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DISCOVERY SCIENTIFIC SOCIETY

Opioids used to manage acute pain crisis in adults with sickle cell disease in emergency department: Systematic review

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ABSTRACT

Background: In Saudi Arabia, sickle-cell disease is among the most prevalent hematologic hereditary illnesses. In SCD patients, vascular-occlusive pain crises are a common reason for emergency room visits, and patients' suffering may go untreated. This research offers a systematic literature review of the current treatments for acute pain crises in SCD patients. *Method:* The authors examined five scientific databases—MEDLINE, PubMed, CENTRAL, CINAHL, and Web of Science—to locate published works through 2023. For every database, a comprehensive search strategy was developed using MeSH keywords. The phrases opioids, anemia, sickle cell, double-blinded, randomized controlled study, acute pain, and clinical trial are used. *Results:* Six full-text articles with 424 patients were included for our review out of the 201 articles initially gathered from databases. Duplication was removed, and the articles were assessed against inclusion criteria. Of the included studies, three were conducted in the United States, one in Connecticut, one in Maryland, and one in Canada. Using guidelines for higher opioid doses for acute painful episodes in SCD patients was related to better pain outcomes and fewer hospitalizations. According to current standards, patients with SCD should get opioid analgesia within 30 minutes of being triaged. *Conclusion:* Almost all SCD patients who were hospitalized as a result of acute pain were provided opioids; there's no set method in strict accordance with guidelines from the Centers for Disease Control and Prevention.

Keywords: Sickle cell disease, acute pain, emergency department, opioid

1. INTRODUCTION

The World Health Organisation has classified sickle-cell disease (SCD), the most prevalent hematologic hereditary condition, as a severe public health issue. The disease's prevalence in Saudi Arabia varies from 2% to 27%. The hemoglobin S

gene is widely distributed, with distribution patterns ranging from 0% to 1% in the northern and central regions to nearly 25% in the eastern areas, and from 7% in the western region to 12% in the southern region (Al-Anazi et al., 2017). Sickle-cell disease can result in acute, chronic, or a combination of pain types. Whether in soft or skeletal tissue, tissue infarction acute pain often manifests as abrupt, erratic, and severe pain. It generally ends after the sickle-cell crisis is resolved. In SCD, chronic pain is not just a result of the vaso-occlusion. Instead, it is typically caused by avascular necrosis of bone in many joints, primarily the hips, shoulders, and ankles, in decreasing order of frequency (Glassberg, 2017; Okpala and Tawil, 2002).

Vaso-occlusive crisis (VOCs) is the most prevalent cause of acute pain of sickle cell illness and the primary cause of visits to the emergency room. VOCs are brought on by blood artery blockage caused by red blood cells' distinctive "sickle" form, which in SCD patients causes ischemia to the supplied organ and consequent pain. Both the frequency and severity of excruciating crises might vary. While some individuals experience six or more episodes yearly, others may experience significantly fewer episodes (Strouse, 2016). For acute pain, regular analgesia is administered. For morphine injections and fast-release formulations, the usual dosage interval is four to six hours; nevertheless, some people develop tolerance to opioids to the point where two-hour doses are required.

Since there is a restricted selection of injectable opioids that may be used in acute painful episodes, every attempt is made to prevent such tolerance from forming in new patients. The dosage of opioids can be reduced by combining analgesics with alternative modes of action, such as diclofenac or paracetamol (Glassberg, 2017; Okpala and Tawil, 2002). The purpose of this study is to conduct a comprehensive assessment of the drugs currently utilized to treat sickle cell disease patients who arrive at the emergency room experiencing an acute pain crisis.

2. METHOD

The study design complied with the recommendations for meta-analyses of interventional studies set out by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The authors searched five scientific databases to find published works until 2023: MEDLINE, PubMed, CENTRAL, CINAHL, and Web of Science. Using MeSH keywords, a thorough search strategy was created for each database. The following terms are used: double-blinded, randomized controlled study, opioids, sickle cell, anemia, acute pain, and clinical trial. The authors also manually examined the other bibliographies from the included research, which were considered for references offered to other studies that were overlooked in the original electronic search, in addition to using Google Scholar for additional searches.

Two hundred one papers were first gathered from databases; after duplication was removed, 172 articles were evaluated for their title and abstract, and 20 full-text articles were left for evaluation by all authors by the inclusion criteria. Six full-text studies were then included for our review. Every author conducted a separate database search. To determine eligibility by the criteria, they also independently assessed the relevance of the retrieved studies and looked over the full-text publications. All investigators came to a resolution to address any disagreements over including full-text studies. We included studies taken by adult SCD patients who were above the age of 18 and were having an acute pain episode brought on by VOC and were managed by intravenous opioids for pain.

