Sultan Qaboos University Med J, February 2024, Vol. 24, Iss. 1, pp. 58–62, Epub. 28 Feb 24
Submitted 2 Jul 23
Revision Req. 9 Aug 23; Revision Recd. 20 Aug 23
Accepted 6 Sep 23
https://doi.org/10.18295/squmj.12.2023.083

CLINICAL & BASIC RESEARCH

Predictors of Developing a Complex Course of Osteomyelitis in Patients with Sickle Cell Anaemia

Al Zahra Al Hashmi,[1] Ethar Al Fazari,[1] Mustafa Al Ward,[2] Reema Al Masruri,[1] Shahad Al Balushi,[1] Mohammed Al Mutani,[2] *Ahmed Al Ghaithi,[2] Wafa Al Baluki[2]

abstract: ***Objectives:*** Despite the numerous advances in management strategies, treating osteomyelitis in individuals with sickle cell disease (SCD) remains a significant challenge, leading to severe long-term consequences. This study aimed to assess the key factors potentially linked to a complex progression of osteomyelitis in patients diagnosed with SCD. ***Methods:*** A cohort of 34 patients was identified and their progress was monitored over a span of 12 months during a 10-year period (2010–2020). The variables under investigation encompassed demographic and clinical traits, laboratory analyses and imaging data, as well as the treatment strategies employed. ***Results:*** The risk prediction model pinpointed 5 factors (severity of SCD, involvement of lower limbs, presence of bacteraemia, magnetic resonance image [MRI] findings and utilisation of surgical debridement) that exhibited an area under the curve (AUC) exceeding 0.7. Causative organisms were identified in 9 out of the total 34 patients (26.47%). A total of 17 patients displayed a severe course of SCD (AUC = 7.88), with MRI being highlighted as a valuable contributing factor (AUC = 7.88). Furthermore, 13 patients (38.2%) underwent surgical debridement, a procedure that yielded a statistically significant *P* value of 0.012 and an AUC of 0.714. ***Conclusion:*** Osteomyelitis within the context of severe SCD, particularly when accompanied by lower extremity infection, bacteraemia, positive MRI findings and the need for surgical debridement, emerges as a cluster of risk factors predisposing individuals to osteomyelitis relapse and a more complex disease course.

Keywords: Anemia, sickle cell; Bacteremia; Debridement; Disease Severity; Osteomyelitis.

Advances in Knowledge

- *This study evaluated individual factors that may be associated with the severe course of sickle cell disease (SCD) osteomyelitis.*
- *A complex course of osteomyelitis in SCD was found to be associated with lower extremity infection, bacteraemia, positive magnetic resonance image findings and surgical debridement.*

Application to Patient Care

- *The identification of risk factors associated with a severe course of osteomyelitis in patients with SCD could have a positive impact on morbidity and mortality and may significantly reduce disease-related economic losses.*

Sickle cell disease (SCD) is an inherited haemoglobinopathy that is more prevalent among individuals of African or Indo-Arab descent.[1] Meanwhile, osteomyelitis is a common, serious and debilitating complication of SCD. Optimising overall health alongside antimicrobial treatment and surgical intervention, if necessary, is the standard of care for acute osteomyelitis.[2] However, the treatment of SCD-associated osteomyelitis remains complex despite considerable advancements in management strategies. This leads to consequential long-term effects such as recurrences, chronic osteomyelitis and pathological fractures necessitating multiple rounds of surgical debridement, prolonged courses of parenteral antibiotics and extended hospital stays.[3]

Prior research on acute osteomyelitis has assessed the utility of individual variables to predict a severe disease course. These variables include demographics, laboratory measurements, clinical presentation, microbiological factors and treatment approaches. Lin *et al.* investigated the correlation between laboratory inflammatory markers and osteomyelitis recurrence and concluded that the erythrocyte sedimentation rate exhibited greater sensitivity, specificity and independent association with a complex disease course compared to C-reactive protein (CRP).[4] Another study has identified links with infection location, abscess formation and chronic morbidity.[5]

In addition to the current uncertainty surrounding them, the factors under scrutiny may lack specificity to SCD-associated osteomyelitis and can exhibit variability. Patients with SCD suffer from an impaired immune system and experience compromised blood circulation in the bones, rendering them susceptible to adverse complications.[1] This study aimed to explore distinct factors that potentially correlate with a severe course of osteomyelitis in individuals with SCD within a single-centre context. Such an investigation holds the promise of positively influencing both morbidity and mortality outcomes while also addressing the considerable economic burdens associated with the disease.

