A Novel Risk Score to Guide the Evaluation of Acute Hematogenous Osteomyelitis in Children

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abstract

OBJECTIVES: To identify independent predictors of and derive a risk score for acute hematogenous osteomyelitis (AHO) in children.

METHODS: We conducted a retrospective matched case-control study of children >90 days to <18 years of age undergoing evaluation for a suspected musculoskeletal (MSK) infection from 2017 to 2019 at 23 pediatric emergency departments (EDs) affiliated with the Pediatric Emergency Medicine Collaborative Research Committee. Cases were identified by diagnosis codes and confirmed by chart review to meet accepted diagnostic criteria for AHO. Controls included patients who underwent laboratory and imaging tests to evaluate for a suspected MSK infection and received an alternate final diagnosis.

RESULTS: We identified 1135 cases of AHO matched to 2270 controls. Multivariable logistic regression identified 10 clinical and laboratory factors independently associated with AHO. We derived a 4-point risk score for AHO using (1) duration of illness >3 days, (2) history of fever or highest ED temperature ≥38°C, (3) C-reactive protein >2.0 mg/dL, and (4) erythrocyte sedimentation rate >25 mm per hour (area under the curve: 0.892, 95% confidence interval [CI]: 0.881 to 0.901). Choosing to pursue definitive diagnostics for AHO when 3 or more factors are present maximizes diagnostic accuracy at 84% (95% CI: 82% to 85%), whereas children with 0 factors present are highly unlikely to have AHO (sensitivity: 0.99, 95% CI: 0.98 to 1.00).

CONCLUSIONS: We identified 10 predictors for AHO in children undergoing evaluation for a suspected MSK infection in the pediatric ED and derived a novel 4-point risk score to guide clinical decision-making.

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WHAT'S KNOWN ON THIS SUBJECT: Current guidelines on acute hematogenous osteomyelitis in children do not provide a framework for clinicians to interpret clinical and laboratory data to determine which patients require definitive diagnostic testing, such as MRI or bone biopsy.

WHAT THIS STUDY ADDS: A novel 4-point risk score is introduced using clinical and laboratory predictors to inform the decision to pursue or forego definitive diagnostic testing for acute hematogenous osteomyelitis in children being evaluated for a suspected musculoskeletal infection.

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Acute hematogenous osteomyelitis (AHO) has an annual incidence of approximately 2 to 8 cases per 100 000 children in high-income countries.[1–3] Although relatively uncommon, recent studies have reported rising case rates and severity of pediatric bone infections attributed to increased community virulence factors.[4–7] Classic presenting signs of AHO include pain, fever, and impaired mobility, which elicit a broad differential diagnosis including skin and soft tissue infections, noninfectious musculoskeletal (MSK) pathologies, and primary rheumatologic conditions.[1,8,9] Definitive diagnosis of AHO is most often made by MRI or histopathology of bone biopsy and debridement samples.[8–10] Barriers to obtaining these studies in the outpatient setting include availability, cost, time, and need for sedation in young children.[11] Delays in the diagnosis and treatment of pediatric AHO can result in sepsis, chronic infection, appendicular growth arrest, and pathologic fractures.[12] A primary dilemma for providers when evaluating a child for suspected AHO is deciding when to pursue these invasive studies, as there is a paucity of data examining how to differentiate AHO from competing diagnoses.

To address this knowledge gap, we conducted a multicenter matched case-control study to define clinical and laboratory factors associated with AHO in children undergoing evaluation for a suspected MSK infection in the pediatric emergency department (ED) and to derive a clinical score to inform providers' decision to pursue or forego definitive diagnostic testing for AHO.

METHODS

Study Design

We conducted a retrospective matched case-control study of children undergoing evaluation for a suspected MSK infection between January 1, 2017 and December 31, 2019 at 23 pediatric EDs associated with the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) of the American Academy of Pediatrics. Participating sites included 22 EDs in the United States and 1 in Spain. The study was approved by the PEM CRC Steering Committee and the research ethics boards of all participating institutions with permission for data sharing.

