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

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Abstract

Objective: Despite the numerous advances in management strategies, treating osteomyelitis in individuals with sickle cell disease 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 sickle cell disease. ***Methods:*** A cohort of thirty-four patients was identified, and their progress was monitored over a span of twelve months, during a ten-year period (2010-2020). The variables under investigation encompassed demographic and clinical traits, laboratory analyses, imaging data, as well as the strategies employed for treatment. ***Results:*** The risk prediction model has pinpointed five factors (severity of sickle cell disease, involvement of lower limbs, presence of bacteraemia, MRI findings, and utilization of surgical debridement) that exhibited an Area Under the Curve (AUC) exceeding 0.7. Causative organisms were identified in 9 out of the total cases, constituting 26.47% of the patient cohort. Among the 34 patients, 17 displayed a severe course of sickle cell disease (AUC 7.88), with MRI being highlighted as a valuable contributing factor (AUC 7.88). Furthermore,

thirteen 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 sickle cell disease, particularly when accompanied by lower extremity infection, bacteraemia, and positive MRI findings, and necessitating surgical debridement, emerges as a cluster of risk factors predisposing individuals to osteomyelitis relapse and a more intricate disease trajectory.

Keywords: Sickle cell disease, Osteomyelitis, Disease Severity, Debridement, bacteraemia

Advances in Knowledge:

- This study found evaluate individual factors that may be associated with the severe course of SCD osteomyelitis.
- Complicated course of osteomyelitis in SCD associate with lower extremity infection, bacteraemia, positive MRI findings, and surgical debridement.

Application to Patient Care:

- Identification of risk factors associated with severe course of osteomyelitis in SCD could have a positive impact on morbidity and mortality, as well as significantly reduce disease-related economic losses.

Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy that is more prevalent among individuals of African or Indo-Arab descent.1 Meanwhile, osteomyelitis is a common, serious, and debilitating complication of SCD. Optimizing 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 intricate despite considerable advancements in management strategies, which 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 Z et al. investigated the correlation between laboratory inflammatory markers and osteomyelitis recurrence. They concluded that the erythrocyte sedimentation rate (ESR) exhibited greater sensitivity, specificity, and independent association with complicated courses compared to C-reactive protein (CRP).[4] Other studies have identified links with infection location, abscess formation, and chronic morbidity.[5]

Despite the ongoing uncertainty surrounding the factors under scrutiny, they may lack specificity to SCD-related 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 aims to explore distinct factors that potentially correlate with the severe trajectory of osteomyelitis in individuals with sickle cell disease 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.

Methods

A retrospective cross-sectional review was conducted at a specialized center, specifically Sultan Qaboos University Hospital in Muscat, Oman, spanning a duration of ten years (2010-2020). 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 (MERC number #).

All patients diagnosed with sickle cell disease 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.

Various data points were gathered and regarded as associated variables indicating a complex disease course. These encompassed the 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, C-reactive protein, haemoglobin S levels, blood culture, bone biopsy), and imaging studies (radiographs, MRI). Additionally, information regarding the frequency of surgical debridement's and readmissions was also included. Patients with other hemoglobinopathies and chronic osteomyelitis were excluded from the study. We utilized the SCD severity scoring system established by Shah and colleagues to classify disease severity. This validated tool quantifies the overall impact of sickle cell disease by considering complications, organ involvement, and clinical manifestations. Its inclusion enables a nuanced understanding of patients' disease burden and a comprehensive assessment of the link between SCD severity and osteomyelitis progression.[6]

A Complicated course of osteomyelitis was defined as requiring readmission within 6 weeks, 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 a meticulous cleansing of the affected bone. This procedure was aimed at effectively removing necrotic tissue, purulent material, and any other debris from the site.

Statistical analysis

Continuous variables, such as means and standard deviations, or medians and interquartile ranges, were assessed using analysis of variance or the Mann–Whitney U test, as deemed appropriate. A risk prediction model was formulated by constructing receiver operating characteristic (ROC) curves. All data were input into the SPSS program for Windows version 22 (SPSS, Chicago, IL, USA), which was employed for subsequent statistical analysis.

Results

A total of one hundred and two cases of patients with sickle cell disease suspected of having skeletal infections were identified over the defined study periods. 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.

Demographic and Clinical Characteristics:

The mean age of the study group was 15 years (ranging from 1 to 38), with a standard deviation of 11.98. Males constituted 64.7% (12 patients), while females accounted for 35.3% (22 patients). Among the 34 patients, 18 were 16 years or younger, and four exhibited complicated courses; conversely, 16 patients were adults, with six experiencing complicated disease courses.

The causative organism was identified in 9 cases (26.47%) among the patients. Among these, 8 (88.9%) infections were attributed to gram-negative bacteria (salmonella, Klebsiella, and E. coli), and one case was linked to MRSA. Utilizing the SCD severity score as described by Shah et al., 17 patients displayed a severe course, 6 patients manifested a moderate course, and 11 experienced a mild course. The most common duration prior to admission was 2 days, ranging from 1 to 120 days. A relatively high incidence of fever and elevated white cell counts was observed in 22 cases (64.7%), with 14 cases displaying high-grade fever of 38°C (100°F).

It is noteworthy that records for the level of haemoglobin S at presentation were not available for all cases; however, the mean baseline haemoglobin S was 64% (ranging from 30 to 91), with a standard deviation of 17.1.

A risk prediction model was devised through the creation of receiver operating characteristic (ROC) curves. The model effectively identified five variables from the study factors, demonstrating acceptable areas under the ROC curve (AUC) of more than 0.7, as illustrated in Figure 1. The model was independently executed for the two age groups (adult vs. children), yielding identical variables.