Research that detailed the results of individuals with complex, severe sickle-cell pain crises, animal trials, and studies that reported the eligible mix of pediatric and adult subjects were eliminated. Every author extracted data from the included studies, which was then examined. Any disagreements were settled amicably with all authors. From each research, two investigators retrieved the general details (Table 1), which all reviewers then cross-checked. The form contained information on the study's location, design, year of publication, citation, and participant characteristics. At the same time, the other form includes the conclusions and outcomes (Table 2).

3. RESULT

Initially, 201 articles were collected from databases; after duplication removal, 172 articles remained, assessed for title and abstract, and 20 full-text articles remained for assessment by all authors against inclusion criteria. We included six full-text articles for our review with a total of 424 patients included (Figure 1) (Table 1); of the included studies three were conducted in united states Molokie et al., (2018), Feliu et al., (2011), Gonzalez et al., (1988), one in Connecticut Solomon, (2010), one in Maryland Carroll et al., (2018) and one in Canada (Gulilat et al., 2023). According to Molokie et al., (2018) applying guidelines for greater opioid doses for acute painful episodes in SCD patients in the critical care unit was associated with improved pain outcomes and fewer hospitalizations when compared to the ED.

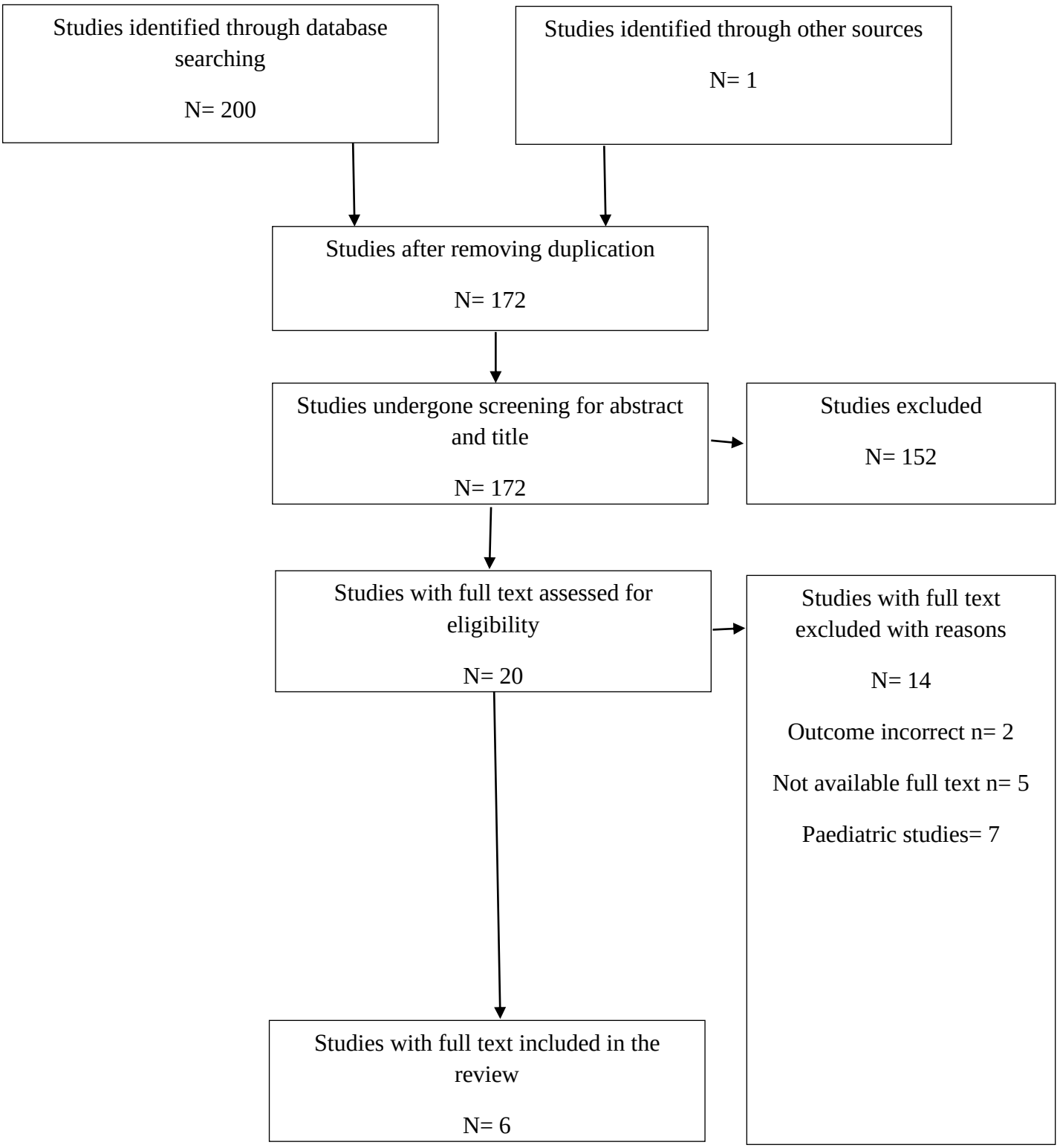

Figure 1 Consort chart of the selection process

This approach to addressing SCD pain in the ED ought to produce better results, such as a decrease in hospital admissions. Current guidelines state that within 30 minutes of being triaged, patients with SCD should get opioid analgesia (Table 2). Studies show this goal is rarely achieved, even in a department where SCD vaso occlusive crises are a common presenting condition. The association between earlier opioid analgesia and order set usage and delivery before physician review highlights potential avenues for shortening the time to analgesia (Gulilat et al., 2023). Narcotic medication is only one component of a comprehensive pain management plan for sickle cell disease patients.

The possibility of giving patients more effective treatment and a higher quality of life can be significantly increased by including behavioral management, interdisciplinary care, and patient initiatives (Feliu et al., 2011). The quantity of opioids required for therapy varies widely and is often greater than what is advised by recommendations. According to Solomon, (2010) study, the length of treatment and the timely administration of opioids are also commonly compromised, which results in delayed pain management, snap decisions regarding the course of treatment, early follow-up appointments, and perhaps avoidable hospital stays.