[2]*Department of Surgery, Sultan Qaboos University Hospital and* [1]*College of Medicine, Sultan Qaboos University, Muscat, Oman*
**Corresponding Author's e-mail: a.alghaithi@squ.edu.om*

Methods

A retrospective cross-sectional review was conducted at Sultan Qaboos University Hospital in Muscat, Oman, spanning a period of 10 years (2010–2020). All patients diagnosed with SCD and presenting with acute osteomyelitis were identified using the health information system. The diagnosis of osteomyelitis was established based on one or more of the following criteria: (a) positive blood culture, (b) positive culture from a bone or joint aspirate and/or (c) typical radiographic findings.

The various data points gathered and considered associated variables indicating a complex disease course were: age at presentation, gender, duration before seeking medical attention, outcomes from physical examinations (including vital signs, affected limb, local swelling, erythema and limited range of motion), laboratory assessments (white blood cell count [WBC], CRP, haemoglobin S levels, blood culture and bone biopsy) and imaging studies (radiographs and magnetic resonance images [MRI]). Additionally, information regarding the frequency of surgical debridement and readmissions was also included. Patients with other haemoglobinopathies and chronic osteomyelitis were excluded from the study. The SCD severity scoring system established by Shah *et al*. was utilised to classify disease severity. This validated tool quantifies the overall impact of SCD by considering complications, organ involvement and clinical manifestations. Its inclusion enabled a nuanced understanding of the patients' disease burden and a comprehensive assessment of the link between SCD severity and osteomyelitis progression.[6]

A complex course of osteomyelitis was defined as requiring readmission within 6 weeks or change of antibiotics or persistence of symptoms while on medical therapy. The surgical debridement process involved a comprehensive approach, incorporating both incision and drainage alongside meticulous cleansing of the affected bone. This process aimed to effectively remove necrotic tissue, purulent material and any other debris from the site.

Continuous variables, such as means and standard deviations or medians and interquartile ranges, were assessed using analysis of variance (ANOVA) or the Mann-Whitney U test as appropriate. A risk prediction model was formulated by constructing receiver operating characteristic (ROC) curves. All data were input into the Statistical Package for the Social Sciences (SPSS) for Windows, Version 22 (IBM Corp., Armonk, New York, USA), which was employed for subsequent statistical analysis.

Ethical approval for the study was obtained from the Medical Research Ethics Committee of the College of Medicine and Health Sciences at Sultan Qaboos University (MREC number #2490).

Results

A total of 102 patients with SCD suspected of having skeletal infections were identified over the defined study period. Among these, 34 patients met the inclusion criteria. Cases with isolated joint infections lacking bone involvement, as well as patients treated for borderline infections as opposed to avascular necrosis without meeting the osteomyelitis definition, were excluded.

The mean age of the study group was 15 ± 11.98 years (range: 1–38 years). The study group was comprised of 12 (64.7%) male patients and 22 (35.3%) female patients. Among the 34, 18 were ≤16 years old and 4 were experiencing complex disease courses; conversely, 16 patients were adults, with 6 experiencing complicated disease courses.

The causative organism was identified in 9 (26.47%) patients; among these, 8 (88.9%) infections were attributed to gram-negative bacteria (*Salmonella*, *Klebsiella* and *Escherichia coli*) and 1 case was linked to methicillin-resistant *Staphylococcus aureus* (MRSA). Utilising the SCD severity score as described by Shah *et al*., 17 patients were deemed to have a severe course of SCD, 6 patients had a moderate course and 11 experienced a mild course.[6] The most common duration of disease prior to admission was 2 days, ranging between 1–120 days. A relatively high incidence of fever and elevated white blood cell counts was observed in 22 (64.7%) patients, with 14 patients displaying high-grade fevers of 38°C (100°F) [Table 1].

