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# Meta-Analysis: Sepsis Approach in Sickle Cell Anaemia

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## Abstract

A comprehensive survey of the distribution of SCD in terms of genetic frequency and variations in treatment strategies is critical to the development of a national framework to manage the disease. Specifically, a very comprehensive understanding of the epidemiology of the disease and various other aspects is required. This study undertook a meta-review of SCD within Saudi Arabia. Five peer-reviewed journals with specific themes relating to the distribution of SCD and other aspects of the condition such as variations in the severity of the condition with age, variations in treatment plans with gender, and even in terms of race were studied. From the review, it was evident that, in order to adopt any specific program to control SCD, one must have a deep understanding of the patterns of the condition within the specific area of interest.

In order to ensure synergy in the management of the condition within Saudi Arabia, there is a need to understand the epidemiology behind the study. In terms of age, this review asserts that the severity of the condition is dependent on the age of patients so that older age lowers the survival rate of the patient. The study equally reveals that there is a lot of variance between males and females in terms of response to pain management for patients with SCD and, thus, practitioners must develop a segmented management program that takes into account these differences in gender, age, and even race. The inferences made in this study are quite relevant to the establishment of SCD management and control schedules. In terms of policy formulation, the conclusion of this study is essential to the development of a planning template to manage SCD within the population.

***Keywords:*** *Acute Chest Syndrome; Sickle Cell Disease (SCD); Systematic Inflammatory Response Syndrome (SIRS); Systematic Organ Failure Assessment (SOFA)*

## Introduction

There is an ongoing debate regarding the most relevant criteria for the diagnosis of sepsis within the realms of clinical practice [1]. Several scholars have proposed different approaches with no single approach endorsed as generally acceptable amongst practitioners.

Some of the approaches suggested include the use of a systemic inflammatory response syndrome (SIRS) strategy. In addition, the use of a sequential organ failure assessment score (SOFA) has been recommended by the majority of practitioners. Some guideline groups, especially in the UK and the US, have equally proposed the use of a risk stratification model [2].

Within the context of sickle cell anaemia, many studies have noted that sepsis is conventionally diagnosed through the clinical identification of a specific infection in a patient who meets the clinical attributes of SIRS. Many studies aver that, for patients with SCD, optimal care, including preventative care, is advised. In fact, as noted by Wailoo, best care is achievable through clinical treatment in institutions that specialise in SCD [3]. Whenever the severity of the condition can be assessed, self-treatment at home is usually advisable through a combination of various treatment plans, such as the use of oral analgesia, bed rest, and hydration if possible [4]. However, patients with SCD should only present themselves to the emergency department for treatment if home management fails.

The sepsis approach of managing SCD thus entails an elaborate strategy through which SCD can be evaluated within the sepsis spectrum of diseases, especially in instances where there is a systemic and dysregulated response by the host to a specific infection. The focus of this exposition is on providing insightful discourse on the sepsis approach to the treatment of SCD. The study will be limited to the treatment of adults with SCD.

### Objectives and Justification of the Study

The objective of this study is to offer an in-depth discussion on current sepsis approaches to the treatment and management of sickle cell anaemia. The study reviews various relevant and contemporary studies to achieve this objective. The rationale for this study is to come up with relevant evidence-based practices used in the management of sickle cell anaemia amongst adults. SCD has quite a high prevalence rate within the Middle East, and, therefore, there is a need to develop a very practical, yet effective management framework for the condition [5]. As such, the inferences made in this study will be essential in establishing a framework for the management of the condition. A review of contemporary studies that look at the management of the condition is essential to the establishment of a contemporary management model for the condition.

## Literature Review

### The concept of sepsis

Sepsis is a gamut of diseases where there is a systemic response by the patient or host to a specific infection [6]. Presentation ranges from non-localised symptoms to very severe signs with attestations of multi-organ dysfunction and septic shock. The risk of progression to fulminant ailment is predicated on various factors such as the magnitude of the infective focus, the quality and timing of intervention procedures for the disease, and the genetic predisposition of the patient [6]. Early recognition and diagnosis are necessary since early treatment has been associated with considerable benefit, both in the long term and short term.