Table 1 Characteristics of included studies

Citation	Participant characteristics	Study method	Study country
Molokie et al., 2018	148 adult patients presented to the emergency department with sickle cell pain and who received care.	In a single academic tertiary center retrospective comparative cohort research. The authors gathered information from the medical records about opioid dosages, pain ratings at unit discharge, hospital admission rates, and lengths of stay.	United States
Feliu et al., 2011	63 adults with SCD	To ascertain whether the primary opioids that 63 adult sickle cell disease patients were taking for oral pain management had an impact on their psychological functioning and complaints of pain, the authors examined patterns of narcotic use in the sample. Of the patients, 51% reported using Oxycodone, 35% OxyContin, 24% methadone, and 11% morphine for therapy.	United States
Gulilat et al., 2023	103 patients met the inclusion criteria	This research was an observational retrospective. The percentage of visits when patients got opioid analgesia within 30 minutes of triage was the primary outcome. The time in minutes from triage to the first opioid administration and the time from triage to the delivery of any analgesics were secondary outcomes. Potentially related factors were patient demographics and features of ED encounters.	Canada
Carroll et al., 2018	73 patients	Observational cohort study at the Sickle Cell Infusion Centre to determine if these features might be used to prospectively predict the outcomes of acute pain management, such as visit frequency, total opioid dosages, and pain relief.	Maryland
Solomon, 2010	19 patients	An analysis of vaso-occlusive crises treated in emergency rooms in 2005 was done in the past to identify the need for opioids and obstacles to the application of guidelines.	Connecticut

Gonzalez et al., 1988	18 patients	Each visit, patients were randomly allocated to receive either 2 mg IM butorphanol or 6 mg IM morphine every 30 to 60 minutes, as needed to create a pain intensity of 50 mm or below on the linear analog pain scale, until they were released. Patients were also placed on bed rest and given IV water. At 60 and 120 minutes following each study medication dosage, before future doses, and upon discharge, participants' vital signs, state of alertness, and discomfort were measured using a linear analog scale.	USA

