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Predictive model for surgical intervention in pediatric acute hematogenous osteomyelitis

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Abstract

Background The emergence of multidrug-resistant bacteria has resulted in more complicated disease courses and worsening prognoses for patients with acute hematogenous osteomyelitis (AHO), increasing the necessity for surgical intervention. This research attempts to identify the risk variables related to surgical patients and build prediction models.

Method From December 2015 to December 2022, children admitted to a single quaternary care pediatric hospital with AHO had their charts retrospectively reviewed. Based on the therapy methods, the patients were divided into 3 cohorts: multiple surgery, single surgery, and conservative care. Multivariate logistic regression analysis was used to identify independent risk factors related to single and recurrent surgery. A nomogram was created to visually represent the various risk factors, and a calibration curve was plotted to evaluate the model's goodness of fit. The Hosmer-Lemeshow test and the area under the receiver operating characteristic (ROC) curve were used to assess how well the models matched.

Results A total of 218 patients were included in the analysis, out of which 150 patients underwent surgical procedures, with 21 individuals undergoing multiple surgeries. The multivariate binary logistic regression revealed that an increase in absolute neutrophil counts (ANC) (adjusted odds ratio [aOR], 1.14 [95% confidence interval {CI}, 1.05–1.24]) and the presence of Methicillin-resistant Staphylococcus aureus (MRSA) (aOR, 6.97 [95% CI, 1.94–25.06]) were strong predictors of surgical intervention. The prediction model demonstrated an area under the curve (AUC) value of 0.76, while the Hosmer-Lemeshow test showed $\chi^2 = 7.3$, $P = 0.50$. In another separated model, the C-reactive protein (CRP) level upon admission (aOR, 1.02 [95% CI, 1.00-1.03]) and the CRP level after the initial surgery (aOR, 1.04 [95% CI, 1.01–1.06]) strongly predict multiple surgeries, with the AUC value of 0.91 obtained and HosmerLemeshow test ($\chi^2 = 8.7$, $P = 0.36$) yielded. The calibration curves of the two models were drawn separately, and it was observed that the slopes of both models were close to one.

Conclusion Two prediction models were developed by statistical analysis of clinical data. Their accuracy and discrimination were validated, indicating a promising potential for clinical application.

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Introduction

AHO is an important disease affecting the pediatric population's health, with timely diagnosis and effective treatment significantly minimizing complications and improving clinical outcomes [1]. In 90% of patients with acute infections, a complete cure can be achieved solely through antibiotic therapy [1, 2]. However, in recent decades, there has been a shift in the bacterial spectrum, particularly with the rise of MRSA, which has been documented in the United States; the isolation rate has risen from 11.8% in 2002 to 34.8% in 2010 [3–5]. In China, the MRSA isolation rate has exceeded 30%, with higher prevalence observed in rural healthcare settings compared to urban centers [6]. It contains the Panton-Valentine leucocidin (PVL) gene encoding a potent toxin that causes tissue necrosis and the destruction of white blood cells, which significantly increases tissue destruction and invasion, often necessitating aggressive surgical intervention, even multiple times [4–8].

Surgery, aimed to alleviate bone marrow cavity pressure, eliminate necrotic tissue, reduce bacterial load, and aid in diagnosis, is not typically considered the first choice for AHO but is reserved for cases where pharmacological therapy is ineffective or when there is a substantial local abscess [3, 9]. However, due to the increasing prevalence of "refractory osteomyelitis" caused by drug-resistant bacteria, its significance and indispensability are progressively escalating, and delayed debridement frequently results in irreversible pathological damage [1]. Currently, no consensus has been reached on the optimal surgical indication and timing, and few researchers report relevant indications for multiple operations [10, 11]. The decision is mostly based on the presence of an abscess around the lesion on magnetic resonance imaging (MRI) and the patient's response to antibiotic treatment [12, 13]. Yet, the drawbacks of MRI, including limited instant availability and the potential hazards of anesthesia and sedation, hinder its use in urgent medical settings [14], but delayed surgical debridement following failed conservative treatment does not effectively improve prognosis, often leading to chronic disease and severe bone and joint destruction. Therefore, the primary objective of this study is to identify readily available laboratory indicators that can assist clinicians in making timely surgical decisions, thereby optimizing children's prognoses.

Method

Study population

A retrospective cohort research was carried out at a tertiary children's hospital to collect medical data on all patients treated for AHO from December 2015 to December 2022. The study received approval from our institutional ethics committee board, approval number: [2024]-E-132-R; This study complied with the Declaration of Helsinki, and informed consent was waived for all subjects enrolled.

Inclusion and exclusion criteria

Inclusion criteria (all of these): (1) Age between 1 month and 18 years; (2) Disease duration less than 2 weeks.

