.46). There were no deaths in the 0 to 20 age group.

Table 4.46: Association between mortality and age

Variable	Age Category (N=43)				Fisher's Exact Test
	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Mortality					0.577
Survived	8 (100%)	13 (86.7%)	9 (75%)	7 (87.5%)	
Demised	0 (0%)	2 (13.3)	3 (25%)	1 (12.5%)	

Length of hospital stay

There was a significant association between gender and length of stay ($p=0.024$, Table 4.47). The length of stay of more than 14 days was higher (46.4%, 13/28) in females than in males (6.7%, 1/15).

Table 4.47: Association between length of stay and gender

Varibales	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Length of Stay			0.024
< 8	8 (28.6%)	9 (60.0%)	
8-14	7 (25.0%)	5 (33.3%)	
> 14	13 (46.4%)	1 (6.7%)	

There were no significant association between age and length of hospital stay ($p=0.314$, Table 4.48).

Table 4.48: Association between length of stay and age

Variables	Age Category (N=43)				Fisher's Exact Test
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	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Length of Stay					0.314
< 8	1 (12.5%)	9 (60%)	5 (41.7%)	2 (25%)	
8-14	2 (25%)	4 (26.7%)	4 (33.3%)	2 (25%)	
> 14	5 (62.5%)	2 (13.3%)	3 (25%)	4 (50%)	

Complications

Table 4.49 presents association between complication and gender. There was no statistically significant association between gender and complications ($p>0.05$).

Table 4.49: Association between complications and gender

Variable	Gender (N=43)		Fisher's Exact Test
	Female (n=28)	Male (n=15)	P-value
Complication			
Anaemia	5 (17.9%)	2 (13.3%)	0.702
Acute Renal Failure	4 (14.3%)	3 (20.0%)	0.629
Hyperkalaemia	5 (17.9%)	2 (13.3%)	0.702
Hypoalbuminemia	24 (85.7%)	9 (60.0%)	0.057
Hypokalaemia	13 (46.4%)	3 (20.0%)	0.087
Hyponatremia	15 (53.6%)	9 (60.0%)	0.686
Sepsis	12 (42.9%)	5 (33.3%)	0.543
Hypernatremia	0 (0.0%)	1 (6.7%)	0.167
Lower respiratory tract infection	2 (7.1%)	0 (0.0%)	0.289
Acute liver injury	1 (3.6%)	2 (13.3%)	0.576
Eosinophilia	1 (3.6%)	0 (0.0%)	0.459
Synechiae	1 (3.6%)	0 (0.0%)	0.459
None	2 (7.1%)	1 (6.7%)	0.643

Table 4.50 presents association between complications and age. There was a statistically significant relationship between age and sepsis, acute renal failure and hyperkalaemia ($p<0.05$). Most patients (50%, 4/8) over the age of 60 had acute renal failure compared to other age groups. Most patients aged between 0-20 had hyperkalaemia (50%, 4/8) and sepsis (75%, 6/8) when compared to patients in other age groups. There were no significant association between age and other complications ($p>0.05$).

Table 4.50: Association between complications and age

Variables	Age Category (N=43)	Fisher's Exact Test
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	0-20 (n=8)	21-40 (n=15)	41-60 (n=12)	>60 (n=8)	P-value
Complication					
Anaemia	3 (37.5%)	3 (20%)	1 (8.3%)	0 (0.0%)	0.193
Acute renal failure	1 (12.5%)	0 (0.0%)	2 (16.7%)	4 (50%)	0.044
Hyperkalaemia	4 (50%)	0 (0.0%)	3 (25%)	1 (12.5%)	0.026
Hypoalbuminemia	5 (62.5%)	12 (80%)	10 (84.3%)	6 (75%)	0.433
Hypokalaemia	2 (25%)	7 (46.7%)	4 (33.3%)	3 (37.5%)	0.832
Hyponatremia	5 (62.5%)	7 (46.7%)	6 (50%)	6 (75%)	0.431
Sepsis	6 (75%)	5 (33.3%)	2 (16.7%)	3 (37.5%)	0.031
Hypernatremia	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)	0.591
Lower respiratory tract infection	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (12.5%)	0.527
Acute liver injury	1 (12.5%)	1 (6.7%)	0 (0.0%)	1 (12.5%)	0.505
Eosinophilia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	0.214
Synechiae	1 (12.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.214
None	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (13.3%)	0.440

4.4 Overview of research findings

The demographic characteristics of the study sample, consisting of 43 African subjects, were analysed. Findings include an average age of 39 ± 23 , with a diverse age distribution, majority being ≥ 40 years (60.5%). Females comprised 65%, with 96.4% not pregnant. Most patients had no reported allergies (93%), and 74.4% had no family history of SJS/TEN.

The drug class that caused SJS/TEN was identified in 90.5% of cases. Antibiotics and antiretrovirals were the commonest drug classes, each comprising 19.0%. Allopurinol was identified as the commonest drug cause of the disease spectrum (14.0%). In 20.9% of patients, the drug name could not be identified. The majority of patients (18.6%) had a reaction time beyond 28 days after drug ingestion. Additionally, a majority of patients had a duration of symptoms beyond 72 hours before presenting to Pietersburg hospital.

