Multidrug-Resistant Staphylococcus capitis: An Emerging Challenge in Clinical Settings Found in Adult Patients in Saudi Arabia

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Abstract
The study reveals crucial information on S. capitis, a potentially dangerous bacterium that can cause sepsis in hospitalized adult patients, including its frequency and patterns of drug resistance which could significantly contribute to the existing body of knowledge in this field. This retrospective study was conducted in the King Fahad Medical City (KFMC), Riyadh, Saudi Arabia, from June 2019 to November 2022. The comprehensive data collection and analysis provide valuable information on the prevalence of S. capitis in different infection sites, antibiotic sensitivity profiles, and the association with patient demographics. A total of 219 S. capitis isolates from hospitalized patients with sepsis tested positive. Infection was most common in venous blood (139 patients, 63.5%), followed by central blood (24 patients, 11%). Other locations included venipuncture (48 patients, 21.9%) and cerebrospinal fluid (three patients, 1.4%). The results highlight the clinical significance of S. capitis as a major contributor to sepsis, especially in male patients, and emphasize the need for appropriate antibiotic selection for effective treatment. Furthermore, this study raises concerns about the high rates of methicillin resistance observed in S. capitis isolates, emphasizing the urgency in tackling antibiotic resistance and promoting judicious antibiotic prescription practices. Moreover, the identification of a decreased susceptibility to vancomycin as a potential explanation for its reduced effectiveness in treating S. capitis infections adds a crucial aspect to the discussion of treatment options and underscores the need for alternative therapeutic strategies.

Keyword: Coagulase-negative Staphylococci, Prevalence, Multidrug-resistant Staphylococcus capitis, Hospital-acquired Bacteremia

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INTRODUCTION

Coagulase-negative staphylococci (CoNS) encompass more than 40 recognized species and sub-species that are naturally found on the skin and mucous membranes, and are considered possible pathogens for many nosocomial infections. Among the various CoNS species, the most prevalent organisms include Staphylococcus epidermidis, followed by Staphylococcus citris, Staphylococcus saprophyticus, Staphylococcus pseudointermedius, Staphylococcus capitis, Staphylococcus hominis, and Enterococcus faecalis.

Sepsis is a medical condition that can be life-threatening. It occurs when the body’s response to an infection causes inflammation all over the body, and Staphylococcus capitis (S. capitis) is one of the types of bacteria that has been linked to sepsis. S. capitis is a type of bacteria that is often found on human skin and mucous tissues. It is usually considered part of the normal human microbiota, meaning that it lives in the body without causing harm. However, if the bacterium gets into the bloodstream or other sterile body parts, it can cause an infection that may result to sepsis.

Initially considered a commensal organism, S. capitis is typically regarded as a species with low levels of virulence. It has gained recognition as an opportunistic pathogen associated with various healthcare-associated infections (HAIs) and the organisms most frequently isolated from critically ill newborns diagnosed with hospital-acquired bacteremia in recent years. In addition, CoNS is considered a major threat of infection in individuals on immunosuppressive therapy, individuals using invasive devices, or when the normal body defenses have been impaired by altered antibacterial therapy. The instances of S. capitis infection in humans have been reported in the medical literature, and there is significant concern regarding the emergence of multidrug-resistant strains of S. capitis that poses a considerable challenge to the clinical management of infections caused by this bacterium, leading to increased morbidity and mortality in hospitalized infants, particularly those in neonatal intensive care units (NICUs). The complications of S. capitis infection that are associated with prematurity continue to be the leading cause of death among newborns and it is healthcare costs. In addition, few sporadic cases of S. capitis infections have been reported in adult patients. Among different clones of S. capitis, a single S. capitis clone, NRCS-A clone, appears to be the major pathogen in most hospitalized neonates with high antimicrobial multidrug-resistant profile. One major concern in the context of S. capitis infections is its resistance to beta-lactam antibiotics, including methicillin and other members of the penicillin family. For instance, methicillin-resistant S. capitis (MRSC) strains have been documented in various clinical settings, including NICUs. These resistant strains are often associated with device-related infections such as central line-associated bloodstream infections. Along with other CoNS species, S. capitis has been identified in the past as a cause of native valve endocarditis. This diagnosis was made primarily in individuals who had an underlying cardiac problem that further exacerbated the challenge of managing S. capitis infections. Therefore, it is crucial to understand the mechanisms underlying the development and spread of drug resistance in S. capitis, so as to devise effective strategies for infection control and antimicrobial stewardship. This article aims to investigate the prevalence and potential origins of multidrug-resistant S. capitis infections in adult patients in the Riyadh region. By analyzing the results, we can gain a deeper understanding of this emerging threat and the steps that can be taken to mitigate its impact. Bacterial strains were isolated from patients from King Fahd Medical City, Riyadh Region, Saudi Arabia. The emergence of multidrug-resistant S. capitis in adult patients has raised concerns about the sources, reservoirs, and resistance patterns of this pathogen.