The sepsis approach in SCD is hinged on the SIRS platform. As established by Ribeil, SIRS is the presence of several criteria from an array of clinical signs and laboratory investigations [7]. Many studies have noted that the concept of sepsis has greatly morphed over time. In 2016, the definition of sepsis was effectively updated by the deliberations of the third international consensus group-otherwise dubbed as sepsis – 3-as a way of properly understanding the disease [6]. This step was taken because the SIRS principle was established to be too vague to ascertain exactly what sepsis diseases entail. They defined sepsis conditions as those life-threatening conditions caused by organ dysfunction that emanate from highly unregulated host responses to a specific infection.

Many research findings have established that sepsis is among the most common causes of death amongst hospitalised patients. Catella avers that the death toll of sepsis is in the same range as that of myocardial infarction [6]. In the US alone, studies found that the rate of hospitalisation of patients with sepsis increased by close to 68% in 2015 [6]. Comparatively, based on medical practices in the Middle East and Saudi Arabia, this figure is anticipated to be slightly higher. With advancement in the age of the patient, there is a higher likelihood that sepsis becomes more prominent.

**Diagnostic approaches to sepsis: SCD in context**

Many studies agree that the cause of death in patients with sickle cell is infection [3]. Under the age of five years, as established by Urbinati, as many as 20% of children with sickle cell have been noted to develop sepsis or meningitis with a 25% mortality rate [4]. Children within this age group have been noted to be at a very high risk of developing pneumococcal sepsis. Evidently, from such studies, it is accurate to assert that because mortality in cases of SCD stems from infection, there is a need to develop a diagnostic framework to govern the management of sepsis [8].

Ribeil., *et al.* corroborate this by noting that infection is the biggest contributor to morbidity and mortality in SCD [7]. The sickle gene has been noted to be inherently inclined to confer susceptibility to an infection or various infections [7]. Many studies have concluded that this is especially true of certain bacterial pathogens. Worldwide, such infections remain the leading cause of death, especially in developing countries. In developed countries, as established by the findings of Navalkele., *et al*. measures have been taken by stakeholders in the healthcare sector to prevent infections arising from sickle cell and to eventually treat these complications [2]. Indeed, medical advances in developed countries are gradually revolutionising the treatment model of sepsis associated with SCD. Furthermore, many of these studies note that there is a need for the development of an effective framework to treat SCD within the context of sepsis disease management.

**SCD: a critical analysis**

SCD refers to a number of genetic disorders where the haemoglobin assumes an abnormal shape structurally, thus resulting in the formation of crescent-shaped red blood cells [1]. This leads to a lot of clinical manifestations on an individual. Millions are affected by the condition worldwide. Genetically, the underlying abnormality is a single nucleotide substitution in the gene for β-globins on the $11^{th}$ chromosome, thus replacing glutamic acid residue with valine on the protein surface, HbS [1].

The clinical manifestations of SCD result from two critical pathological procedures: vaso-occlusions and haemolysis. In terms of infection, SCD has been noted to have massive implications for the functionality of the spleen. The spleen has a crucial role in increasing the susceptibility of the body to certain bacterial infections that have been noted in SCD [1]. Individuals with sickle cell disease have been known to suffer from Asplenism based on sluggish circulation through the spleen and high rates of oxygen extraction which deoxygenate HbS, thus promoting sickling leading to congestion and engorgement of the sinusoids, creating sickled cells [1]. Moreover, SCD has been noted to have many implications in regards to the presence of micronutrients in the body.