The severity of reactions in the spectrum varied, with TEN accounting for 37.2% of the patients, followed by SJS/TEN overlap (32.6%), and SJS (30.2%). HIV was the most common comorbid condition (21/43, 48.8%). Blood culture analysis revealed a diverse array of bacterial pathogens, with coagulase negative *Staphylococcus* being the most prevalent. Various mixed infections involving multiple pathogens were also observed.

The most prevalent SCORTEN parameter was TBSA>10% (69.8%, 30/43) followed by Age≥40 (46.5%, 20/43) and tachycardia (30.2%, 13/43). Amongst the patients that eventually demised, a high SCORTEN score of 5 and 4 was recorded in two patients (33.3%, 2/6)

All 43 patients in the study received supportive care. In this cohort, 25.6% of the patients received systemic steroids, 2.3% received cyclosporine and 2.3% received IVIg. Most patients were admitted for less than 8 days (39.5%, 17/43), followed by 8 to 14 days, accounting for 27.9% (12/43). A total of 32.6% (14/43) of the patients were admitted for more than 14 days.

The most common complications included hypoalbuminemia, hyponatremia and sepsis. The majority were hospitalised for less than 28 days (90.7%), with a survival rate of 86.0%.

Age was significantly associated with diabetes mellitus ($p=0.003$), HIV ($p=0.024$) and hypertension ($p<0.001$). Some age groups were significantly associated with tachycardia ≥ 120 b/min, urea >10 mmol/L, the presence of malignancy and age ≥ 40 years ($p<0.05$). The female gender was significantly associated with longer duration of hospitalisation, and age was statistically significantly associated with sepsis, acute renal failure and hyperkalaemia ($p<0.05$).

4.5 CONCLUSION

This chapter presented, interpreted and discussed the findings of the study in accordance with set objectives. It also compared the study results to relevant literature. The next chapter includes recommendations and limitations of the study.

CHAPTER 5

SUMMARY, RECOMMENDATIONS AND CONCLUSION

5.1 INTRODUCTION

This chapter will summarise the research design and interpretation of findings, give recommendations, and discuss limitations of the study. Conclusions will be drawn in relation to the research questions.

5.2 RESEARCH DESIGN AND METHOD

This was a retrospective cross-sectional study analysing hospital records of patients admitted with SJS/TEN. The study population was all patients admitted between January 2018 and December 2022 with SJS/TEN at Pietersburg Hospital, in Limpopo Province. The sample size 43 patients, and a census sampling method was used. Clinical characteristics, severity of TEN using SCORTEN, management outcomes and associations were investigated, wherein statistical tests were utilised.

5.3 INTERPRETATION OF THE RESEARCH FINDINGS

The interpretation of research findings is aligned to the research objectives stated below:

What are the clinical characteristics of SJS/TEN in patients admitted to Pietersburg Hospital?

What is the severity of TEN using SCORTEN among patients admitted with SJS/TEN at Pietersburg Hospital?

What are the management outcomes of patients with SJS/TEN at Pietersburg Hospital?

What is the association between demographic factors and clinical characteristics, disease severity and management outcomes of patients with SJS/TEN at Pietersburg Hospital?

The discussion will be preceded by interpretation and discussion of the demographic factors.

5.3.1 Demographic factors

5.3.1.1 Race

Our study consisted of only Black patients. There were no patients of other races that presented with SJS/TEN during the study period. This finding is line with the demographics of Limpopo province. Census 2011 of statistics South Africa reported that the majority of Limpopo citizens were Black (96.7%) (Statistics South Africa, 2011) A higher prevalence of Black patients (54%), followed by 33% White patients, and 13% patients of other races/ethnicities has been previously reported in North Carolina Jaycee Burn Center (Duplisea, Roberson, Chrisco, Strassle, William et al., 2021).

5.3.1.2 Gender

In the cohort, there was a predominance of female patients (65%). This is similar to a study done by Micheletti et al (2018) and Lehloenya et al (2019). However, this contrasts with a study in the Free State province, South Africa, which showed a predominance of males (58.2%) (Moosa, 2021). On the other hand, there are more females than males in our population. In addition, the male to female ratio of SJS/TEN has been reported to be higher in females.

5.3.1.3 Age

Older age has been characterized as a risk factor for the development of SJS and TEN with patients older than 40-years being reported to have poorer patient outcomes (Bastuji-Garin et al. 2000). In this study, the average age of patients was 39.30 ± 23.11 and the majority were older than age 40 years (60.4%), this is similar to a previous study which reported a mean age of 43.4 ± 21.7 (Yang et al. 2018).

5.3.2 Objectives

5.3.2.1 Objective 1: Clinical characteristics of SJS/TEN in patients

Drug history

Drug ingestion was reported by 90.5% patients (39/43). However, four (9.5 %) patients did not and had no known infections. This result was similar to what Yang et al. reported in China wherein 88.6% (147/166) patients reported drug ingestion whilst 19 (11.4%) patients had no offending drug identified and no known infections (Yang et al. 2018). Definite drug name was unknown in 20.9% of patients, indicating that a significant portion of the cases did not have a definite specific drug name identified.

In this study, antibiotics (19.0%) and antiretrovirals (19.0%) were the most predominant drug classes associated with SJS and TEN. This is in keeping with a previous study which showed that antibiotics, anticonvulsants, and non-steroidal anti-inflammatory drugs are associated with a high risk of SJS and TEN (Abou-Taleb et al. 2020). Interestingly, a study from Nigeria, where the HIV prevalence is 1.4% among adults (15 – 49 years), concluded ART and antibiotics were the most implicated drug classes, with nevirapine and Trimethoprim Sulfamethoxazole being identified as the most frequently implicated drugs.