MATERIALS AND METHODS

Study Design and Settings

The present retrospective investigation was conducted between June 2019 and November 2022 at the King Fahad Medical City (KFMC) in Riyadh, Saudi Arabia.

Inclusion and Exclusion Criteria

Patients who had been diagnosed with isolates of S. capitis collected from hospitalized patients who had been diagnosed with this illness.
constituted the inclusion criterion. At KFMC, the database maintained by the microbiology department was used to select the potential participants in the study. The investigation focused on patients with sepsis who had a clinical diagnosis, and blood cultures were carried out to verify the presence of \textit{S. capitis} infection. In the course of the research, \textit{S. capitis} blood culture isolates were utilized. The construction of a database that included information on age, sex, blood culture, cerebrospinal fluid (CSF), wound, peritoneal, and pleural fluid profiles as well as antibiotic susceptibility was accomplished with the assistance of Microsoft Excel. The data were recorded and coded after being collected. However, the records that lacked any of the aforementioned criteria were not included in the analysis.

\section*{Data Collection}

The ethical approval for this study was obtained from the institutional review board at KFMC with the approval number (23-330) in 25-June - 2023. After receiving approval from the ethical committee, members of the research team contacted the medical microbiology department at KFMC in Riyadh, Saudi Arabia, in order to collect the necessary data. The information was gathered from the patients’ electronic medical records using the data management tools that were present in the hospital. A total of 219 isolates of \textit{S. capitis} were taken from hospitalized patients who had been diagnosed with sepsis. The clinical data included demographic information, and the study utilized \textit{S. capitis} blood culture isolates. Microsoft Excel was used to construct a database containing information on age, sex, blood culture, CSF, wound, peritoneal, and pleural fluid profiles as well as antibiotic sensitivity. The data were recorded and coded.

\section*{Statistical Analysis}

The data in this study were analyzed statistically using SPSS Version 25 (IBM Armonk, New York, USA) and displayed using percentage and frequency distributions. Overall, the study employed a descriptive study design using hospital data where statistical analysis was used to analyze the data collected, and \( p < 0.05 \) was considered significant.

\section*{RESULTS}

The study included 219 isolates of \textit{S. capitis} from hospitalized patients with sepsis, confirmed positive by site of infection, which was varied among the patients. The most common site of infection was venous blood (139 patients, 63.5\%), followed by central blood (24 patients, 11\%). Other sites included venipuncture (48 patients, 21.9\%), CSF (three patients, 1.4\%), arterial line (one patient, 0.5\%), wound (two patients, 0.9\%), peritoneal (one patient, 0.5\%), and pleural fluid (one patient, 0.5\%). The isolates were collected from various wards and clinics, and among the 219 patients, 33 (15.1\%) were younger than 40 years, 46 (21.0\%) were between 40 and 60 years, and 140 (63.9\%) were older than 60 years. The mean age was 63.03 ± 20.63 years, and of the 219 patients, 136 (62.10\%) were male, while 83 (37.89\%) were female, as shown in Table 1. \textit{S. capitis} can cause sepsis in hospitalized patients, with a higher prevalence in males than females. In this study, CoNS was consistently isolated with \textit{S. capitis} in all cases (Table 1), indicating the potential for a synergistic relationship between these two microorganisms. These findings provide valuable insights into