Evidently, there are several infections that emerge in patients of SCD [6]. In fact, many studies have revealed that an overwhelming number of infections are caused by encapsulated bacteria-specifically, *Salmonella* spp and *plasmodium*-in areas where Malaria is prevalent. The fact that these infections emerge as a result of SCD means that there is a need to understand SCD in terms of sepsis if these infections are to be handled well [3]. The majority of article reviews have provided a very elaborate discussion on these infections and how SCD exposes patients to such infections. However, there seems to be a gap in terms of a framework to manage SCD in the context of sepsis. Based on the assertions of Catella, since the principal cause of death amongst patients with sickle cell disease is infection, there is a need to develop a management framework that takes these infections into consideration [6].

## Materials and Methods

Based on the framework of experimental research, meta-analysis is increasingly being employed in health sciences research. Meta-analysis is designed to deal with a large number of empirical studies, in most cases providing contradictory results and inferences [4]. To be able to conduct a meta-analysis, various studies focusing on the topic of interest are collected and compiled in a systematic manner. First, estimated coefficients are selected across various studies and, in a standardised way, recalculated into comparable indicators. Alternatively, in qualitative studies, various themes are selected through which the selected studies are analysed. The themes reflect the extent to which the selected studies are related. Consequently, the studies are combined into a single summary indicator. Meta-analysis, as a research method, has been noted to have many merits as compared to the conventional literature review. The first is its quantitative

disposition. The standard narrative literature review is limited to studying qualitative studies as compared to meta-analysis which allows for a quantitative assessment of the effect of interest. Secondly, it gives the researcher an opportunity to standardise the studied methods of analysis applied and the control variables employed. Based on these merits, this study embraces meta-analysis as the most preferred research design. Meta-analysis, however, is much more confined in its range as compared to the traditional literature review, which is very broad and would even include those studies that are only slightly related to the phenomenon under study.

### Selection of Articles

To be able to undertake a meta-analysis, there are several preliminary steps that need to be taken. The construction of one's own meta-data is critical. The search strategy of this study consisted of three stages: first, the study used the ncbi and Elsevier online journal database. Based on the fact that the Current Contents in the database as revealed during the search were published between the years 2007 and 2017, the selected studies were thus limited to this publication period (2002 - 2017). In order to collect a representative sample of high quality studies, the search was limited to reviewed articles, leaving out working papers and internal research reports. The systematic search was undertaken using a specific combination of selected general keywords (sepsis, sickle cell, anaemia). Applying the systematic search strategy, around 108 potential articles on sickle cell were retrieved. The selection was limited by focusing the selection on those articles that focused on sepsis in adults. This reduced the selected articles to 44 peer-reviewed studies. The limitation of the year of study further lowered the studies to 18. Through a systematic review of the abstract, 5 journals were selected for the meta-analysis choosing publications focusing on the Middle East and Saudi Arabia.

## Results and Discussion

### Sickle Cell Gene in the Population of Saudi Arabia

A comprehensive screening program was initiated in the country to determine the frequency of sickle cell in various regions. Over ten years, 30,055 samples were collected from 36 areas in all provinces of Saudi Arabia. The screening was undertaken using electrophoretic techniques. El-Hazmi., *et al*. established that, overall, the prevalence of Hb AS was 7.36% and Hb SS was 1.06% [9]. This translates to a gene frequency of 0.047. This study also captured the prevalence rates of the five provinces in terms of gene frequencies (HbAS, HbSS, and HbS). For gene frequencies, the prevalence rate of Hb AS ranged from 0 to 25.88%. HB SS ranged between 0 and 5.52%. No cases of Hb AS or Hb SS were identified in certain provinces within the country, especially in the central regions and the northern regions. Within the southern region, both the heterozygote and homozygote Hb S were identified with the exception of Farasan Island.

Through Hardy-Weinberg modelling, it was established that the prevalence of Hb S was considerably high relative to the expected amount and this was attributed to statistical biasness within the samples collected from the hospital. The gene frequency of Hb S in the different regions of the country was found to range from 0 to 0.17.