Allopurinol was found to be the most common culprit agent identified, similar to a previous study (Halevy et al. 2008). Both Trimethoprim Sulfamethoxazole and nevirapine are well-known to cause drug hypersensitivity reactions, in this study, Trimethoprim Sulfamethoxazole and nevirapine were the second and third commonly implicated drugs, respectively.

Consistent with several other studies, a proportion of patients had more than one possible culprit drug being identified and oftentimes a specific drug could not be identified as the definite agent (Sharma, Sethuraman, and Minz 2008; Miliszewski et al. 2016).

Zimmerman et al., 2020 reported that in 5-20% of the cases, the cause of SJS/TEN is unknown. This is in keeping with the findings in this study as the cause was found to be idiopathic in 9.5% of the cases.

Several individual drugs like sodium valproate, enalapril amlodipine, Trifen, Grandpa, methotrexate, diclofenac, Sodium valproate, carbamazepine, abacavir, carbamazepine, aloe, trivage, rifampicin, grandpa and grape seed oil, amoxicillin, and Tribuss, each account for 2.3% of cases. This diverse range of drugs suggests that various pharmaceutical agents can potentially trigger SJS/TEN.

Past history of allergies/drug reactions

In our cohort, only 7% patients reported history of allergies. This percentage doubled in a study that focused on macrolide antibiotics induced SJS/TEN, wherein 14.8% of the patients had a positive history of allergic drug reaction (Pejčić., 2021). The low percentage in our study may be a reflection that our patients population who have known drug allergies avoid the use similar drug which may trigger a second episode of drug reaction such as SJS/TEN.

Co-morbidities

Of the 43 participants in the study, 37 participants (86%) reported co-morbidities. Therefore, 14% had no co-morbidities. The most prevalent co-morbidity in our cohort was HIV (21/43;48.8%). This prevalence is higher than the HIV prevalence reported in South Africa (19.1%)(UNAIDS and AIDSinfo. Country factsheets South Africa, 2020). The high prevalence rate in our cohort can be attributed to HIV infection being an independent risk factor for the development of SJS/TEN, an immune-mediated drug reaction (Peter, Choshi and Lehloenya., 2019). Also, HIV infection often than not involves polypharmacy, opportunistic infections like Tuberculosis and immune dysregulation (Peter et al.,2019). A retrospective study conducted in South Africa, Free State province identified HIV infection as the most prevalent (70%) co-morbidty (Moosa., 2021).

After HIV, hypertension (4.7%), diabetes mellitus (4.7%) and epilepsy (4.7) were the most prevalent comorbid conditions. This is in contrast to a study done in India, where the most common co-morbid conditions were found to be seizure disorder (21%) followed by hyperuricemia/gout (17.7%) and HIV infection (12.9%) (Manvi, Mahajan, Mehta, Chauhan and Vashist et al., 2022).

Family History

Most patients had no family history of SJS/TEN (74.4%). The prevalence of family in patients with SJS/TEN have not been reported previously in literature.

Reaction time/duration between drug ingestion and onset of symptoms

Duration in days between drug ingestion and onset of symptoms varied among patients. Most of the patients (18.6%) had a reaction time period from drug initiation to drug reaction beyond 28 days, followed by 0-3 days (16.3%), 4-7 days (16.3%), 8-14 days (16.3%) and 15-28 days (11.6%), highlighting the prolonged time since onset of symptoms before presenting to our hospital. It is in keeping with a study done by Charlton et al. (2020), where symptoms started within 8 weeks after drug ingestion, with most cases appearing between 4 days and 4 weeks of starting a drug (Charlton et al., 2020).

Duration of symptoms prior to hospital visit

Most patients had a duration of symptoms beyond 72 hours (69.8%) before presenting to Pietersburg hospital. No patients presented to hospital in less than 24 hours from the onset of symptoms. This is comparable to 5.04 ± 3.35 days delay between the onset of symptom and presentation to tertiary hospital reported by Thakur et al. (2021). This may be explained by that our hospital is a tertiary referral hospital with most patients initially presenting to their local hospital, which leads to increase in the time interval before presentation to our hospital.

Prodromal symptoms

In the study cohort, prodromal symptoms were mostly not provided in most patient's medical records (51.2%). Some patients (14.0%) did not report any prodromal symptoms. This could be because the attending doctor did not enquire or/and record such clinical history. The most commonly reported prodromal symptom was fever (18.6%) followed by odynophagia (14%), stinging eyes (9.3%) and asthenia (7.0%). In other studies, fever was the reported prodromal symptom in 63 – 65% of the patients (Weinkle, Pettit, Jani, Keller, Lu, 2019, Bequignon, Duong, Sbidian, Valeyrie-Allanore, Ingen-Housz-Oro, 2015).

Mucous membrane involvement

All patients in the study had mucous membrane involvement. This correlated with reports from Kanagarajan et al. (2023) who observed mucosal involvement in all patients, in whom the oral mucosa was involved in all patients (100%), followed by urogenital mucosa (76.5%), and conjunctiva (64.7%), then pharynx and nasal

mucosa in eight patients each (47.1%) (Kanagarajan, Murthy, Moni and Palanivel, 2023). This study did not evaluate specific mucous membranes involved.