\begin{table}[h!]
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\begin{tabular}{l|c}
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\textbf{Characteristics} & \\
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\textbf{Age:} & \\
Age <40 & 33 (15.1\%) \\
Age 40–60 & 46 (21.0\%) \\
Age >60 & 140 (63.9\%) \\
Mean age (±SD) & 63.03 ± 20.63 \\
\hline
\textbf{Gender:} & \\
Male & 137 (62.6\%) \\
Female & 82 (37.7\%) \\
\hline
\textbf{Site:} & \\
ARTERIAL LINE & 1 (0.5\%) \\
WOUND & 2 (0.9\%) \\
BLOOD, CENTRAL & 24 (11\%) \\
BLOOD, VENOUS & 139 (63.5\%) \\
CSF & 3 (1.4\%) \\
PERITONEAL FLUID & 1 (0.5\%) \\
PLEURAL FLUID & 1 (0.5\%) \\
VENI PUNCTURE & 48 (21.9\%) \\
Culture Growth \textit{STAPHYLOCOCCUS CAPITIS} & 219 (100\%) \\
\hline
\end{tabular}
\caption{Statistical and clinical characteristics of patients}
\end{table}
the epidemiology of sepsis caused by *S. capitis*, and could inform the development of targeted prevention as well as treatment strategies.

Table 2 summarizes the results of the chi-square test of independence for the effectiveness of 11 antibiotics (amoxicillin-clavulanate, cephalothin, clindamycin, daptomycin (DAP), erythromycin, linezolid, oxacillin, rifampicin, teicoplanin, trimethoprim-sulfamethoxazole, and vancomycin). This test was conducted to determine if there is a significant difference in the effectiveness of the antibiotics against *S. capitis*. The study found that *S. capitis* isolates showed high resistance to oxacillin, amoxicillin-clavulanate, and cephalothin, with resistance rates of 78.99% (173/219), followed by erythromycin with a resistance rate of 76.71% (168/219). In contrast, clindamycin, rifampicin, and trimethoprim-sulfamethoxazole showed low-to-moderate resistance rates, with resistance rates of 36.52% (80/219), 31.5% (69/219), and 29.22% (64/219), respectively. Conversely, vancomycin, linezolid, teicoplanin, and DAP were found to be the most effective antibiotics against *S. capitis* isolates, with a high susceptibility rate. These findings suggest that the selection of appropriate antibiotics is crucial for the treatment of the sepsis caused by *S. capitis*, as some antibiotics may be ineffective due to high resistance rates. Furthermore, the identification of effective antibiotics in this study could inform the development of treatment guidelines for sepsis caused by *S. capitis*, as shown in Table 2.

Table 3 summarizes the results of the chi-square test of independence for the effectiveness of 11 antibiotics (amoxicillin-clavulanate, cephalothin, clindamycin, DAP, erythromycin, linezolid, oxacillin, rifampicin, teicoplanin, trimethoprim-sulfamethoxazole, and vancomycin) against *S. capitis* in three age categories (<40, 40-60, and >60). The test was conducted to determine if there is a significant difference in the effectiveness of the antibiotics against *S. capitis* in different age categories. The chi-square statistics for teicoplanin in the >60 age category was 5.894, which was the only result greater than 3.841. This suggests that there may be a marginally significant difference in the effectiveness of teicoplanin against *S. capitis* in the >60 age category. However, the p-value for

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<th>Expected N</th>
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teicoplanin in this age category was 0.053. Since this p-value was greater than 0.05, we cannot conclude that there is a statistically significant difference in the effectiveness of teicoplanin against the two strains of bacteria in the >60 age category.

Overall, the results of the chi-square test suggest that there is no statistically significant difference in the effectiveness of the 11 antibiotics against *S. capitis* in the different age categories.

Table 4 summarizes the results of the chi-square test of independence for the effectiveness of 11 antibiotics (amoxicillin-clavulanate, cephalothin, clindamycin, DAP, erythromycin, linezolid, oxacillin, rifampicin, teicoplanin, trimethoprim-sulfamethoxazole, and vancomycin) against *S. capitis* in two sex categories (male and female). The test was conducted to determine if there is a significant difference in the effectiveness of the antibiotics against *S. capitis* in different sex categories. The p-value, which is a measure of the probability of obtaining the observed data if there is no difference in effectiveness.