Conclusively, the study showed that the frequency of the occurrence of the gene Hb S in several parts of Saudi Arabia was higher. Based on the fact that the frequency of Hb S was higher, there is an urgent need for the implementation of various control measures and relevant programs in the country to reduce cases of HbS homozygous. In terms of planning and policy formulation, the inferences made in this study are quite critical in the planning of control programs for SCD in Saudi Arabia.

Alabdulaali undertook a retrospective study to establish the severity of SCD amongst patients in the eastern province of Saudi Arabia in terms of chest syndrome [5]. The study evaluated the prevalence and outcomes of acute chest syndrome (ACS) and SCD patients from the specified area in Saudi Arabia. This was compared to patients with African haplotypes.

The study involved 317 patients using a retrospective approach at King Fahad Hospital Hofuf between January and May, 2003. In the study, 26 patients had different causes of acute chest syndrome while 11 of them were found to have pathologies other than acute chest syndrome (ACS) but had experienced the condition in the past. Two hundred and eighty patients presented with different pathologies

but not ACS. Various clinical features such as arterial oxygen saturation and blood transfusion rates were studied. Multiple regression analysis was then performed to assess the influence on acute chest syndrome. The study then compared the SCD patients with acute chest syndrome from the patients in the eastern province and those with African haplotypes.

Most of the patients with ACS were noted to have had only a single episode of ACS but five of the patients had more episodes of ACS. One patient died. A comparative evaluation between the SCD patients of African haplotypes and those from the eastern province of Saudi Arabia indicated that any form of recurrence was considerably lower in the patients from the eastern province as compared to those patients with African haplotypes. This was in addition to a reduced mortality rate, though it was not statistically significant.

Conclusively, ACS amongst patients of SCD from the eastern province of Saudi Arabia seems to be relatively uncommon. Nevertheless, it is associated with significant mortality and morbidity. Comparatively, its prevalence and recurrence is low if patients of African haplotypes are considered. For practitioners, this study brings to the fore the need to refocus on diagnostic tools and management of SCD patients in clinical settings through biomarkers.

**Differences between males and females in adult sickle cell pain crisis**

Udezue and Girshab noted that there are significant differences between males and females in terms of demographics and patterns of SCD patients' responses to pain treatment [10]. The study observed the discharge records for SCD patients between 200 and 2002. Specifically, patients admitted in the hospital's stabilization unit between the specified years were examined. Between 2000 and 2002, a total of 2184 patients were admitted to the stabilization unit. Twenty percent of them were transferred to hospital. Out of the 391 patients with SCD, 193 were males while 198 were females.

The study suggested that females do better as compared to males in acute SCD pain crisis. Pharmacokinetic variances have been noted in the metabolism of opiates and morphine between males and females. Slower clearances are evident in the case of females meaning that longer duration of analgesic action is witnessed. Males, on the other hand, require 40% more dosage as compared to women to achieve the same analgesic action.

The study reveals that males were frequently admitted to the stabilisation unit during the specified period. Providently, males were over-represented amongst those whose pain persisted for more than 47 hours and required hospitalisation. The female patients in the study were evenly distributed across age groups whereby there were fewer males as compared to females in the older age groups.

SCD management, based on these findings, differs significantly between males and females. Specifically, the management of pain crises between males and females varies immensely. But other than gender as a determinant of pain management strategies amongst patients with SCD, it is notable that the age group of the patients is critical to the establishment of a management program for people with SCD. Evidently, females do better compared to men in terms of managing acute pain in people with SCD. These inferences, evidently, reveal that the management program for SCD must be cognizant of these variances between males and females in terms of their response to treatment. For practitioners, these findings endorse the use of a differentiated treatment plan where the management of acute pain in individuals living with SCD is cognizant of gender.