Selection of Cases and Controls

Eligible subjects included children >90 days to <18 years of age presenting to a participating ED during the study period. We identified potential cases by searching the electronic health record for International Classification of Diseases 10th Revision diagnosis codes for osteomyelitis (Supplemental Table 5). Potential cases underwent chart review to confirm a diagnosis of AHO by meeting any of the following criteria: (1) advanced imaging findings (MRI, computed tomography, or nuclear medicine bone scintigraphy) consistent with a diagnosis of osteomyelitis; (2) operative or histopathology findings consistent with a diagnosis of osteomyelitis; or (3) clinical presentation consistent with osteomyelitis and either a causative pathogen identified by blood culture or clinical improvement after standard-of-care treatment of osteomyelitis (combined intravenous or oral antibiotic course ≥3 weeks, with or without operative bone debridement). These criteria were derived ad hoc based on consensus review of the latest society guidelines on pediatric osteomyelitis.[8–10]

We defined controls as patients evaluated for a suspected MSK infection not diagnosed with osteomyelitis, septic arthritis, or pyomyositis. Potential controls were identified based on laboratory and imaging studies performed in the ED, including: (1) (all of the following) complete blood count with differential, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR); and (2) (at least 1 of the following) plain radiograph of an extremity or joint and/or ultrasound of a joint. To ensure that the work-up of potential controls was directed at evaluating for a suspected MSK infection, ED provider documentation was required to state that MSK infection was considered in the patient's differential diagnosis or ruled out by their evaluation.

Cases and controls were excluded based on the following criteria: duration of symptoms >14 days; location of concern including the axial skeleton; evaluation associated with presence of a pressure ulcer, overlying open wound, penetrating trauma (including bite wounds), or implanted orthopedic hardware; neuromuscular impairment severely limiting participation in the medical evaluation; immunocompromised status; inherited skeletal dysplasia; sickle cell disease; or diagnosis or past medical history of chronic recurrent multifocal osteomyelitis. Controls were further excluded if later diagnosed with osteomyelitis, septic arthritis, or pyomyositis within 30 days of their index ED visit, based on screening hospital discharge summaries and return ED encounters.

All eligible cases were included in the final study sample. Each case was matched with 2 controls from the same study site by closest date to the case ED visit.

Study Protocol

Study variables were defined a priori in a shared manual of operations. A standardized data collection form was used by site investigators for structured chart review. All investigators reviewed study materials for clarity and consistency before study commencement. Deidentified data were entered electronically into a Research Electronic Data Capture tool (Vanderbilt University, Nashville, TN), a secure, web-based electronic database, hosted by the PEM CRC Data Center at Baylor College of Medicine.[13,14]

Data collected for all subjects included demographics, presenting symptoms, vital signs, physical examination findings, and laboratory results, using the ED record as

the primary data source. All available microbiology data were recorded for cases, including results of blood, joint aspirate, and bone tissue cultures, and bacterial polymerase chain reaction from any body site. Final diagnoses were recorded for controls from either their ED encounter or associated inpatient hospitalization. In the event of missing data, investigators sourced data regarding ED presentation from associated subspecialty consult notes or hospital admission notes, when available. In cases of disagreement in the medical record, a hierarchy for data abstraction prioritized documentation by the most senior practitioner.

To minimize bias associated with abstracting potentially subjective variables from the medical record, we provided restrictive keywords to define items such as fever (eg, "felt warm," "tactile temperature," etc), and pain (eg, "fussy," "irritable," "uncomfortable," etc). Duration of illness was counted based on calendar days of symptoms, with "day 1" being the first day a patient experienced any relevant symptoms associated with their presenting illness. Impaired mobility, as either a presenting symptom or physical examination finding, was defined to include limp, nonweight bearing, pseudoparalysis, or reduced joint or extremity use or range of motion.

Statistical Analysis

We identified 21 candidate predictor variables based on previously demonstrated associations in the literature (Table 1).[1,2,7–10] Patient characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables. We compared variables between case and control groups using the Wilcoxon rank-sum test for continuous variables and the X^2 test or Fisher's exact test for categorical variables, as appropriate.