The chi-square statistics for clindamycin in the female category was 0.028, which was the only result greater than 0.01. This suggests that there may be a marginally significant difference in the effectiveness of clindamycin against the two strains of bacteria among female patients. However, the p-value for clindamycin in this category was 0.866. Since the p-value was greater than 0.05, we cannot conclude that there is a statistically significant difference in the effectiveness of clindamycin against the two strains of bacteria in the female category.

Overall, the results of the chi-square test suggest that there is no statistically significant difference in the effectiveness of the 11 antibiotics against *S. capitis* in different sex categories.

**DISCUSSION**

*Staphylococcus capitis* (*S. capitis*) is
A type of bacteria that lives on the skin and in mucous tissues. It is thought to be a cause of many nosocomial infections.\textsuperscript{1} \textit{S. capitis} is usually associated with sepsis when the bacteria get past the body’s natural defences such as the skin or mucus membranes and invade deeper tissues or the bloodstream. Once in the bloodstream, the bacteria can rapidly proliferate and release toxins, resulting in widespread inflammation. This overactive immune reaction can cause sepsis, which can progress to septic shock if not promptly treated. It is important to note that \textit{S. capitis} is just one type of bacteria that can cause sepsis. The development of sepsis depends on a number of factors such as the virulence of the bacteria, the host’s immunocompetence as well as the presence of comorbidities.\textsuperscript{1} There have been reports of \textit{S. capitis} infections in humans, and the emergence of multidrug-resistant strains of the bacterium is a major cause for concern. Amoxicillin, cephalothin, DAP, and vancomycin kill bacteria by preventing peptidoglycan synthesis, which stabilizes their cell wall. Clindamycin and erythromycin inhibit bacterial protein synthesis by binding to 23S RNA of the 50S subunit of the bacterial ribosome. Linezolid and oxacillin act by inhibiting protein synthesis. Rifampicin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase. When used alone trimethoprim and sulfamethoxazole each acts in a bacteriostatic manner. However, when used in combination as sulfamethoxazole-trimethoprim, they block two steps in the bacterial biosynthesis of essential nucleic acids and proteins. This is because these strains make it harder to treat infections caused by this bacterium, which can lead to more illness and death in hospitalised babies, especially in neonatal intensive care units (NICUs).\textsuperscript{5-7} The purpose of this research is to investigate the prevalence of multidrug-resistant \textit{S. capitis} infections among adult patients in the Riyadh region, Saudi Arabia.
*Staphylococcus epidermidis* has traditionally been the predominant species in CoNS bacteremia; however, recent studies have highlighted the emergence of *S. capitis* as a significant pathogen. This was unexpected because *S. capitis* is usually a non-pathogenic species and a member of the commensal flora.¹ *S. capitis* accounted for up to 46% of all cases of positive blood cultures in neonates (median 13%, interquartile range [10–20%]) and 19% of all CoNS strains isolated from the blood cultures of neonates.²⁰

Multidrug-resistant *S. capitis* has recently emerged as a significant pathogen in adult patients, causing bloodstream infections in hospital settings. The present study highlights the prevalence and epidemiology of sepsis caused by *S. capitis*, a potentially harmful microorganism in hospitalized patients. The study collected 219 isolates of *S. capitis* from various wards and clinics and confirmed their positive presence through blood culture and other sources. The results indicated that *S. capitis* is a significant cause of sepsis in hospitalized patients, and that this is more prevalent among men than among women, with 62.10% of the isolates being from male and 37.89% from female patients with confirmed sepsis that allowed for a comprehensive analysis of the site of infection. Similarly, researchers found that *S. capitis* isolates with a high incidence in prepubescent, school-aged children between the ages of 6 and 10 years. Nonetheless, this infection occurs across age and sex categories, with males reporting a higher incidence.²¹-²³

The findings from this indicate that *S. capitis* can indeed cause sepsis in hospitalized patients, with various anatomical sites being affected. Among the patients included in the study, venous blood was the most common site of infection, accounting for 63.5% of cases. This is consistent with the findings previous research highlighting the propensity of *S. capitis* to colonize and infect indwelling medical devices such as central venous catheters. The high prevalence of sepsis originating from venous blood emphasizes the need for stringent infection control measures, particularly in the management of invasive procedures and medical devices.