Severity assessment

The study demonstrated more TEN (37.2%) than SJS/TEN overlap (32.6%), and SJS (30.2%) cases. This is in contrast with results observed by Isaac et al. (2021), whose study demonstrated more SJS (85.7%) than TEN (10.7%) and SJS/TEN overlap (3.5%) (Isaac, Damayanti, Fatimah and Hidayati, 2021).

Blood cultures

The positive blood culture results showed a diverse array of bacterial pathogens identified in the samples. Most of the isolated pathogens were hospital acquired pathogens which included *coagulase negative Staphylococcus aureus*, *Escherichia coli*, *Bacillus species*, *Acinetobacter baumannii*, *Enterococcus faecium*, and *Enterococcus faecalis*. Some patients had more than one organism isolated. Koh et al. reported similar organisms such as *Acinetobacter baumannii*, *Staphylococcus aureus* and *Enterobacteriaceae* as the commonly isolated organisms in patients who developed sepsis (Koh et al., 2019).

5.3.2.2 Objective 2: Severity of TEN using SCORTEN

SCORTEN parameters

The most prevalent SCORTEN parameter was TBSA>10% (69.8%, 30/43) followed by age ≥ 40 (46.5%, 20/43) and tachycardia (30.2%, 13/43). Records which had insufficient SCORTEN data on admission comprised 44%. The missing variables were serum bicarbonate, glucose and urea. A similar challenge was encountered in a study conducted in Free State province, South Africa, where SCORTEN was removed as an objective due to insufficient data, mainly serum bicarbonate, as it was not routinely performed (Moosa, 2021). This challenge was also noted by other researchers (Lehloenyha, Haitembu, Basera and Peter, 2019).

SCORTEN score

Of the patients that demised, one patient (16.7%) had a SCORTEN score of 5 and another (16.7%) a SCORTEN score of 4, with a predicted mortality of 90% and 58% respectively. The rest (66.7%) of the patients that demised had a SCORTEN score

of ≤ 3 with a predicted mortality of $\leq 35\%$. Literature reports that SCORTEN is a good predictor of mortality in patients with TEN (mortality (Torres-Navarro, Briz-Redón and Botella-Estrada, 2021; Zhang et al., 2022)).

5.3.2.3 *Objective 3: Management outcomes*

Management

In our institution, the mainstay of treatment is supportive treatment, which entails withdrawal of the possible culprit drug, wound care, including oral mucosa and eye care, pain management, nutritional support, fluid and electrolyte management. A multidisciplinary approach adopted includes internal medicine, ophthalmology and dietetics. All 43 patients in the study received supportive care, however, our study did not investigate the finer details and extent to which supportive care was implemented, such as the type wound dressings used, type of intravenous fluid given or specific drug name of antibiotic administered.

Treatment with antibiotics is recommended only if there are clinical signs of infection or microbiological evidence of infection (Creamer et al., 2016). In our cohort, most patients received systemic antibiotics (81.4%).

Consensus regarding the use of adjunctive therapies such as systemic corticosteroids, disease-modifying agents, IVIg, cyclosporine, intravenous immunoglobulins and more recently, tumour necrosis factor-alpha (TNF α) inhibitors has not been reached (Frantz et al., 2021). These adjunctive therapies nowadays are often utilised, however, there is still a debate on the most effective adjunctive therapy (Pisano, Brown and Jambusaria., 2023). In our study, 25.6% of the patients received systemic steroids, 2.3% received cyclosporine and 2.3% received IVIg. Based on the current data, standardised management approach is not yet clear. It is therefore advised that decisions regarding such treatment be made on a case-by-case basis until further data are available (Schneider and Cohen, 2017).

Length of stay

The majority of patients were admitted for less than 8 days (39.5%, 17/43), followed by 8 to 14 days, accounting for 27.9% (12/43). A total of 32.6% (14/43) were admitted for more than 14 days. Amongst the patients admitted over 14 days, two (4.7%) patients were hospitalised for more than 28 days. This is comparable to a

length of stay of less than 10 days for most patients and one patients hospitalised for more than 40 days reported by Arantes et al. (2017).

Patients admitted for more than 14 days (64.3%) had sepsis as a complication, in contrast to those with shorter stays (less than 14 days). Systemic antibiotics were mostly administered in patients with prolonged duration of hospitalisation. This could be explained by the fact that long hospital stays predispose patients to nosocomial infections, hence sepsis and will therefore necessitate systemic antibiotic administration. The relationship between sepsis, systemic antibiotic administration and long duration of hospitalisation is not well reported in literature.

Complications

The complications observed in this study in patients with SJS/TEN are wide and varied, reflecting the systemic nature and severity of these conditions. Notably, the most prevalent complication was hypoalbuminemia (72.1%) followed by hyponatremia (51.2%) and sepsis (41.9%). Girish et al. (2023) reported hypoalbuminemia in 55% of the patients, which is lower than 72.1% reported in the present study. El-Hamd et al. (2017) reported hyponatremia in 57% of the patients which is higher than 51.2% reported in this cohort. The sepsis complication observed in this study reflects the results of several other studies, indicating that infection is a major problem in this group of patients (Diao et al., 2020).