For the multivariable analysis, we excluded covariates with $P \geq .2$ in their univariate association test and/or those with ≥20% missingness. To account for missing data in the remaining covariates of interest, we performed missing value imputation by random forests.[15] We generated receiver operating characteristic (ROC) curves for each continuous variable to determine optimal cut-points for dichotomization before inclusion in the multivariable model. Collinearity between predictor variables was assessed using Spearman's correlation tests before modeling and variance inflation factors after modeling. For covariates with high collinearity ($\rho > 0.7$ and/or variance inflation factor >2.5), variables were retained in the multivariable analysis based on area under the curve (AUC) of their respective ROCs. We conducted multivariable regression analysis using a stepwise selection and linear mixed-effects model to obtain adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for covariates independently associated with the diagnosis of AHO. In the final model, we adjusted for random effect of the study site.

We derived an AHO risk score by assigning points to the top performing independent predictor variables from the multivariable model. Guiding principles for the development of this risk score included: (1) favoring selection of variables with greater estimated effect size (aOR); (2) limiting the total number of included variables to ≤5 to facilitate use in the clinical setting; and (3) favoring selection of objective over subjective variables. We calculated the score's total area under the curve (AUC) and sensitivity, specificity, positive and negative likelihood ratios, and diagnostic accuracy at each score cut-point. The AUC of the risk score was validated internally by bootstrap resampling 1000 times on the study cohort. Statistical analyses were conducted using R Statistical Software (version 4.1.2).[16] All tests were 2-sided with a significance level of $\alpha = .05$.

RESULTS

We identified 1135 cases of AHO matched to 2270 controls. Sites contributed 2 to 112 cases, and 4 to 224 controls, with a median of 47 cases per site (Supplemental Table 6).

Patient Characteristics

Patient characteristics and univariate analyses are summarized in Table 1. Among patients with AHO, the most common presenting symptoms were pain (98.3%), impaired mobility (94.9%), and history of fever (79.0%), and the most common physical examination findings were impaired mobility (87.5%) and focal bony tenderness (86.5%). At least half of patients with AHO (54.3%) had a temperature ≥ 38°C during their ED visit. All candidate variables demonstrated statistical significance in univariate analyses ($P < .05$) except for sex and presence of impaired mobility by history.

The most common site of osteomyelitis among case patients was the tibia (22.4%), followed by the femur (20.9%), pelvis (18.4%), and fibula (10.9%); the humerus (6.9%) was the most common site in the upper extremity (Supplemental Table 7).

A causative pathogen was detected in 67.4% (765 of 1135) of cases. Patients with AHO had positive microbiology testing on 45.2% (480 of 1063) of blood cultures, 64.4% (275 of 427) of joint aspirate cultures, 77.8% (389 of 500) of bone tissue cultures, and 58.9% (103 of 175) of bacterial polymerase chain reaction testing from any site (Supplemental Table 8). The most common pathogens isolated were methicillin-sensitive *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Streptococcus pyogenes*, and *Kingella kingae* (Supplemental Table 9).

The most common alternate diagnoses assigned to control patients after their ED visit or associated inpatient