Central blood was the second most frequent site of infection (observed in 11% of the patients). This finding suggests that *S. capitis* may have a predilection for the blood stream, warranting increased vigilance in early detection and prompt initiation of appropriate antimicrobial therapy. The occurrence of *S. capitis* infections in other sites such as venepuncture sites, CSF, arterial line, wound, peritoneal fluid, and pleural fluid—albeit in smaller proportions—highlights the potential for dissemination and multi-site involvement of this pathogen.

In addition, a chi-square test of independence was conducted to examine the relationship between the effectiveness of 11 antibiotics (Amoxicillin-Clavulanate, Cephalothin, Clindamycin, DAP, Erythromycin, Linezolid, Oxacillin, Rifampicin, Teicoplanin, Trimethoprim-Sulfamethoxazole, and Vancomycin) against *S. capitis*, a type of bacteria, across three distinct age categories (<40, 40-60, and >60). The primary aim was to determine whether there exists a notable difference in antibiotic effectiveness concerning *S. capitis* across these varying age groups.

The analysis revealed intriguing insights regarding Teicoplanin in the age category of >60. The calculated chi-square statistic for Teicoplanin in this age group stood at 5.894, surpassing the critical threshold of 3.841. This suggests the possibility of a marginal or subtle difference in the effectiveness of Teicoplanin against *S. capitis* within the >60 age category. However, when considering the associated p-value of 0.053, which exceeds the conventional significance level of 0.05, it becomes evident that no statistically significant distinction can be established in the effectiveness of Teicoplanin against the two bacterial strains within the >60 age category.

In a broader context, the collective outcomes of the chi-square test indicate that, overall, there is no statistically significant variance in the effectiveness of the 11 antibiotics against *S. capitis* across different age categories. This implies that, within the scope of this study, the age groups do not significantly influence the effectiveness of the antibiotics against *S. capitis*.

A chi-square test of independence was performed to investigate the relationship between the effectiveness of 11 antibiotics (Amoxicillin-Clavulanate, Cephalothin, Clindamycin, DAP, Erythromycin, Linezolid, Oxacillin, Rifampicin, Teicoplanin, Trimethoprim-Sulfamethoxazole, and
Vancomycin) against S. capitis, a type of bacteria, across two distinct sex categories (Male and Female). The primary objective of the test was to ascertain whether there exists a significant disparity in antibiotic effectiveness against S. capitis based on different sex categories.

The analysis unveiled a noteworthy observation specifically concerning Clindamycin in the Female sex category. The calculated chi-square statistic for Clindamycin in this group was 0.028, which is the only statistic exceeding the threshold of 0.01. This observation hints at a possible marginal difference in Clindamycin’s effectiveness against the two strains of bacteria in the Female sex category. However, upon considering the associated p-value of 0.866, which is greater than the conventional significance level of 0.05, it becomes evident that there is insufficient evidence to conclude a statistically significant distinction in Clindamycin’s effectiveness against the two bacterial strains within the Female sex category.

In a broader context, the comprehensive outcomes of the chi-square test collectively indicate that there is no statistically significant divergence in the effectiveness of the 11 antibiotics against S. capitis across distinct sex categories. This implies that, within the scope of this analysis, sex categories do not play a significant role in influencing the effectiveness of the antibiotics against S. capitis.

Overall, this study provides valuable information regarding the epidemiology of S. capitis and its potential impact on the health of hospitalized patients.

The emergence of antimicrobial resistance is a major concern worldwide, and it is vital to identify the most effective antibiotics for treating bacterial infections. In a recent study, S. capitis isolates were found to be highly resistant to oxacillin, amoxicillin-clavulanate, cephalexin, and erythromycin. These results suggest that these antibiotics may not be effective for treating sepsis caused by S. capitis. In 2019, a Swedish study showed increased number of neonates with bacteremia since 2010 in Region "Rebro County, Sweden, as a result of the dissemination of the MDR S. capitis NRCS-A clone, although this clone was introduced early in 2001. This is a strong evidence that NRCS-A S. capitis is extremely preserved and has altered the NICU setting lately.24

In this Swedish study, fusidic acid, cefoxitin, and gentamicin resistance was the most common multi-drug resistance profile in congruence with many previous studies.24 In contrast, clindamycin, rifampicin, and trimethoprim-sulfamethoxazole showed low-to-moderate resistance rates. Therefore, these antibiotics may be effective for treating sepsis caused by S. capitis. Nevertheless, it is essential to consider individual patient factors such as allergies and drug interactions before prescribing these antibiotics.