Exclusion criteria (any of these):1) Penetrating trauma or prosthesis implantation within 30 days; 2) Concurrent systemic diseases (immunodeficiency, malignant tumor, diabetes mellitus) or non-infectious inflammatory reactions (rheumatic fever, eczema, juvenile idiopathic arthritis); 3) History of osteomyelitis surgery at other institutions; 4) Insufficient clinical data.

Definition of terms

The diagnosis of AHO included meeting any of the following along with typical symptoms and elevated laboratory markers: 1) bacterial culture from blood, pus, or bone marrow; 2) signs of edema in the medullary cavity and deep abscesses on MRI; 3) confirmation of acute inflammation through bone tissue biopsy [15]. Hypoproteinemia was defined as a serum albumin level below 30 g/L, hyponatremia as less than 135mmol/L, and hyperfibrinogenemia as fibrinogen levels surpassing 4 g/L. The disseminated diseases encompass multifocal osteomyelitis (involving three or more bone locations), deep-vein thrombosis, septic pulmonary emboli, pneumonia, endocarditis, and pleural effusion. The delay in therapy was considered as the interval between the onset of clinical symptoms and the initial antibiotics administration. Multiple/repeated operations refer to procedures involving debridement two or more times. Surgical indications included: no response to medical treatment for 3 to 4 days (persistent high fever or local inflammation) and bone marrow cavity abscess formation or periosteal elevation > 2 mm [16]. The denotations for multiple operations were as follows: After the initial fenestration and lavage, continuous irrigation and drainage were maintained for 7 days, but upon removal of the drainage device, a significant amount of purulent material remained within the medullary cavity. The primary surgical techniques employed included cortical fenestration, debridement of perforations, and ongoing irrigation and drainage.

Management

For patients with suspected AHO, characterized by persistent high fever and evident local swelling and pain, we generally chose to use vancomycin and ceftriaxone as empirical antibiotic treatment due to the high prevalence of MRSA, which makes up more than 30% of pathogenic bacteria [17]. Semi-synthetic penicillin or first/second-generation cephalosporins (e.g., cefazolin, cefuroxime)

are sufficient for patients with stable conditions and mild clinical symptoms. For patients who have failed treatment, we will conduct a comprehensive evaluation again. This may involve strategies such as switching vancomycin to linezolid, adding rifampin, or upgrading cephalosporins to carbapenem antibiotics (e.g., ertapenem, meropenem). After admission, peripheral and central venous blood samples or pus samples are collected for bacterial culture based on whether temperature exceeds 38.5℃ or soft tissue effusion presents, and then the most appropriate antibiotic is selected through drug sensitivity testing. The intravenous medicinal duration typically lasts for 2 to 4 weeks. Once the C-reactive protein (CRP) level returns to normal (< 10 mg/L), along with resolution of local symptoms and cessation of fever, oral antibiotics are administered for a period ranging from 2 to 6 weeks Fig. 1.

Data collection

A list of eligible patients was generated from an electronic medical record database query for patients using the *International Classification of Diseases, Ninth Revision, and Tenth Revision (ICD-9/10)* codes with osteomyelitis. Two resident physicians not involved in the study collected their demographic data, clinical care details, as well as imaging and laboratory information. The imaging interpretation was delivered by professional radiologist reports, guaranteeing an unbiased review of the images. Patients were classified into three groups based on their treatment techniques and number of operations: conservative treatment group, single operation group, and multiple operation group.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.0 software (IBM Corp., Armonk, NY). Continuous data were expressed by $\bar{x} \pm s$ or median and interquartile range (IQR) according to the Kolmogorov–Smirnov test. Categorical variables were described by frequencies with proportions (%). Univariate analysis was performed to identify statistically significant variables (A two-sided p-value < 0.05), which were included in multivariate logistic regression models (enter method) to determine related independent risk factors associated with simple or repeated surgeries and calculate odds ratios (ORs) and 95% confidence intervals (95%CIs). R Statistical Software version 4.3.0) was utilized to construct a nomogram illustrating the relationship between various risk factors in the logistic model for intuitive representation. The model's fitting effect and goodness of fit were assessed and validated through the AUC, Hosmer-Lemeshow test, and calibration curve.