TABLE 1 Patient Characteristics and Univariate Analyses			
Candidate Predictor	**Case, *n* = 1135[a]**	**Control, *n* = 2270[a]**	**Missing Data, *n* (%)**
Demographics			
Age, y, median (IQR)	8 (4–11)	5 (3–9)	0 (0.0)
Sex, male, *n* (%)	712/1135 (62.7)	1367/2270 (60.2)	0 (0.0)
History of presenting illness			
Duration of illness, days, median (IQR)	5 (3–7)	2 (1–4)	225 (6.6)
Fever, *n* (%)	889/1126 (79.0)	668/2218 (30.1)	61 (1.8)
Highest temperature, °C, median (IQR)[b]	38.9 (38.7–39.4)	38.9 (38.3–39.4)	2336 (68.6)
Pain, *n* (%)	1102/1121 (98.3)	2105/2198 (95.8)	86 (2.5)
Swelling, *n* (%)[b]	530/908 (58.4)	804/1745 (46.1)	752 (22.1)
Redness, *n* (%)[b]	285/806 (35.4)	375/1449 (25.9)	1150 (33.8)
Impaired mobility, *n* (%)[c]	999/1053 (94.9)	2000/2118 (94.4)	234 (6.9)
ED vital signs			
Triage temperature, °C, median (IQR)	37.3 (36.8–38.1)	36.9 (36.7–37.3)	11 (0.3)
Highest temperature, °C, median (IQR)	38.1 (37.3–39.0)	37.1 (36.8–37.5)	11 (0.3)
Physical examination			
Focal bony tenderness, *n* (%)	931/1076 (86.5)	1281/2080 (61.6)	249 (7.3)
Swelling, edema, or joint effusion, *n* (%)	596/1058 (56.3)	809/2048 (39.5)	299 (8.8)
Overlying erythema, *n* (%)	347/1015 (34.2)	423/1884 (22.5)	506 (14.9)
Impaired mobility, *n* (%)	921/1052 (87.5)	1785/2148 (83.1)	205 (6.0)
Laboratory results			
WBC, cells × 10^3/μL, median (IQR)	10.5 (8.0–14.4)	9.4 (7.4–12.1)	12 (0.4)
ANC, cells × 10^3/μL, median (IQR)	6.7 (4.6–9.9)	4.8 (3.4–6.9)	171 (5.0)
Bands, %, median (IQR)[b]	0.0 (0.0–5.0)	0.0 (0.0–0.1)	2275 (66.8)
CRP, mg/dL, median (IQR)	6.3 (3.2–12.8)	0.4 (0.0–1.7)	23 (0.7)
ESR, mm per hr, median (IQR)	43 (27–64)	12 (7–24)	53 (1.6)
PCT, ng/mL, median (IQR)[b]	0.5 (0.2–2.5)	0.1 (0.0–0.4)	3340 (98.1)

PCT, procalcitonin.
[a] Data are reported as *n* (%) for categorical variables and median (IQR) for continuous variables.
[b] Excluded from multivariate analysis for missing data ≥20%.
[c] Excluded from multivariate analysis for $P \geq .2$.

hospitalization were transient synovitis (32.2%), pain not otherwise specified (21.0%), and cellulitis or superficial abscess (15.2%) (Supplemental Table 10).

Multivariable Analysis

Before performing multivariable analysis, ROC curves defined the following cut-points to dichotomize continuous variables: age >8 years, duration of illness >3 days, triage temperature ≥37.3°C, highest ED temperature ≥38.0°C, white blood cells (WBC) >13.0 cells × 10^3/μL, absolute neutrophil count (ANC) >6.0 cells × 10^3/μL, CRP >2.0 mg/dL, and ESR >25 mm per hr (Supplemental Fig 2). High collinearity was identified in 2 pairs of candidate predictor variables: (1) triage temperature and highest ED temperature, and (2) WBC and ANC. We preferentially selected highest ED temperature and ANC for consideration in the final multivariable model as these had greater AUCs.

Variables independently associated with AHO in multivariable regression analysis included age >8 years; male sex; duration of illness >3 days; history of fever; highest ED temperature ≥38°C; focal bony tenderness; swelling, edema, or joint effusion; overlying erythema; CRP >2.0 mg/dL; and ESR >25 mm per hour (Table 2).

AHO Risk Score

We derived a clinical risk score, ranging from 0 to 4 points, using the top performing independent clinical and laboratory predictors of AHO from the multivariable regression model, with each of the 4included factors assigned 1 point (Table 3). In this scoring model, history of fever and highest ED temperature ≥38°C were condensed into 1 factor, to account for the possible confounding effect of having received antipyretics at home or in the ED.