Table 2 Main findings and conclusion of included studies

Citation	Findings	Conclusion
Molokie et al., 2018	At admission, the average pain score in the ED was 8.7, while in the ACU, it was 8.0. At discharge from the ED, the average pain score was 6.4, while in the ACU, it was 4.5. 37% of the 73 ACU visits and 70% of the 144 ED visits led to hospital admissions. Inpatients from the ED and ACU experienced similar lengths of stay. There were notable variations in the first and hourly opioid doses between the ED and ACU.	When compared to the ED, applying guidelines for higher opioid dosage for acute painful episodes in individuals with SCD in the critical care unit was linked to better pain outcomes and fewer hospitalizations. Adopting this strategy for SCD pain in the ED should lead to better outcomes, such as fewer hospital admissions.
Feliu et al., 2011	The use of Oxycodone was found to have a significant influence in a multivariate model of covariance. The average weekly pain intensity, as well as the sensory and summary index of pain as assessed by a visual analog scale, were all impacted by oxycodone use. Oxycodone users reported more vivid sensory sensations.	For sickle cell disease patients, narcotic medicine is but one part of an all-encompassing strategy to manage chronic pain. Incorporating behavioral management, multidisciplinary care, and patient initiatives can increase the likelihood of providing patients with more effective care and a better quality of life.
Gulilat et al., 2023	Only 5.2% of visits resulted in patients receiving opioid analgesia within 30 minutes after triage. It took an average of 80 minutes from triage to the start of opioid analgesia. Shorter delays to opioid analgesia were linked to using an order set and having opioid analgesia before seeing a doctor.	According to current guidelines, patients with SCD should get opioid analgesia within 30 minutes of being triaged. Even in a department where SCD vaso occlusive crises are a frequent presenting issue, studies indicate that this aim is rarely fulfilled. Potential paths for accelerating the time to analgesia are highlighted by the correlation between earlier opioid analgesia and order set utilization and delivery before physician assessment.
Carroll et al., 2018	A 12-month follow-up period was conducted with 73 individuals, and 378 visits were tallied to track treatment results and SCIC	It was anticipated that the first opioid dosage would have an impact on treatment outcomes. It is not unexpected that those with more

	use. Higher baseline opioid dosages, higher socioeconomic levels, more pain-related anxiety, more aggressive treatment for sickle cell disease, more elevated markers of worse illness severity, and a history of psychiatric therapy were all linked to increased use. Overall, higher use and higher baseline opioid dosages were related to poor responsiveness to acute pain therapy.	refractory acute pain and chronic pain should also have higher opioid tolerance. The stronger the association was, the more intriguing thing was how consistently the baseline opioid dose was shown to be the factor most consistently linked to both increased utilization and subpar acute care response. Once more, there is a good chance that the link will be complicated since greater opioid dosages may both induce and result in more intense and resistant pain.
Solomon, 2010	In 30% of visits, the start of opioid therapy did not occur for more than two hours; in 26% of visits, the period between the first and second opioid doses surpassed one hour and increased with consecutive doses; and in 21% of visits, the whole duration of treatment was less than one hour. In 53% of patients, the dosage of opioids surpassed 10 mg, ranging from 4 to 26.7 mg. There were 25 instances of hospitalization, with 48% of patients being hospitalized following three or fewer opioid doses and 50% following less than three hours of therapy. Furthermore, nine out of thirty-two home discharges with treatment durations of less than three hours on the previous visit resulted in repeat trips to the emergency room within three days.	The amount of opioids needed for therapy varies greatly and is frequently higher than recommended by guidelines. Therapy duration and the prompt administration of opioids are also often impaired, which leads to delayed pain management, hasty judgments about how to proceed, early return visits, and potentially needless hospital hospitalizations.
Gonzalez et al., 1988	There were forty-five randomizations to therapy, with six patients receiving just morphine, six receiving only butorphanol, and six receiving each drug at some point throughout the trial period. Vital signs, degree of alertness, and discomfort or reduction of pain ratings did not substantially differ between the two regimens. With morphine and butorphanol, the discharge rates were 69.6% and 68.2%, respectively. With morphine and butorphanol, the incidence of side effects was 13% and 23%, respectively.	Both butorphanol and morphine work equally well to relieve sickle cell crisis pain.

4. DISCUSSION

VOC is a significant contributor to morbidity and frequently the cause of ED visits, which puts SCD patients in the hospital after that. The preferred course of treatment for reducing the immediate and severe pain brought on by VOC is still opioid analgesics. An acute pain crisis that necessitates a clinic visit or hospitalization is the most common manifestation of SCD. Multifactorial events, such as infection, fever, dehydration, acidosis, exposure to high temperatures, humidity, and pain itself, can cause VOCs, which can lead to

excruciating crises (Darbari et al., 2020). The clustering of sickle-shaped red blood cells into the microcirculation is the cause of these pain episodes. This obstruction of blood flow impairs the oxygen supply, resulting in inflammation, infarction/reperfusion injury, and eventual tissue destruction (Telfer and Kaya, 2017). The production of various chemical mediators linked to this inflammation activates different nociceptive neural receptor pathways in various nervous system regions.