Results

Demographics

403 individuals were discharged with a primary diagnosis of "osteomyelitis" during the research period. Exclusions comprised 185 (46.0%) cases: 121 (65.4%) cases with course of disease > 2 weeks, 28 (15.1%) with incomplete clinical data, 14 (7.6%) with immune diseases, 12 (6.5%) neonates, 8 (4.3%) cases involving surgeries conducted in other hospitals, and 2 (1.1%) penetrating trauma cases, leaving only 218 (54.0%) patients who met the inclusion criteria. The surgical treatment group consisted of 150 patients, including 21 (14.0%) patients in the multiple surgery subgroup. Medical treatment alone was administered to 68 patients Fig. 2. The median age of the patients was 6.5 years, and the male-to-female ratio was 1.3:1. Patients in the conservative-management group were older than those in the surgery group ($P = 0.025$). Most patients (96%, $n = 210$) had a fever before admission, and nearly all (98.2%, 214/218) showed lesion soreness and swelling. The median time of onset was 8 days (range 6 ~ 12 days), and there was no significant difference between the two groups. An MRI was conducted on 190 patients, revealing local abscesses in 175 (92.1%) cases, with 39 (20.5%) children exhibiting concurrent MRSA infection requiring abscess drainage. Biopsy confirmed acute inflammation in 20 patients for an uncertain diagnosis. Before being admitted, 36 individuals had radiographic signs of reduced bone density.

Microorganisms

The positive rate of pus culture was 69.5% in 161 patients, and the blood culture was 57% in 123 patients. The difference was statistically significant ($P = 0.028$). 70% of patients (152/218) had a pathogen isolated, of which 94.1% (143/152) were Staphylococcus aureus (methicillin-sensitive S. aureus, 101/143; methicillin-resistant S. aureus, 42/143), followed by Streptococcus pyogenes (2/152, 1.3%), Streptococcus pneumoniae (3/152, 2.0%), Klebsiella pneumonia (1/152, 0.7%), Salmonella enterica (2/152, 1.3%), and Streptococcus lactis (1/152, 0.7%). The results of bacterial culture were obtained from other institutions in 14 (9.2%) cases and prior to surgery in 62 (40.8%) cases, including 12 cases of MRSA.

Sites of infection

The femur and tibia were the most frequent sites of infection, accounting for 39.9% and 26.1% respectively, followed by the humerus (13.3%), fibula (10.1%), ulna (3.2%), and radius (2.8%). Eighty-seven patients exhibited septic arthritis (hip: 33 cases, knee: 19 cases, shoulder: 14 cases, elbow: 11 cases, ankle: 10 cases), and out of these individuals, 35 underwent simultaneous incision and drainage. Fourteen patients with multiple infection sites occurred mostly around the hip and ankle joints.