**Lifespan and pattern of sickle cell disease**

The severity of SCD has been noted to be correlated with the age of the patient [11]. This study sought to establish this concept by enrolling patients with SCD who are aged 50 years and above. This was done through the in-patient stay or through the clinical visits of the patients at King Khalid University Hospital. Each medical record of the patients was reviewed to obtain their demographic attributes and other SCD complications such as overt stroke, priapism, leg ulcers, gallstones, acute chest syndrome, and splenomegaly. During the steady sate of the patients, lab workup was performed. Descriptive analysis was undertaken in addition to the t-test to obtain categorical predictors between the various groups in the study. The analysis equally involved a comparison of SCD complication frequency between the various age groups using the chi-square test.

From the cohort, only 5 patients out of 261 were older than 50 years. The median age was 51 years with 3 females and 2 males.

The study noted that there was a significant variability in the clinical and laboratory attributes of patients based on their age. HbF, notably, was high amongst older patients relative to younger patients. This study, while cognizant of the fact that the severity of SCD is significant correlated with the age of patients, notes that the sampled study may not be sufficiently extrapolated to reflect the situation in Saudi Arabia. However, the study makes an admission that, with the advancement in age of SCD patients, the severity of the disease significantly increases in Saudi Arabia.

These findings are significant in terms of management of the condition. Specifically, the need to have a clustered approach in the development of a control program of SCD should be considered. Any effective SCD management program should take into account the age factor of the patients. Elderly patients require a more elevated management schedule based on the fact that the severity of SCD increases with age.

**Consanguinity in Sickle Cell Patients: effects on prognosis of SCD**

There has been suggestion that consanguinity has a significant effect on the prognosis of disease and the outcomes of SCD [12]. The study was undertaken in Maternity and Child hospital in Madina by analysing the medical records of patients. One hundred and twenty samples were collected with an age variance of between 6 months and 18 years. Descriptive analysis was undertaken for the categorical variables while chi-square tests were applied in the identification of the main factors under study though the use of statistical significance. The study further incorporated backward logistic regression to establish if there was any kind of relationship between various factors.

Incidences of sickle cell in Al Madina, as established in the study, are 1:2:100,000. In terms of the prevalence of SCD, the ratio was established to be 1:2650. The analysis revealed that 45% of the patients under study were sired in a consanguineous relationship. Regardless of the fact that both the non-consanguine and consanguine groups had a lot of complications, the consanguineous group was more inclined to have more serious complications, such as vaso-occlusive crisis, and they were more prone to undergo splenectomy based on the complications of SCD.

Non-consanguineous patients seemed to suffer from several complications arising from SCD. However, debilitating these conditions are, they are less severe as compared to the consanguineous groups which are likely to develop more serious complications such as vaso-occusive crisis. Their inclination to undergo surgical procedures such as cholecystectomy and splenectomy is equally more eminent.

**Limitations of the study**

Few studies have examined the prevalence of SCD in Saudi Arabia today, especially in “smaller hospitals.” The majority of the articles reviewed in this study were limited to bigger hospitals in the country.

Essentially, this means that the inferences made in the majority of the reviewed studies may not be a true reflection of the actual situation in the country.

## Conclusion

This review brings to the fore one very critical issue in the management of SCD both within a global context and Saudi Arabia. There is a need to have a deeper understanding of the epidemiology of the disease if a case management program is to be instituted. Mapping the patterns of SCD and its prevalence rates within the various regions of Saudi Arabia is crucial to the development of a management plan for the condition. The development of a disease treatment and management plan must be pegged on various factors; key among them is the epidemiology of the disease. For Saudi Arabia, this is relevant to the development of a comprehensive plan in terms of resource allocation and clinical procedures to manage the problem.

Developing a clear understanding of morbidity and mortality patterns, the variations between males and females with SCD, lifespan patterns, survival rates, and even variations of SCD with age would aid in establishing a robust treatment plan for the condition. Understanding all these variables would give stakeholders a different, yet relevant perspective of the disease and equip them with sufficient grounds on which they can base their decisions within the context of following an effective treatment and management plan for SCD.

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