Patients with AHO had a higher median risk score (3, IQR: 3–4) than control patients (1, IQR: 0–2). A score of ≥3, used to differentiate patients with AHO from those without, correctly classified 84% (95% CI: 82% to 85%) of patients, with a sensitivity of 0.78 (95% CI: 0.75 to 0.80), specificity of 0.86 (0.85 to 0.88), positive likelihood ratio of 5.73 (95% CI: 5.14 to 6.39), and negative likelihood ratio of 0.26 (95% CI: 0.23 to 0.29). Score performance and statistics at different cut-points are shown in

TABLE 2 Step-wise Selection and Linear Mixed-Effects Model to Predict AHO		
Candidate Predictor	**Adjusted Odds Ratio (95% CI)**	***P***
Demographics		
Age >8 y	1.35 (1.08–1.69)	.008[a]
Sex, male	1.30 (1.05–1.61)	.01[a]
History of presenting illness		
Duration of illness >3 d	3.27 (2.63–4.07)	<.001[a]
Fever	2.60 (2.06–3.28)	<.001[a]
ED vital signs		
Highest temperature ≥38°C	2.98 (2.35–3.77)	<.001[a]
Physical examination		
Focal bony tenderness	2.82 (2.14–3.71)	<.001[a]
Swelling, edema, or joint effusion	1.36 (1.06–1.75)	.02[a]
Overlying erythema	0.70 (0.54–0.92)	.01[a]
Impaired mobility	1.33 (0.99–1.80)	.06
Laboratory results		
CRP >2.0 mg/dL	4.68 (3.67–5.98)	<.001[a]
ESR >25 mm per hour	3.70 (2.95–4.62)	<.001[a]

[a] Statistically significant, $P < .05$.

Table 4. The risk score's overall AUC for predicting AHO is 0.892 (95% CI: 0.881 to 0.901; Fig 1). Internal validation of the AUC by bootstrap analysis revealed a mean difference of −0.00024 (95% CI: −0.00056 to 0.00008).

DISCUSSION

In this 23-site multicenter case-control study, we derived a novel 4-point risk score to predict AHO in children undergoing diagnostic evaluation for suspected MSK infection. Current guidelines on pediatric bone and joint infections from the United States, Canada, and Europe provide clinicians with a summary of the common presenting features of osteomyelitis and recommendations on laboratory and imaging tests that can aid in diagnosis.[8–10] Our study builds on this framework by delineating the predictive value of easily obtainable clinical and laboratory findings associated with AHO within a broad sample of pediatric patients for whom MSK infection was a diagnostic concern and by providing a simple clinical-decision tool to guide further evaluation.

We identified 4 independent factors to guide clinical decision-making in children presenting with features of a suspected MSK infection: (1) duration of illness >3 days; (2) history of fever or highest ED temperature ≥38°C; (3) CRP >2.0 mg/dL; and (4) ESR >25 mm per hour. Our study followed a similar approach used by Kocher et al in their derivation of a clinical prediction algorithm to differentiate septic arthritis from transient synovitis in children presenting with an acutely irritable hip.[17] However, unlike septic arthritis of the hip, AHO may have a more varied clinical presentation that elicits a wider range of potential mimic diagnoses. Rather than compare AHO to a single alternate diagnosis, we sought to compare patients diagnosed with AHO to those evaluated for a MSK infection (ie, osteomyelitis, septic arthritis, or pyomyositis) that was ruled out. We used a specific combination of laboratory and imaging tests performed on ED patients and queried ED provider documentation to identify our comparative group of control patients undergoing evaluation for any suspected MSK infection. Our findings cannot be used to differentiate AHO from other MSK infections.

TABLE 3 AHO Risk Score	
Factor	**Points (Present/Absent)**
Duration of illness >3 d	1/0
History of fever or highest ED temperature ≥38°C	1/0
CRP >2.0 mg/dL	1/0
ESR >25 mm per hr	1/0

The highlighted cut-point of ≥3 maximizes overall diagnostic accuracy of the proposed risk score to differentiate patients with and without AHO. In practice, clinicians may favor applying a lower or higher cut-point when deciding to pursue or forego advanced diagnostics, depending on the relative value placed on favoring greater sensitivity versus greater specificity or on shared decision-making discussions with caregivers. Additional considerations that may influence the application of this risk score include the need for sedation to obtain an MRI or bone biopsy, local resource limitations, and the reliability of establishing close outpatient follow-up. Prior population-based studies that sought to enroll all children evaluated for a possible MSK infection have reported a prevalence of AHO in 5.6% to 8.6% of patients.[2,18] By applying the likelihood ratios of our risk score to these population estimates, patients with a risk score of 0 would have an absolute risk of AHO of 0.2% to 0.3%, and those with a risk score of 4 would have an absolute risk of 37.9% to 49.1%.