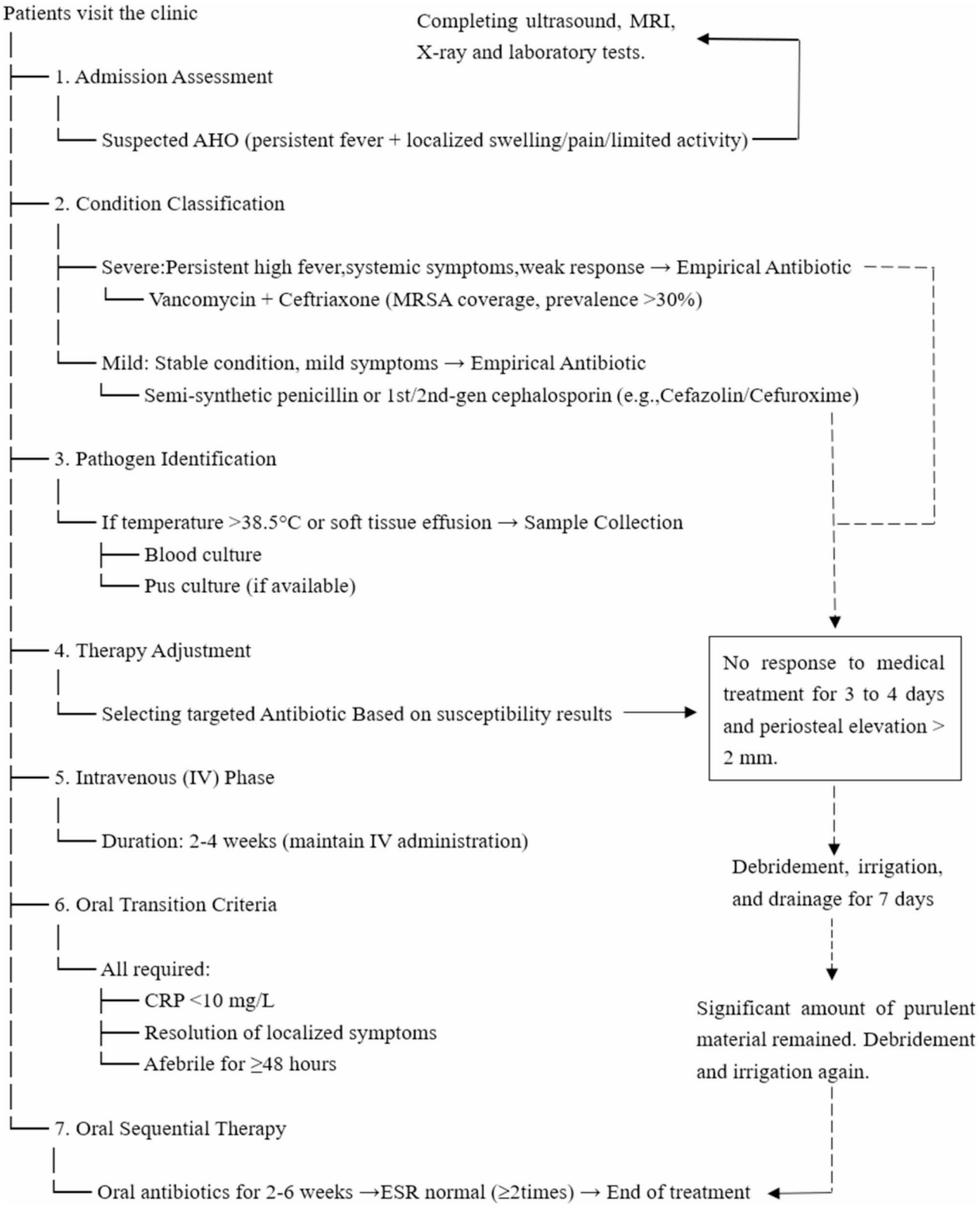

Fig. 1 Flowchart for the treatment of children with acute hematogenous osteomyelitis