After all other causes of pain are ruled out, these acute painful crises are typically identified for the first time in the emergency room. Each sad episode lasts four to five days on average, although occasionally, it can take up to a week to go away (Costa and Fertrin, 2016). When treating acute and severe pain, opioids are a commonly used and accepted type of painkiller. To help SCD patients undergoing excruciating VOCs, the National Heart, Lung, and Blood Institute established guidelines for level two triage assessment of acute painful crisis patients, IV opioid administration within 60 minutes of ED presentation, and the implementation of a customized dose regimen for supplemental analgesics, if necessary (Masese et al., 2019). When using a patient-specific protocol with patient-controlled analgesia (PCA) for acute SCD pain in the ED, compared to patients following a weight-based protocol, there was a significant reduction in pain scores, a decrease in hospital admission rates, and an acceptable side effect (Tanabe et al., 2018).

Furthermore, only one trial demonstrated a significant difference between the efficacy of sustained-release oral versus intravenous morphine in the mean overall pain scores as well as the frequency/severity of adverse effects. This suggests that oral morphine may be an option for treating acute pain in SCD patients (Dunlop and Bennett, 2014). The study compared nine randomized controlled trials (RCTs) using the pharmacological treatment for acute pain in SCD. The pharmacokinetics and pharmacodynamics of the opioid, the patient's subjective pain score, past opioid requirements, and the existence or lack of a history of chronic opioid usage all influence how much opioid is needed. Better pain management, a shorter hospital stay, and a reduction in overall opioid intake are all linked to opioid administration to reduce VOC (Brandow and DeBaun, 2018). Although they have been utilized as the preferred first-line intravenous opioid analgesics for acute pain crises, morphine, and hydromorphone are regarded as less desirable forms of analgesics due to several problems.

It has also been mentioned that fentanyl can be used instead of or in addition to morphine. It is more effective than morphine and has a shorter half-life. It also works more quickly in the central nervous system and may be delivered in several ways (Telfer et al., 2014). In one study, the opioid doses administered to patients with SCD during acute pain episodes in the critical care unit (ACU) were significantly lower than in the emergency department (ED). This was explained by the fact that pain medication was administered more quickly in the ACU and that higher mg/kg doses of hydromorphone or morphine were used to manage SCD patients' acute pain episodes than were used in the ED. These measures improved patient care and quality of life, reduced the need for hospital admissions, and reduced overall medical expenses (Molokie et al., 2018). According to a literature study by Ballas et al., (2012) respiratory depression, overdose, excessive sedation, nausea, changed mental state, itching, vomiting, and bowel habits changes are among the recognized acute side effects of morphine.

These adverse effects are caused by morphine, which is classified as the most histaminergic opioid and is primarily eliminated in the urine (Ballas et al., 2012). It also has side effects on both neuronal and non-neural targets. Although SCD patients appear to use opioid analgesics extensively, the mortality statistics for those individuals show that the disease's complications—rather than opioid usage—are the cause of death. The abuse of opioids is the root cause of the issue (Ballas, 2021). Using a multidisciplinary team approach and several patient and carer education sessions, Al-Zahrani et al., (2020) assessed SCD patients with opioid use disorder to lower the number of ED visits and hospital admissions. Along with establishing a palliative/pain clinic and an SCD addiction clinic, they also put in place a sufficient system for tracking opioid prescriptions. They reevaluated the process of assessing pain to prevent pointless interventions (Al-Zahrani et al., 2020).

5. CONCLUSION

Treatment outcome affected by the initial opioid dose. It is not surprising that increased opioid tolerance is also associated with more refractory acute pain. The more consistently the baseline opioid dosage was found to be the component most consistently connected to both greater utilization and substandard critical care response, the more fascinating the connection became. Within 30 minutes of being triaged, patients with SCD should get opioid analgesia. The majority of SCD patients hospitalized due to VOC were prescribed opioids for pain management, according closely to the Centers for Disease Control and Prevention's recommendations. There isn't a standard approach. More research is necessary.

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Author Contributions
Dr Ahmed Saad Aleid, Dr Haitham Mohammed Alhussain, Dr Sultan Suwailem Alghannami, and Dr Yazeed Ibrahim Altheiban contributed equally to the conception, design, and execution of this research.

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Ethical approval
Not applicable.

Informed consent
Not applicable.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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