Vancomycin, linezolid, teicoplanin, and DAP were found to be the most effective antibiotics against S. capitis isolates, with a high susceptibility rate. These antibiotics may be considered the first-line treatment for sepsis caused by S. capitis, although it is crucial to note that their indiscriminate use may lead to the emergence of resistance to these antibiotics in the future. However, the NICU isolates showed methicillin and aminoglycoside resistance, and either resistance or hetero-resistance to vancomycin; none of the S. capitis isolates in the present study were resistant to rifampicin, which was in contrast to previous studies reporting on the antimicrobial susceptibility pattern for the NRCS-A clone (24). In 2002, Amsterdam VU Medical Centre initiated a study after the detection of a case of ongoing sepsis caused by CoNS in a premature neonate, as determined by several positive blood cultures, and treatment with vancomycin was not effective.7 The sepsis was caused by a strain of S. capitis that was heteroresistant to vancomycin. Screening of more than 200 isolates of CoNS from cultures of blood from neonates in the VU University Medical Centre NICU showed that this S. capitis strain had been endemic in the unit since 1998, and that it was the causative agent of about one-third of all cases of bacteremia caused by CoNS in the VU University Medical Centre NICU.7 Adult patients infected with S. capitis must be regarded a true pathogen, the decreased susceptibility to vancomycin may contribute to the ineffectiveness of vancomycin treatment.

The findings from the present study highlight the importance of selecting appropriate antibiotics for the treatment of sepsis caused by S. capitis. Therefore, clinicians should be aware of the resistance patterns of S. capitis to be able to make
informed decisions regarding antibiotic selection. In addition, the identification of effective antibiotics could inform the development of treatment guidelines for sepsis caused by *S. capitis*. These guidelines could help to prevent the emergence of antimicrobial resistance and ensure that patients receive appropriate treatment. Moreover, understanding the clonality, transmission routes, and persistence of *S. capitis* is crucial for developing effective prevention and control strategies. By gaining a more comprehensive understanding of the epidemiology and resistance patterns of *S. capitis*, we can better safeguard vulnerable patients and curb the spread of this multidrug-resistant pathogen.

**CONCLUSION**

This research provides valuable insight into how widespread *S. capitis* infection is, as well as how resistant the bacterium is to antibiotic treatment. *S. capitis* is a potentially dangerous microorganism that can cause sepsis in hospitalized patients. The results from the study suggest that *S. capitis* is a major cause of sepsis, especially among male patients, and that the presence of CoNS could complicate the infection. Due to the high rate of resistance to commonly used antibiotics, the study also highlights the importance of choosing the right antibiotics to treat sepsis caused by *S. capitis*. Clinicians should choose antibiotics based on what they know about them and how they will work for each patient to stop antimicrobial resistance. More research is needed in this area to further highlight effective ways of preventing and treating sepsis caused by *S. capitis* as well as for reducing its frequency and severity.

Future research should focus on investigating potential sources and reservoirs of *S. capitis* within healthcare settings, improving disinfection procedures, exploring alternative disinfectant molecules, and evaluating the efficacy of steam-based disinfection methods. Additionally, future studies should continue to monitor the role of caregivers in *S. capitis* transmission and emphasize the importance of strict adherence to hand hygiene protocols. By gaining a deeper understanding of the epidemiology and resistance patterns of *S. capitis*, we can better protect vulnerable patients and reduce the spread of this multidrug-resistant pathogen. Also, more research is required to better control its spread in each ICU and around the world.

**ACKNOWLEDGMENTS**

None.

**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest.

**AUTHORS’ CONTRIBUTION**

JAA, SAA, AOA and NSDA conceptualized the study. JAA and SAA carried out the preliminary literature review. JAA and AOA specified research objectives, data collection, and organisational structure. EME analysed and interpreted the data. All authors read and approved the final manuscript for publication.

**FUNDING**

None.

**DATA AVAILABILITY**

All datasets generated or analyzed during this study are included in the manuscript.

**ETHICS STATEMENT**

This study was approved by the Institutional Review Board, King Fahad Medical City, Riyadh, Saudi Arabia, with the approval number (23-330) dated June 25, 2023.

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