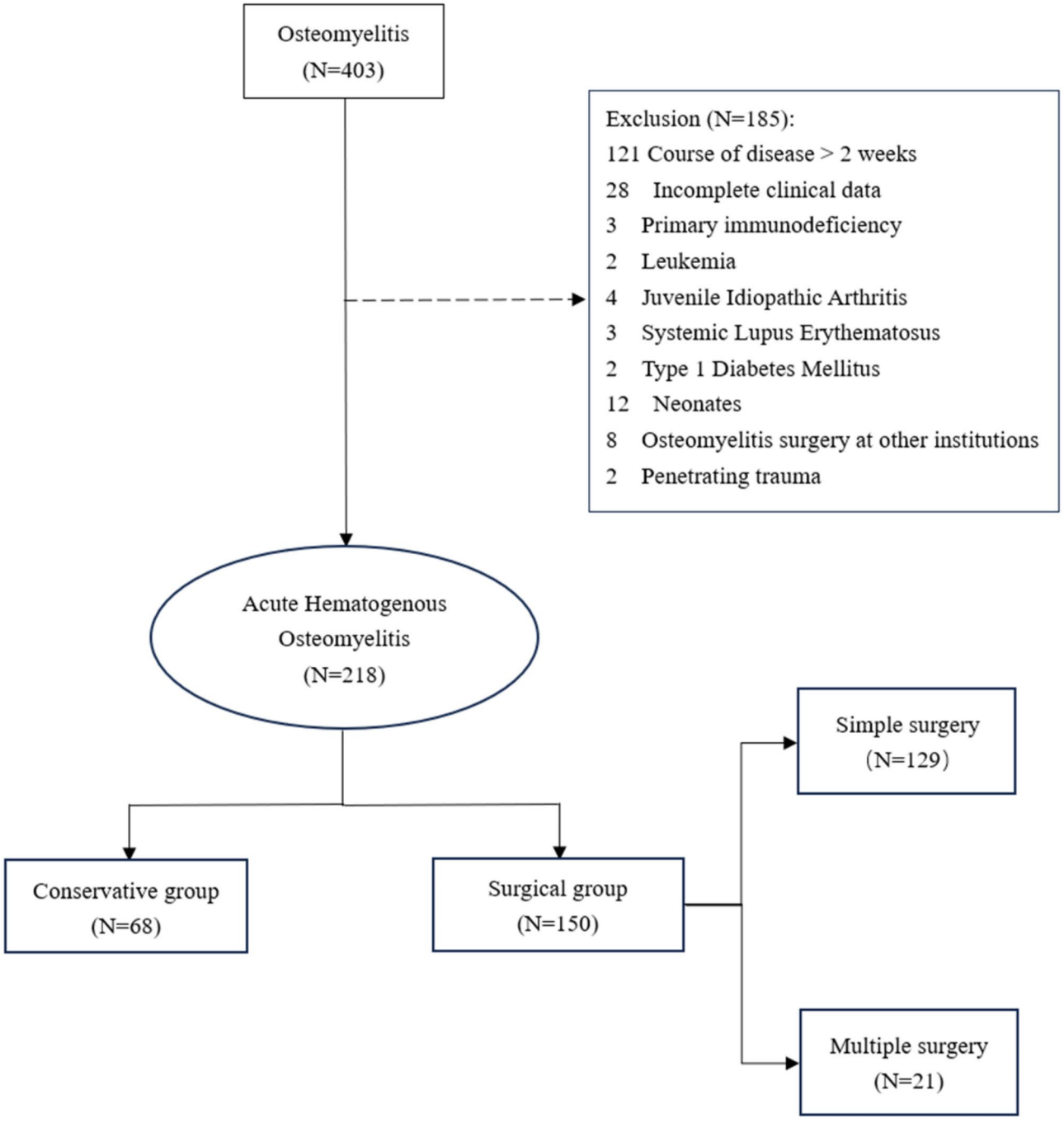

Fig. 2 Patients enrollment flow chart

Clinical features and laboratory parameters

With a similar time to onset, the surgery group had nearly twice the CRP level on admission (60 vs. 31 mg/L, $P=0.005$) and was more likely to have hypoalbuminemia (30% vs. 11.7%, $P=0.004$), hyperfibrinogenemia (82.7% vs. 42.7%, $P=0.003$), hyponatremia (55.3% vs. 33.8%, $P=0.003$), and hyperpyrexia on admission (36% vs. 19%, $P=0.012$) and Methicillin-resistant Staphylococcus aureus infection (26.5% vs. 5%, $P<0.001$). Additionally, these pediatric patients exhibited a significantly prolonged duration of fever and an elevated ANC (8 vs. 6 days, $P=0.012$; 9.1 vs. 4.8 mg/L, $P<0.001$), Fig. 3. In the univariate analysis, the multiple surgery group had significantly higher inflammation indicators levels than the single surgery group, especially an 11-fold increase in the median CRP level after the initial surgery (79.4 vs. 8.0 mg/L, $P<0.001$), a 2-fold increase in CRP upon admission (154.1 vs. 50.0 mg/L, $P<0.001$), and a higher