Additionally, a variety of less common complications were observed, ranging from acute renal failure (16.3%), to acute liver injury (7%), anaemia (16.3%) and synechiae (2.3%). Patients had multiple complications, indicating the propensity for multi-organ involvement and systemic complications in these patients. These findings emphasise the need for comprehensive supportive care and close monitoring to address the complications timeously. Other researchers reported transaminitis, acute kidney injury, pneumonia and leucopenia as complications observed in their studies (Yang et al., 2020; Thakur et al., 2021; Girish et al., 2023).

Overall, the management of SJS/TEN requires a multidisciplinary approach, with particular attention to fluid and electrolyte balance, infection control, and prompt recognition and management of systemic complications to optimise patient outcomes.

Mortality of SJS/TEN

The majority of patients survived (86.1%), with equal proportions of males and females among the demised patients. The total mortality rate observed was 14%, mostly occurring in the TEN group (66.7%) than SJS/TEN overlap (16.7%) and SJS group (16.7%). This is in contrast to another study wherein mortality was higher in SJS/TEN overlap group than in TEN and SJS (Hsu, Brieva, Silverberg and Silverberg, 2016). Sepsis was a common complication (83.3%) among patients that demised.

Supportive care and systemic antibiotics were the predominant treatment of choice in patients that succumbed to death. Comparatively, a study done in South Africa found that patients treated with IVIg and systemic steroids in combination had a survival rate of 97% (Chateau et al., 2019). However, another study suggested that IVIg combined with corticosteroid does not significantly reduce mortality but could reduce recovery period for SJS and TEN (Ye, Zhang and Zhu, 2016).

5.3.2.4 Objective 4: Association between demographic factors and clinical characteristics, disease severity and management outcomes

Association between demographic factors and clinical characteristics

Older age, above 60 years, was significantly associated with diabetes mellitus ($p=0.003$) and hypertension ($p<0.001$). The age group 21 to 40 was significantly associated with HIV ($p=0.024$). In literature, older age has been documented as a risk factor of diabetes mellitus type 2 and hypertension (Halim and Halim., 2019; Bui Van, Vo Hoang, Bui Van, Anh and Minh et al., 2019). Mabasa et al. (2019) found that the age group 25-49 years, 50 years and older, was associated with a higher prevalence of HIV infection (Mabaso, Makola, Naidoo, Mlangeni, Jooste et al., 2019).

Statistical analysis revealed no significant associations between drug history, past history of drug allergies, condition for which the patient was taking the drug, family history of drug reaction, reaction time, duration of symptoms prior to hospital visit, prodromal symptoms, mucous membrane involvement, severity of illness and

demographic factors such as age and gender. These results suggest that these factors did not significantly differ between the different age groups and gender within the study population neither is such associations described in the current available literature.

Association between demographic factors and SCORTEN parameters

Some age groups were significantly associated with tachycardia, ≥ 120 b/min, urea > 10 mmol/L, the presence of malignancy and the parameter age ≥ 40 . Tachycardia and malignancy were most prevalent in the 0-20 age group ($p < 0.05$). Association with malignancy in this young group is due to childhood leukemia patients reacting to chemotherapy. Majority of patients (73%) in the 41-60 age group and above 60 years had urea levels above 10 mmol/L ($p < 0.001$). The correlation between the 41-60 years and above 60 years age groups with age ≥ 40 years SCORTEN parameter is expected because this parameter contributes to the SCORTEN scale. These associations have not been reported previously in literature.

Statistical analysis revealed no significant associations between gender and SCORTEN parameters. In addition, this study did not find any associations between the SCORTEN scores and demographic factors such as age and gender. Currently, association between demographic factors and SCORTEN scores is not well established in literature.

Association between demographic factors and management outcomes

Female gender was significantly associated with a longer duration of hospitalisation ($p = 0.018$). This finding has been documented previously, wherein females had a significantly longer lengths of stay than males ($P = 0.001$) (Duplisea et al., 2022).

Age had an associated link with sepsis, acute renal failure and hyperkalaemia ($p < 0.05$). Acute renal failure was significantly associated with patients over 60 years of age ($p = 0.044$). This could be due to subtle insults to the kidneys over the years and SJS/TEN dealing a blow and causing a major insult. Hyperkalaemia showed a statistically significant association with the 0-20 age group ($p = 0.026$). Sepsis was significantly associated with the 0-20 age group ($p = 0.031$). These associations have not been described before in literature and could be incidental.

There were no other statistically significant association between demographic factors and management outcomes. These results suggest that these factors did not significantly differ between the different age groups and gender within the study population.

Overall, these findings provide valuable insights into the demographic, clinical characteristics and treatment outcomes of SJS/TEN patients in our setting. They underscore the multifaceted nature of these condition and highlight the importance of comprehensive management strategies to optimise patient care and outcomes. Further research is warranted to elucidate the underlying mechanisms and risk factors associated with SJS/TEN development in diverse patient populations.

Of the patients that demised, one patient (16.7%) had a SCORTEN score of 5 and another (16.7%) a SCORTEN score of 4 with a predicted mortality of 90% and 58%, respectively which demonstrated the accuracy of SCORTEN in predicting mortality.

In our setting, most patients were treated conservatively with supportive care. Only a few patients received cyclosporine (2.3%) or IVIg (2.3%), signifying the global lack of consensus on institution of systemic immunomodulatory therapies in SJS/TEN.