Two variables that were not selected for use in our AHO risk score deserve special mention. Overlying erythema was found to have a negative association with AHO (aOR 0.70, 95% CI: 0.54 to 0.92) despite more case patients having this finding present on physical examination than control patients (34.2% cases versus 22.5% controls). This suggests that, after controlling for other covariates, the presence of overlying erythema is more likely to be associated with an alternate underlying diagnosis, such as cellulitis. Although we also found the odds of AHO were greater among children >8 years old than among children ≤8 years old (aOR 1.35, 95% CI: 1.08 to 1.69), this does not mean that older age is a risk factor for AHO. Indeed, prior studies have cited a higher incidence of AHO in younger children, with an overall mean age of 6.6 years.[1,2] Rather, we believe that this result reflects the methodology used for defining control patients, which required laboratory and imaging studies to be

TABLE 4 Performance of the AHO Risk Score at Different Cut-Points					
Cut-Point[a]	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	Accuracy (95% CI)
≥1	0.99 (0.98–1.00)	0.38 (0.36–0.40)	1.60 (1.55–1.66)	0.03 (0.01–0.05)	59 (57 to 60)
≥2	0.94 (0.92–0.95)	0.69 (0.67–0.71)	3.01 (2.82–3.20)	0.09 (0.07–0.12)	77 (76 to 79)
≥3	0.78 (0.75–0.80)	0.86 (0.85–0.88)	5.73 (5.14–6.39)	0.26 (0.23–0.29)	84 (82 to 85)
=4	0.43 (0.40–0.46)	0.96 (0.95–0.97)	10.27 (8.35–12.65)	0.59 (0.57–0.63)	78 (77 to 80)

[a] At each cut-point, reported test statistics apply to the comparison of patients at or above the proposed cut-point (those presumed to have AHO) to patients below the proposed cut-point (those presumed to not have AHO).

eligible for inclusion. Young children are more challenging to evaluate and may be more likely to have these tests performed during their ED evaluation, favoring recruitment of younger children to our control patient cohort. A similar paradoxical association with age was reported in a prior study on children undergoing evaluation for suspected MSK infections that required laboratory and imaging studies as control eligibility criteria.[18] Nevertheless, by including age in our final multivariable model, the reported aORs of the remaining variables are effectively controlled for age to account for this.

Our study had limitations consistent with the challenges of accurate and complete data recovery inherent to retrospective study design. The abstraction of historical and clinical features was potentially subjective, and we did not assess interrater reliability of data abstraction. However, we used restrictive parameters and provided a standardized approach to chart review through a manual of operations for training and consistency. Though significant missingness was an issue for a minority of variables, we attempted to control for this by performing missing value imputation for candidate predictors with <20% missingness and by excluding those with ≥20% missingness from the multivariable analysis. Nonetheless, our model cannot comment on potential associations of several factors with AHO, including procalcitonin. It is also possible that some controls were diagnosed with AHO following their index visit. We attempted to mitigate this possibility by screening return ED visits and inpatient hospitalizations within 30 days. We recognize that these methods do not account for possible AHO diagnoses made outside of the participating centers. Though fever by history and highest ED temperature ≥ 38°C were collected as separate variables, we combined these into 1 factor for our AHO score, thus sacrificing some precision for ease of applicability. Our findings are not generalizable to cases of nonhematogenous osteomyelitis, osteomyelitis of the axial skeleton, or patients with orthopedic hardware, sickle cell disease, immunocompromised status, and primary neuromuscular disability. Lastly, although our AHO risk score should be externally validated before broad implementation, prospective validation may be challenging given the low incidence of AHO in children. We sought to mitigate this