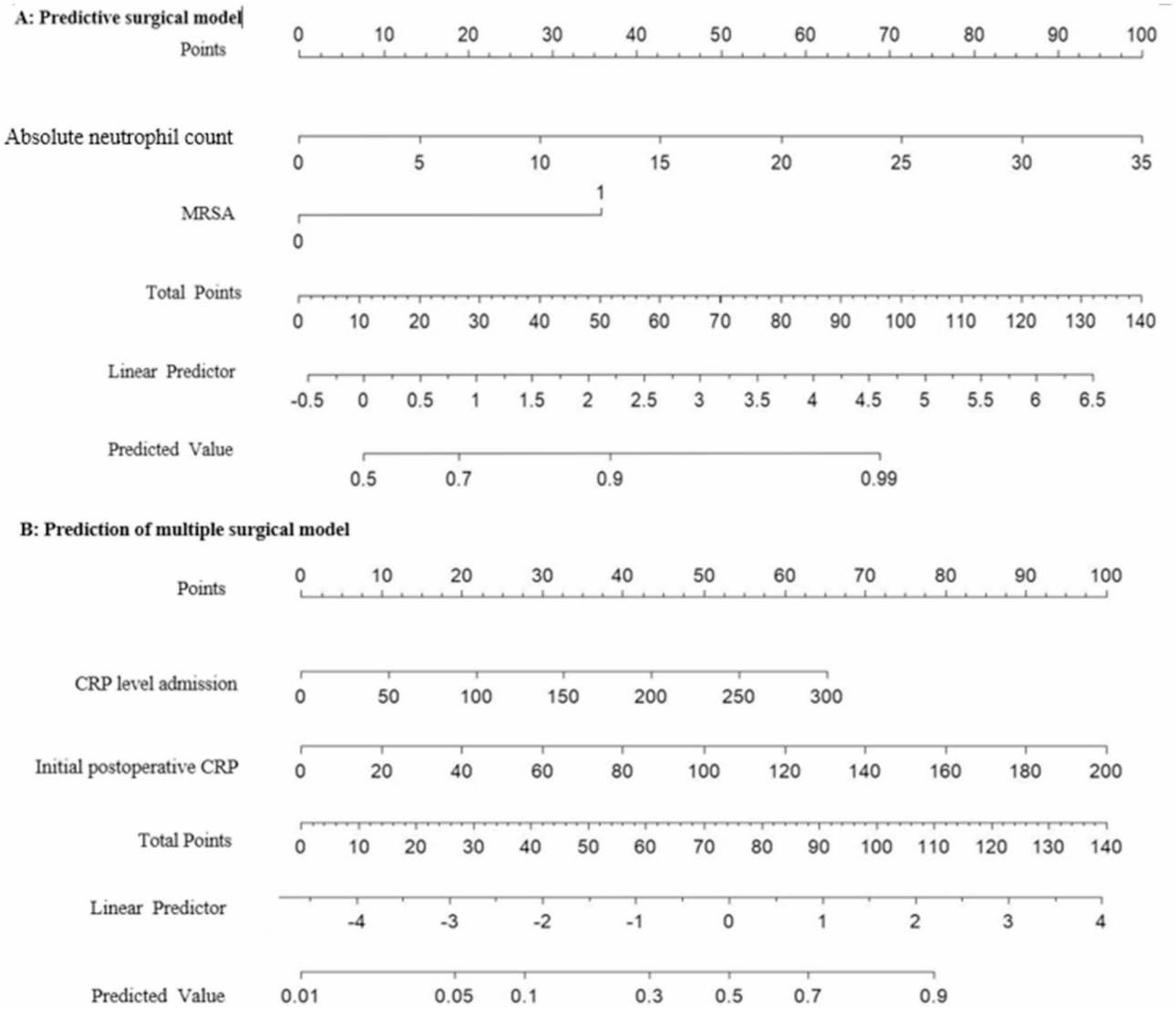

Fig. 3 Comparison of laboratory parameters and clinical characteristics between groups. Note: FDOA: Febrile days on antibiotics; DINA: Duration of intravenous antibiotics; TAD: Total antibiotic duration; TNO-CRP: Time to normalization of CRP; INP-CRP: Initial postoperative CRP; LOS: Length of stay

likelihood of admission to the intensive care unit (3.1% vs. 23.8%, $P=0.001$), disseminated disease (26.4% vs. 52.4%, $P=0.016$), and co-infection with MRSA (22% vs. 55%, $P=0.003$). As expected, the surgical group and the multiple surgery group exhibited longer durations of intravenous antibiotics, hospital stays, and CRP recovery times compared to the conservative treatment group ($P<0.05$). Similarly, the multiple surgery group was more likely to have complications such as adjacent septic arthritis and multifocal infections, but the differences did not reach statistical significance, Table 1.

Model prediction

We included as many potentially influential clinical and laboratory parameters as possible in the model to identify the optimal predictors for surgical and repeated operations. Covariates with significant differences in univariate analysis ($P<0.05$) were included in the multivariate binary Logistic regression model, and two covariates were found to independently predict surgical treatment ($N=218$, *Hosmer and Lemeshow* $P=0.50$), Table 2: ANC (aOR, 1.14 [95% CI, 1.05–1.24], cutoff = 6.9 [Youden index], sensitivity of 65%, specificity of 75%). MRSA (aOR, 6.97 [95% CI, 1.94–25.06], positive predictive value of 92.8%, negative predictive value of 36.9%). We evaluated the issue of multicollinearity between ANC and MRSA, and calculated the correlation coefficient ($r=0.12$, $P=0.06$) and the Variance Inflation Factor (VIF) value (ANC: VIF = 1.016; MRSA: VIF = 1.02), indicating no significant correlation between the variables. Additionally, the VIF values are within a safe range, thus the model is robust. Similarly, in another separate model,

Table 1 Univariate comparisons of clinical and laboratory parameters of acute hematogenous osteomyelitis in the surgery group compared with the No-Surgery group and the Single-Surgery group compared with the Multiple-Surgery group