The length of stay was less than 8 days in the majority of patients, which may be viewed as a good outcome. Multi-organ complications observed were diverse and may have impacted mortality. The mortality rate was 14% (6/43), mostly occurring in the TEN group (66.7%) than SJS/TEN overlap (16.7%) and SJS group (16.7%) which is anticipated as TEN is the most severe category.

Younger age group was significantly associated with tachycardia $>120\text{b/min}$, ($p=0.018$). This is probably due to a higher average heart rate in younger patients. The significant association ($p<0.001$) between elevated urea level of $>10\text{mmol/L}$ and older age could be due to increased risk of kidney injury in older patients. Female gender was significantly associated with longer duration of hospitalisation ($p=0.018$). This association has been reported before which is quite intriguing to further asses the science behind this association. A statistically significant relationship was observed between sepsis, hyperkalaemia, acute renal failure and various age groups ($p<0.05$). Such associations have not been reported previously in literature.

5.4 RECOMMENDATIONS

The knowledge obtained from this study should be shared with colleagues from Dermatology department at Pietersburg hospitals, doctors from referring hospitals in the Limpopo province and dermatology departments in various hospitals in South Africa as a whole.

The use of causality assessment tools such as the Algorithm for Drug Causality for Epidermal Necrolysis (ALDEN) in instances where history is not sufficient to ascertain the causative drug is recommended. The use of patch test and/or lymphocyte transformation test is recommended to identify the definitive culprit drug in patients who are on more than one drug and/or combination drugs at the time of onset of SJS/TEN.

It is recommended that clinicians ascertain taking detailed history, complete through physical examination and record detailed notes accordingly to aid future retrospective studies.

Longitudinal follow-up to assess the long-term outcomes and complications of patients with SJS and TEN is recommended. Tracking these patients over an extended period can provide insights into the chronic effects and recurrence rates of these conditions.

Incorporation of other severity scoring systems to predict mortality such as CRISTEN score is recommended as it entails clinical parameters only. Wherein SCORTEN score cannot be completed due to unavailability of laboratory parameters such as bicarbonate and urea, CRISTEN score is helpful.

Future prospective studies are recommended to complement the retrospective findings as prospective research can provide real-time data and enable the collection of additional details that may not be available in retrospective reviews.

Future studies which will address manifestations of SJS/TEN outside of the skin, eyes, and oral mucosa are recommended as this entity is not well recognized, and, therefore, are often not addressed. This entails chronic complications in affected

organ systems (pulmonary, gynaecologic, gastrointestinal/hepatic, oral, otorhinolaryngologic, genitourinary, and renal systems), as well as significant psychosocial, nutritional, and pain consequences and management of SJS/TEN.

Collaborate with multiple healthcare centers to increase the diversity and representativeness of the study sample. Involving multiple centers can lead to a more comprehensive understanding of the clinical characteristics and outcomes of SJS and TEN across various settings.

5.5 CONTRIBUTIONS OF THE STUDY

This was, to the best of the researcher's knowledge, the first study to be conducted at Pietersburg Hospital and in Limpopo Province. The findings of the study will contribute to the body of knowledge in dermatology. The findings will also guide policy development, standard operating procedures, treatment guidelines and health promotion strategies.

5.6 LIMITATIONS OF THE STUDY

The study was constrained by its retrospective design, and the small sample size. The single-centre approach makes the findings not generalisable to South Africa as a country. The lack of standardisation in data entry into patient files, attributable to the involvement of various medical practitioners, is a significant limitation in this study. Additionally, there may be a potential for observer bias, when estimation of skin detachment is calculated. The presence of missing data in medical records hinders the ability to compute some variables such as SCORTEN scores.

5.7 CONCLUSIONS

In conclusion, this retrospective study showed the predominance of Black race, females and age ≥ 40 in patients with SJS/TEN. Antibiotics and antiretroviral drug classes were the commonest cause of SJS/TEN in this study with Allopurinol most common culprit drug. SCORTEN parameters requiring laboratory investigation or machinery device were not recorded in many of the patients which posed a

challenge in calculating SCORTEN scores. All patients received supportive care and most received antibiotic treatment with good outcome as most patients survived SJS/TEN. Immunomodulatory therapies were infrequently used. The total mortality rate was low at 14%. The female gender was significantly associated with longer duration of hospitalisation, which correlates to what has been previously described

Some associations that have not been described before in literature included diabetes mellitus ($p=0.003$), hypertension ($p<0.001$) and age above 60, middle age group and HIV ($p=0.024$). Some age groups were significantly associated with tachycardia $> 120\text{b/min}$, urea $> 10\text{mmol/L}$, the presence of malignancy and age ≥ 40 ($p<0.05$). Age categories were statistically significantly associated with sepsis, acute renal failure and hyperkalaemia ($p<0.05$). These associations have not previously been reported in the literature, to the best of this researcher's knowledge.

CHAPTER 6

SUMMARY AND CONCLUSIONS

6.1 CHAPTERS SUMMARY

6.1.1 Chapter 1

Chapter one entailed an introduction of the study, briefly defined SJS/TEN and provided a short section on the literature review addressing the prevalence of SJS/TEN world-wide, Africa and South Africa and classified the SJS/TEN disease spectrum. In addition, it addressed the research problem. The aim, objectives, research questions and methodology of the study were outlined. The ethical considerations and the significance of conducting this study were highlighted.