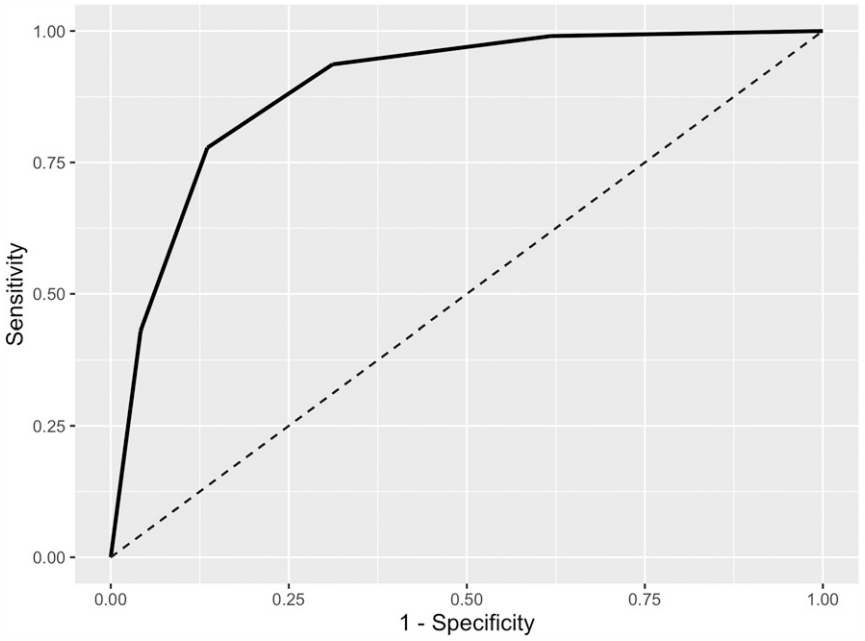

FIGURE 1
AHO risk score ROC curve. The AUC was 0.892 (95% CI: 0.881–0.901). Internal validation by bootstrapping analysis (resampling 1000 times on the study cohort) revealed a mean AUC of 0.892 (95% CI: 0.882 to 0.902) and a mean difference of −0.00024 (95% CI: −0.00056 to 0.00008).

limitation by providing the results of an internal validation analysis by bootstrap resampling.

CONCLUSIONS

In this large, multicenter study of children undergoing evaluation for suspected MSK infections, we identified 10 variables independently associated with a diagnosis of AHO. We derived an AHO risk score using top-performing predictors (duration of illness >3 days; history of fever or highest ED temperature ≥38°C; CRP >2.0 mg/dL; ESR >25 mm per hour), which may be easily applied in the ED setting to inform the decision to pursue or forego definitive diagnostic testing in children for whom the diagnosis of AHO is being considered.

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ABBREVIATIONS

AHO: acute hematogenous osteomyelitis
ANC: absolute neutrophil count
aOR: adjusted odds ratio
AUC: area under the curve
CI: confidence interval
CRP: C-reactive protein
ED: emergency department
ESR: erythrocyte sedimentation rate
IQR: interquartile range
MSK: musculoskeletal
ROC: receiver operating characteristic
WBC: white blood cells

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Dr Stephan conceptualized and designed the study, designed the data collection instruments, performed data collection and regulatory activities at their site, coordinated and supervised data collection and transfer from other sites, performed data analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Kaplan participated in the study design, performed data collection and regulatory activities at their site, assisted in data analyses interpretation, and reviewed and revised the manuscript; Drs Platt, Levine, and Klein participated in the study design, assisted in data analyses interpretation, and reviewed and revised the manuscript; Ms Qiu conducted initial and subsequent data analyses, contributed to the writing of the methods and results, and reviewed and revised the manuscript; Drs Buchhalter, Lyons, Gaines, Cruz, Sudanagunta, Hardee, Eisenberg, Tamas, McAneney, Chinta, Yeung, Root, Fant, Dunnick, Pifko, Campbell, Bruce, Srivastava, Pruitt, Hueschen, Ugalde, Becker, and Granda performed data collection and regulatory activities at their sites, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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