	Surgical Group (*N* = 150)	**Conservative treatment group (*N* = 68)**	***P*-value**	**Simple-surgery group (*N* = 129)**	**Multiple-surgery group (*N* = 21)**	***P*-value**
Age, years	7.5 (2.6 ~ 10.4)	4.8 (1.3 ~ 11.8)	**0.025**	6.8 (2.3 ~ 10.3)	8.4 ± 4.3	0.077
Gender, male (n/%)	81 (54%)	44 (58%)	0.139	72.0 (55.8%)	10 (47.6%)	0.484
CRP (mg/L)	60 (20.5 ~ 129)	31 (11 ~ 81)	**0.005**	50.0 (18 ~ 102)	154.1 ± 58.7	**0.000**
ESR (mm/h)	58.7 ± 26.1	54.4 ± 27.8	0.269	61.1 ± 28.1	58.3 ± 25.9	0.650
PCT (ng/mL) *	0.3 (0.1 ~ 2.0)	0.2 (0.1 ~ 0.8)	0.211	0.2 (0.04 ~ 1.1)	2.1 (1.0 ~ 10.5)	**0.000**
WBC (10^9 cells/L)	12.0 (8.4 ~ 15.9)	10.8 (7.2 ~ 14.5)	0.078	11.2 (8.0 ~ 15.3)	15.1 ± 5.6	**0.014**
D-dimer peak (mg/L) *	1.4 (0.7 ~ 2.6)	1.0 (0.6 ~ 3.3)	0.402	1.3 (0.5 ~ 2.4)	2.5 (1.2 ~ 5.2)	**0.009**
ANC (10^9/L)	9.1 ± 4.8	4.9 (2.9 ~ 7.0)	**0.000**	7.9± (5.3 ~ 11.6)	11.4 ± 4.5	**0.018**
ALC (10^9/L)	2.6 (1.9 ~ 4.0)	2.8 (2.1 ~ 4.0)	0.719	2.8 (2.0 ~ 4.2)	1.9 (1.3 ~ 2.8)	**0.008**
Hematocrit (%)	33.4 ± 4.8	32.8 ± 4.5	0.813	33.6 ± 4.8	31.8 ± 4.5	0.108
CRP peak > 100 mg/L	78 (52%)	26 (38.2%)	0.059	59.0 (45.7%)	19.0 (90.5%)	**0.000**
ESR peak (mmh)	73.5 ± 28.2	58.0 (38.8 ~ 86.8)	**0.020**	68.6 ± 26.6	99.2 ± 27.2	**0.000**
WBC peak (10^9 cells/mL)	15.7 ± 7.2	14.5 (10.6 ~ 18.7)	0.508	14.8 (9.4 ~ 18.8)	21.2 ± 7.7	**0.000**
PLT peak (10^9 /L)	523.0 ± 189.4	532.5 ± 174.7	0.960	519.3 ± 179.8	545.2 ± 244.5	0.563
Hypoproteinemia (n/%)	45 (30%)	8 (11.7%)	**0.004**	30.0 (23.3%)	15 (71.4%)	**0.000**
Hyperfibrinogenemia (n/%)	124 (82.7%)	44 (64.7%)	**0.003**	105.0 (81.4%)	19 (90.5%)	0.479
Initial postoperative CRP (mg/L)	9.0 (7 ~ 29)	~	~	8.0 (7.0 ~ 20.0)	79.4 ± 47.5	**0.000**
Initial postoperative ESR (mm/h)	47.5 (29 ~ 74.3)	~	~	44 (27 ~ 70)	80.0 ± 39.8	**0.001**
Duration of antibiotic use before admission (day)	5 (3 ~ 8)	6 (4 ~ 9)	0.079	5 (3 ~ 8)	5.3 ± 3.7	0.596
Time to onset (day)	8.0 (6 ~ 12)	8.5 (6 ~ 12)	0.390	9 (6 ~ 12)	7 (6 ~ 11)	0.449
Febrile days on antibiotics (day)	8 (5 ~ 11)	6 (2.2 ~ 9)	**0.012**	7 (4 ~ 10)	11.2 ± 6.7	**0.013**
Delay antibiotic time (day)	3 (1 ~ 4)	2 (1 ~ 4)	0.361	3 (1 ~ 4)	3.2 ± 2.7	0.770
Length of stay (day) *	14.5 (11 ~ 23.3)	15.0 (12 ~ 23)	0.953	14 (11 ~ 19.5)	27 (24 ~ 48.8)	**0.000**
Total antibiotic duration (day) *	40.0 (30.8 ~ 50.3)	34.5 (30 ~ 42)	**0.000**	37 (30 ~ 48.5)	48 (41 ~ 65)	**0.001**
Duration of intravenous antibiotics (day) *	20 (15 ~ 26)	20 (16 ~ 26.8)	**0.000**	19 (14 ~ 23)	27 (23 ~ 34)	**0.000**
Time to normalization of CRP (day) *	16 (13 ~ 22)	14 (11 ~ 20)	**0.035**	15 (12.0 ~ 20.5)	29 (21 ~ 40.5)	**0.000**
Days of fever (day)	9 (6 ~ 14)	8 (6 ~ 11.8)	0.152	8 (6 ~ 12)	14 (8 ~ 20.5)	**0.003**
Fever (n/%)	54 (36%)	13 (19%)	**0.012**	42 (32.6%)	12 (57.1%)	**0.030**
MRSA (n/%)	39 (26.5%)	3 (4.4%)	**0.000**	28 (22.0%)	11 (55.0%)	**0.003**
Combined arthritis (n/%)	58 (38.7%)	29 (42.6%)	0.578	47 (36.4%)	11 (52.4%)	0.164
Hyponatremia (n/%)	83 (55.3%)	23 (33.8%)	**0.003**	68 (51.9%)	15 (71.4%)	0.110
Multifocal infection (n/%)	9 (6%)	5 ((7%)	0.937	6 (4.7%)	3 (14.3%)	0.219
Disseminated disease (n/%)	45 (30%)	17 (25%)	0.448	34 (26.4%)	11 (52.4%)	**0.016**
Admission to ICU (n/%)	9 (6%)	1 (1.5%)	0.258	4 (3.1%)	5 (23.8)	**0.001**