It is worth noting that records of all the patients' haemoglobin S levels at presentation were not available; however, the mean baseline level of haemoglobin S was 64 ± 17.1% (range: 30–91).

A risk prediction model was devised through the creation of ROC curves. The model was independently executed for the two age groups (adults versus children), yielding identical variables. The model effectively identified 5 variables from the study factors, demonstrating acceptable areas under the ROC curve (AUC) of >0.7 [Figure 1].

Discussion

This study examines the factors most likely linked to a complex course of osteomyelitis in patients with SCD. A complex course was observed in 26.5% of

Table 1: Demographic and clinical characteristics of patients enrolled in the study, in addition to multivariate analyses of potential predictors of complex disease course (N = 34)

Characteristic	n (%)	*P* value*
Mean proceeding days with symptoms	10.8	0.478
Affected body part		0.086
Lower limbs	17 (50)	
Upper limbs	14 (40.6)	
Axial	3 (9.4)	
Markers of severity		
Severity of SCD†		0.019
Mild	11	
Moderate	6	
Severe	17	
Tmax mode in °C	38	0.848
Range of motion restriction	18 (52.9)	0.080
Local erythema	10 (29.4)	0.879
Local swelling	27 (79.4)	0.977
Local tenderness	26 (76.5)	0.585
Admission WBC mode	13	0.068
Admission neutrophils mode	5.6	0.690
Bacteriemia	9 (26.5)	0.017
Admission CRP mg/L mode	40	0.633
Baseline HBS mode	80.0	0.223
Radiological imaging		
X-ray		0.852
None	12 (35.4)	
Periosteal reaction	4 (11.8)	
Intraosseous abscess	1 (2.9)	
Soft tissue swelling	5 (14.7)	
MRI with contrast	0	0.050
No pathological findings	12 (35.3)	
Bone marrow oedema	4 (11.8)	
Intraosseous abscess	11 (32.4)	
Subperiosteal abscess	6 (17.6)	
Severity of illness score		
Surgical intervention	13 (38.2)	0.013
Multiple debridement's	10 (29.4)	0.012

SCD = sickle cell disease; WBC = white blood cells; CRP = C-reactive protein; HBS = haemoglobin S; MRI = magnetic resonance imaging

**Multivariate analyses of potential predictors of complicated disease course*

†*As described by Shah et al.*[6]

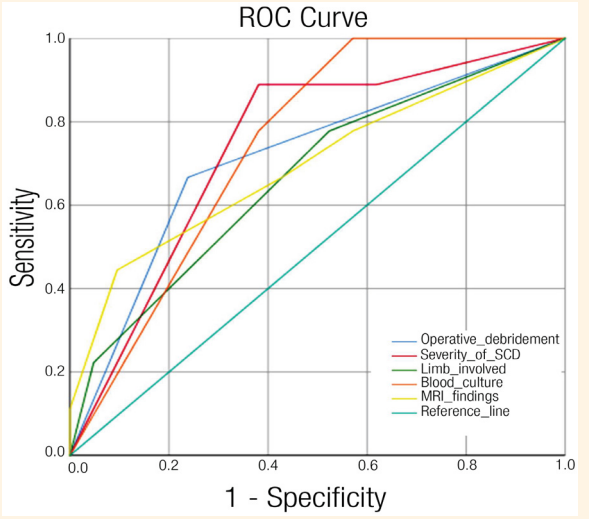

Figure 1: Receiver operating characteristic (ROC) curves showing positive predictors of a complex disease course. The figure includes those factors with acceptable areas under the ROC curve (AUCs >0.7).

ROC = receiver operating characteristic; SCD = sickle cell disease; MRI = magnetic resonance imaging.

the patients followed for at least 12 months. The risk predictive model identified SCD severity, lower limb involvement, bacteraemia, MRI findings and surgical debridement as factors independently associated with a complex disease course.