6.1.2 Chapter 2

Chapter two contained a critical evaluation, analysis and synthesis of recent literature on SJS/TEN, relevant to this study. The prevalence, demographic factors, clinical features, severity of TEN using SCORTEN, management outcomes and associations between demographic factors and clinical characteristics, disease severity and management outcomes were discussed in detail.

6.1.3 Chapter 3

This chapter provided a comprehensive discussion on research methodology followed in conducting this study. The research design, sampling methods, data collection methods and tools, data analysis, ethical issues related to the study, internal and external validity of the study were all discussed.

6.1.4 Chapter 4

Chapter four presented, the research findings. There were 43 Black patients of which the majority were females (65.1%). The average age of the studied patients was 39.30 ± 23.11 years. Allopurinol (14.0%, 6/43) was the most common cause of SJS/TEN, and HIV was the most common co-morbid condition (34.9%, 15/43) observed. Reaction time from drug ingestion to drug reaction was beyond 28 days in most of the patients (18.6%, 8/43).

Most patients had TEN (37.2%) than SJS/TEN overlap (32.6%), and SJS (30.2%) cases. The mainstay of treatment was supportive care. The length of stay was less than 8 days in majority of the inpatients (37%, 16/43). The total mortality rate was 14% (6/43), mostly occurring in the TEN group (66.7%, 4/6).

The study identified association between demographic factors, clinical characteristics, disease severity and management outcomes

6.1.5 Chapter 5

Chapter five interpreted and summarised the study findings. It also gave recommendations and discussed limitations of and contributions to the study.

6.2 CONCLUSION

This chapter summarised all the chapters of the study. The findings of the research study shed light on several critical aspects related to SJS and TEN in general and the disease spectrum in Limpopo Province, South Africa. The study uncovered the drug causes of SJS/TEN in our setting, of which in minority of cases, were secondary to herbal medicine ingestion. The study confirms the importance of prompt diagnosis and appropriate treatment, emphasising the significance of detailed clinical history taking, clinical examination and recording clinical findings.

Additionally, the research identifies potential areas for improvement in healthcare practices, including the need for standardized protocols and multi-centre collaborations to gather more diverse and representative data. The thesis concludes with a call for continued research efforts in South Africa to advance our

understanding of SJS and TEN, ultimately contributing to improved patient outcomes and the development of preventive measures.

The aim of the study was to describe the clinical characteristics and evaluate treatment outcomes of patients with Stevens-Johnson syndrome and Toxic epidermal necrolysis. This study has successfully achieved that and added to the body literature on SJS/TEN in the country.

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Annexure A:

Data collection tool

ID/Code:

Section A – Demographic data

1. Age

2. Gender

Female

Male

3. Pregnancy (in females)

Yes

No

4. Race

Black	White	Coloured	Other
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Section B – Clinical characteristics

1. History

Drug history- Most probable causative drug.

		Drug group	Drug name
A	Antibiotics		
B	Antiepileptics		
C	Antiretrovirals		
D	NSAIDS		
E	Anti TB Treatment		
F	Herbal medication		
G	Other		

H	Not identified		
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2. Past history of allergies/drug reactions

Yes No

3. Co-morbidities

		Yes	No
A	HIV		
B	Epilepsy		
C	Gout		
D	Tuberculosis		
E	Diabetes mellitus		
F	Hypertension		
G	Malignancy If yes, type of malignancy:		
H	Other		

4. Condition for which the patient was taking the drug

		Yes	No
A	HIV		
B	Epilepsy		
C	Gout		
D	Tuberculosis		
E	Diabetes mellitus		

F	Malignancy		
G	Urinary tract infection		
H	Pharyngitis/tonsillitis		
I	Gastroenteritis		
J	Influenza		
K	Other		
L	Not provided		

5. Family history of drug reaction

A. Yes ☐

B. No ☐

C. Not provided ☐

6. Reaction time/duration between drug ingestion and onset of symptoms

A	0-3 days	
B	4-7 days	
C	8-14 days	
D	15- 28 days	
E	> 28 days	
F	Not provided	
G	Not applicable	

7. Duration of symptoms prior to hospital visit

A	<24 hours	
B	24-48 hours	

C	49- 72 hours	
D	>72 hours	

8. Prodromal symptoms

A	Fever	
B	Odynophagia	
C	Stinging eyes	
D	Asthenia	
E	Other	
F	None	
H	Not provided	

9. Skin and mucous membranes – clinical examination

9.1 Mucous membranes involvement

A. Yes ☐

B. No ☐

9.2 Severity assessment

A	SJS	
B	SJS/TEN overlap	
C	TEN	

10. SCORTEN

10.1 SCORTEN parameters

		Yes	No	Not done
A	Age > 40 years			
B	Malignancy			
C	Tachycardia (120/min)			
D	TBSA >10%			
E	Serum urea > 10mmol/L			
F	Serum glucose > 14mmol/L			
G	Bicarbonate < 20mmol/L			

10.2 Classification (Score)

	Score	Predicted mortality(%)	
A	0-1	3	
B	2	12	
C	3	35	
D	4	58	
E	≥5	90	

11. Blood cultures

A	Staphylococcus aureus	
B	Klebsiella pneumoniae	
C	Acinetobacter	
D	Other (Specify)	
E	Other (Specify)	
F	Negative	
G	Not done	