Discussion

This study examines the factors most likely linked to a complex course of osteomyelitis in patients with SCD. A complicated course was observed in 26.5% of 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-value of 0.012 and AUC 0.714). Among the thirteen patients who underwent surgical debridement, ten underwent multiple debridement's. Interestingly, 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 sickle cell disease, 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 weakened bone structure.[8] This could explain the higher relapse rates and poorer outcomes among cases with severe courses of SCD (P-value of 0.019 and AUC 0.741). Notably, the surgical technique used in severe cases solely involved extensive bone debridement, while published reports suggest that incorporating local flap coverage may yield more promising patient outcomes.[9–11]

In contrast to published reports, this study failed to establish a connection between SCD osteomyelitis outcome and clinical presentation (e.g., fever, local erythema, heat, or erythema) or inflammatory blood markers (CRP or WBC). 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 complicated 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 courses of disease.

Moreover, blood cultures tend to be negative unless hematogenous osteomyelitis is present.[13] In this study, eight 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 undergoing surgical debridement. This differs from Pääkkönen et al.'s findings, where patients

with bacteraemia had similar treatment durations and outcomes to those without.[14] Another study by Zaid et al. indicated that bacteraemia was among the factors contributing to severe disease, yet the associated P-values were 0.17 for acute complications and 0.28 for chronic complications. The risk prediction model emphasized the significance of MRI, yielding an AUC of 7.88, consistent with published work by Zaid et al., which established bone abscess formation as a predictor of acute complications.

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 intricate nature of managing osteomyelitis and combating antibiotic resistance arises from a confluence of factors. These encompass 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 osteomyelitis associated with sickle cell disease (SCD) amplifies the intricacy. The distinctive complications stemming from bone necrosis magnify the complexity. The compromised blood circulation inherent in SCD intensifies the intricacies of osteomyelitis management, heightening the demands of achieving effective antibiotic concentrations at the site of infection. Turning our focus to the ambit of this study, it is imperative to acknowledge certain inherent limitations. Exploring the diagnosis of osteomyelitis cases, particularly in regard to the timing of assessments post the onset of symptoms, presents a pronounced challenge. This challenge is accentuated within the framework of a retrospective series, where procuring precise and comprehensive time points 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.

Recognizing additional limitations of this study is essential. The study's small sample size, originating from a solitary centre, might not comprehensively reflect outcomes on a more extensive population scale.

Conclusion

Osteomyelitis in patients with severe sickle cell disease, with lower extremity infection, bacteraemia, and positive MRI findings, requiring surgical debridement are risk factors for relapse of osteomyelitis and a complex course of the disease.

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.

Conflict of Interest

No potential conflict of interest was reported by the authors.

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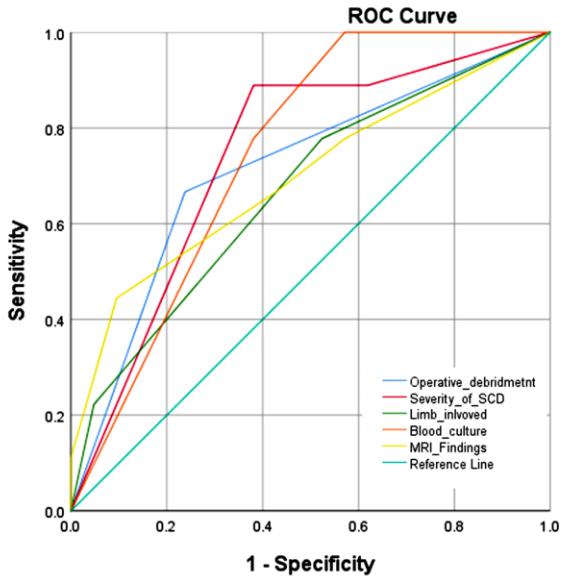

Figure 1: Receiver operating characteristic (ROC) curves showing positive predictors of a complicated disease course. The figure includes those factors with acceptable areas under the ROC curve (AUC) (more than 0.7).

Table1: Demonstrates Demographic and Clinical Characteristics of Patients Enrolled in the Study, in addition to Multivariate Analyses of Potential Predictors of complicated disease course.

[a] as described by Shah et al

Characteristic	**Demographic and Clinical Characteristics of Patients Enrolled in the Study N (%)**	**Multivariate Analyses of Potential Predictors of complicated disease course** ***P value***
Number of patients	34	
Proceeding Symptoms days (mean)	10.8	.478
Affect body part:		.086
Lower Limbs	17 (50)	
Upper Limbs	14 (40.6)	
Axial	3 (9.4)	
Markers of severity:		
Severity of SCD[a]		**.019**
Mild	11	
Moderate	6	
Sever	17	
T_{max} mode, °C	38	.848
Range of motion restriction	18(52.9)	**.**080
Local erythema	10(29.4)	.879
Local swelling	27(79.4)	.977
Local tenderness	26(76.5)	.585
Admission WBC mode	13	.068
Admission neutrophils mode	5.6	.690
Bacteriemia	9(26.5)	**.017**
Admission CRP mg/L mode	40	.633
Baseline HBS mode	80.0	.223

Radiological imaging		
X-ray		.852
none	12 (35.4)	
Periosteal reaction	4 (11.8)	
Intraosseous abscess	1 (2.9)	
Soft tissue swelling	5 (14.7)	
MRI (with contrast)		**.050**
	0	
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)	**.013**
Multiple debridement's	10 (29.4)	**.012**

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