The analysis revealed that cases necessitating surgical debridement were associated with unfavourable outcomes (P = 0.012; AUC = 0.714). Of the 13 patients who underwent surgical debridement, 10 underwent debridement multiple times. This contradicts published reports on osteomyelitis in patients with co-morbidities, where surgical debridement correlated with improved outcomes compared to non-intervention groups.[7] This incongruity can be attributed to the inherent clinical progression of SCD, where patients experiencing multiple bone-occlusive crises exhibit difficulty in distinguishing infection. Consequently, infection diagnosis is delayed until the later stages of the disease, facilitating infection spread through the patients' weakened bone structure.[8] This could explain the higher relapse rates and poorer outcomes among patients with severe courses of SCD (P = 0.019; AUC = 0.741). Although published reports suggest that incorporating local flap coverage may yield more promising patient outcomes, the surgical technique used for the patients with severe courses of SCD only involved extensive bone debridement.[9–11]

In contrast to published reports, this study failed to establish a connection between SCD-associated osteomyelitis outcomes and clinical presentation (e.g. fever, local erythema, heat or erythema) or inflammatory blood markers (CRP or WBC).[1] This

can be attributed to the fact that both osteomyelitis and avascular necrosis have the potential to induce inflammation and subsequently trigger an increase in neutrophil count and CRP level.[12] On the other hand, the risk prediction model underscored the significance of lower limb involvement as a risk factor for a complex disease course. This observation can be attributed to several factors. Lower limbs typically have comparatively lower blood supply compared to upper limbs and their role as weight-bearing extremities can contribute to the challenges in managing infections. Furthermore, lower limbs tend to have less robust soft tissue coverage when compared to upper limbs, making them more susceptible to the spread of infections and potentially leading to complex disease courses.

Moreover, blood cultures tend to be negative unless haematogenous osteomyelitis is present.[13] In this study, 8 patients exhibited bacteraemia with a *P* value of 0.017, strongly correlating with the prediction of a complex infection course with high sensitivity. Culturing bacteria from the debrided tissues proved challenging due to the administration of antibiotics to these patients prior to surgical debridement. This differs from Pääkkönen *et al.*'s findings, where patients with bacteraemia had similar treatment durations and outcomes to those without it.[14] Another study by Alhinai *et al.* indicated that bacteraemia was among the factors contributing to severe disease, yet the associated *P* values were 0.17 and 0.28 for acute and chronic complications, respectively.[3] The risk prediction model emphasised the significance of MRI, yielding an AUC of 7.88, consistent with Alhinai *et al.*'s research, which established bone abscess formation as a predictor of acute complications.[3]

Ensuring the necessary antibiotic concentrations at the infection site is critical to achieving successful treatment outcomes. Nevertheless, this task is not devoid of challenges. The complex nature of managing osteomyelitis and combating antibiotic resistance arises from a confluence of factors: the constrained blood supply to bones, the emergence of tenacious biofilms that shield bacterial colonies and the concurrent presence of diverse bacterial species, all of which contribute to the complexities of the infection. Furthermore, delving into the specific realm of SCD-associated osteomyelitis amplifies the complexity of treatment due to the distinctive complications stemming from bone necrosis. Additionally, the compromised blood circulation inherent in SCD patients intensifies the complexity of managing osteomyelitis, heightening the demands of achieving effective antibiotic concentrations at the site of infection.

Considering the scope of this study, it is imperative to acknowledge certain inherent limitations. Exploring the diagnosis of osteomyelitis cases, particularly regarding the timing of assessments subsequent to the onset of symptoms, presents a pronounced challenge. This challenge is accentuated within the framework of a retrospective series, where procuring precise and comprehensive timeframes can prove to be a formidable task. Consequently, an exhaustive examination of this facet may encounter inherent complexities stemming from the retrospective nature of the study. It is also essential to recognise an additional limitation of this study: the small sample size, originating from a single centre, might not comprehensively reflect outcomes on a more extensive population scale.

Conclusion

In osteomyelitis patients with severe SCD, lower extremity infection, bacteraemia, positive MRI findings and the need for surgical debridement are risk factors for osteomyelitis relapse and a complex disease course.

AUTHORS' CONTRIBUTION

ZH, EF, MW, RM, SB and MM jointly conceived and designed the study, collaboratively performing experiments and analysing data. They all contributed equally to drafting the manuscript. WB, AG and MT provided critical revisions, ensuring intellectual content and clarity. WB and AG reviewed the manuscript, guaranteeing its academic integrity. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No funding was received for this study.

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