12. Outcome

A. Survived

B. Demised

Section C - Management

1. Supportive care

A. Yes ☐

B. No ☐

2. Systemic steroids

A. Yes ☐

B. No ☐

3. Cyclosporine A

A. Yes ☐

B. No ☐

4. Intravenous immunoglobulins

A. Yes ☐

B. No ☐

5. Oral/IV Antibiotics

A. Yes ☐

B. No ☐

6. Length of stay

A	< 3 days	
B	3-7 days	
C	8-14 days	
D	15-28 days	
E	>28 days	

7. Complications

A	Sepsis	
B	Acute renal failure	
C	Lower respiratory tract infection/ Acute respiratory distress syndrome	
D	Hyperkalaemia	
E	Hypokalaemia	
F	Hypernatremia	
G	Hyponatremia	
H	Hypoalbuminemia	
I	Symblepharon	
J	Phimosis	
H	Corneal scarring	
I	Other	
J	None	

Annexure B: Turfloop Research Ethics Committee Clearance Certificate



University of Limpopo
Department of Research Administration and Development
Private Bag X1106, Sovenga, 0727, South Africa
Tel: (015) 268 4713, Fax: (015) 268 2306, Email: moore.hutamo@ul.ac.za

TURFLOOP RESEARCH ETHICS COMMITTEE
ETHICS CLEARANCE CERTIFICATE

MEETING: 22 May 2023

PROJECT NUMBER: TREC/130/2023: PG

PROJECT:

Title: Clinical characteristics and treatment outcomes of patients with Stevens-Johnson syndrome and toxic Epidermal Necrolysis at Pietersburg Hospital.
Researcher: MK Rafumbedzani
Supervisor: Dr AR Sema-Ramashala
Co-supervisor: N/A
School: Medicine
Degree: Master of Medicine (Dermatology)

PROF D MAPOSA
CHAIRPERSON: TURFLOOP RESEARCH ETHICS COMMITTEE

The Turfloop Research Ethics Committee (TREC) is registered with the National Health Research Ethics Council, Registration Number: **REC-0310111-031**

Note:

- i) This Ethics Clearance Certificate will be valid for one (1) year, as from the abovementioned date. Application for annual renewal (or annual review) need to be received by TREC one month before lapse of this period.
- ii) Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee, together with the Application for Amendment form.
- iii) PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

Annexure C: Approval to conduct a study from Limpopo Department of Health



LIMPOPO
PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

DEPARTMENT OF
HEALTH

Ref : LP_2023-06-002
Enquires : Dr Ramalivhana NJ
Tel : 015-293 6028
Email : Phoebe.Mahlokwane@dhsd.limpopo.gov.za

MIKOVHE KARYN RAFUMBEDZANI

PERMISSION TO CONDUCT RESEARCH IN DEPARTMENTAL FACILITIES

Your Study Topic as indicated below;

CLINICAL CHARACTERISTICS AND TREATMENT OUTCOMES OF PATIENTS WITH STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS AT PIETERSBURG HOSPITAL

1. Permission to conduct research study as per your research proposal is hereby Granted.
2. Kindly note the following:
 - a. Present this letter of permission to the Office of Clinical Executive Director a week before the study is conducted.
 - b. This permission is **ONLY for Pietersburg Hospital**.
 - c. In the course of your study, there should be no action that disrupts the routine services or incur any cost on the Department.
 - d. After completion of study, it is mandatory that the findings should be submitted to the Department to serve as a resource.
 - e. The researcher should be prepared to assist in the interpretation and implementation of the study recommendation where possible.
 - f. **The approval is only valid for a 1-year period.**
 - g. If the proposal has been amended, a new approval should be sought from the Department of Health
 - h. Kindly note that, the Department can withdraw the approval at any time.

Your cooperation will be highly appreciated.

pp

Head of Department

14/07/2023

Date

Private Bag X9302, Polokwane 0700
Fidel Castro Ruz House, 18 College Street, Polokwane 0700
Tel: 015 293 6000. Fax: 015 293 6211. Website: www.doh.limpopo.gov.za

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Annexure D: Permission to conduct study by the Pietersburg hospital Chief Executive Officer



LIMPOPO

PROVINCIAL GOVERNMENT
REPUBLIC OF SOUTH AFRICA

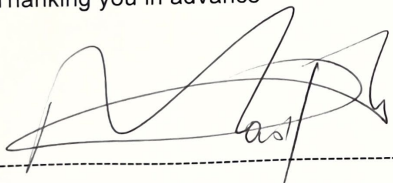
DEPARTMENT OF
HEALTH
Pietersburg Hospital

REF : 4/2/2
ENQ : MOLOKOMME N
TO : DR RAFUMBEDZANI MK
RESEARCHER
FROM : DR MC MASIPA
ACT CEO: PIETERSBURG HOSPITAL
DATE : 24 JULY 2023

RE : REQUEST FOR RESEARCH

1. The above matter refers.
2. Your request to conduct research is hereby granted.
3. You will be expected to avail the report to the institution upon completion.

Thanking you in advance



DR MC MASIPA
ACTING CHIEF EXECUTIVE OFFICER
PIETERSBURG HOSPITAL

24/07/2023

LIMPOPO PROVINCE	DATE
DEPARTMENT OF HEALTH	
PIETERSBURG HOSPITAL	
PRIVATE BAG X9316	
0700	
2023 -07- 26	
CHIEF EXECUTIVE OFFICER	

EXCELLENCE IS OUR PASSION

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