Unspecified laboratory parameters such as *CRP*, *ESR*, *PCT*, *WBC*, et al were measured on admission. **Initial postoperative CRP/ESR** measured 3 to 5 days after the initial surgery. *CRP* C-reactive protein, *ESR* blood sedimentation, *PCT* procalcitonin, *WBC* white blood cell, *D-dimer* d-dimers, *ANC* absolute neutrophil count, *ALC* absolute lymphocyte count, *PLT* platelet. The multivariate regression analysis did not incorporate parameters marked with "*".[a]Statistical analysis: Student' t test, nonparametric Mann-Whitney U test, or Chi-square test as appropriate

Table 2 The odds ratio in the AHO patients for surgery (generalized linear model analysis, surgery as a dependent variable)

Risk Factors	**OR value (95% confidence interval)**	***P*-value**
Absolute neutrophil count	1.140 (1.047–1.242)	0.003
Methicillin-resistant Staphylococcus aureus	6.974 (1.941–25.057)	0.003

Table 3 The odds ratio in the AHO patients for multiple-surgery (generalized linear model analysis, multiple-surgery as a dependent variable)

Risk Factors	**OR value (95% confidence interval)**	***P*-value**
CRP Admission	1.016 (1.001–1.030)	0.034
CRP Primary surgery	1.036 (1.010–1.062)	0.006

we found that the same two covariates independently predicted multiple surgeries ($N = 150$, Hosmer and Lemeshow $P = 0.37$), Table 3: CRP level on admission (aOR, 1.02 [95% CI, 1.00-1.03], cutoff = 123.5 [Youden index],

sensitivity of 81%, specificity of 84%), CRP level after primary surgery (aOR, 1.04 [95% CI, 1.01–1.06], cut-off = 29.5 [Youden index], sensitivity of 86%, specificity of 85%). We evaluated the issue of multicollinearity between CRP on admission and CRP after primary surgery, and calculated the correlation coefficient ($r = 0.44$, $P < 0.01$) and the Variance Inflation Factor (VIF) value (CRP admission: VIF = 1.52; CRP primary surgery: VIF = 1.52). This indicates that although there is a significant correlation, the low VIF value suggests that multicollinearity does not affect the stability of the model.

The findings of the logistic regression analysis were integrated into the R software data package to create prediction model nomograms for surgery and multiple surgical therapy, as depicted in Fig. 4. The overall score in model B was determined by combining the scores of parameter values for two continuous variables (ranging from 0 to 100 points) and identifying the prediction probability using the predicted line on the nomogram. The A model assigns a weight of around 35 points to MRSA. By combining this score with the absolute neutrophil count, one can calculate the anticipated probability of undergoing surgery. The ROC curve test assessed the predictive model's ability to discriminate. The area under the curve for neutrophil was 0.72, for MRSA was 0.61, and for the combined parameters was 0.76. The sensitivity was 72% and the specificity was 75%. The AUC of admission CRP was 0.85 after the initial surgery was 0.90, and the combined variables were 0.91 with a sensitivity of 0.95 and a specificity of 0.78, as shown in Fig. 5. To evaluate the accuracy of the prediction model, we used R software to create calibration curves to verify the modeling set internally and observed that the overall slopes of the two models were close to 1 in Fig. 6.

Discussion

Insufficient recognition of indications for single and multiple operations in patients with AHO can delay effective treatment and lead to long-term sequelae. We have consolidated the patients' clinical characteristics, treatment methods, and prognostic outcomes in Table 4 for reference.

Our study's major predictors of single operation were ANC and MRSA. Previously, few studies had mentioned the surgical predictive value of ANC in pediatric patients with AHO. As a special type of white blood cell, its role in acute inflammatory response and the molecular mechanism mediated has been elucidating. When the body encounters hazardous stimuli, it demonstrates robust responsiveness and exceptional agility, first entering the interstitial space, and then attracting other inflammatory cells to clear pathogens [18, 19]. Rosenfeld's [20] research revealed that ANC > $8.6*10^9$ cells/L can serve as a predictive indicator for septic arthritis accompanied by adjacent infections. In this study, for every increase of $5*10^9$ cells/L in ANC, there was a corresponding increment of 14 points in the risk weight. Moreover, if a patient has an admission ANC greater than $6.9*10^9$/L and is also infected with MRSA, the associated surgical risk will surpass 90%. Wenz and Henriquez et al. have found the utility of ANC in predicting infection and assessing its severity, which may in part explain our findings that

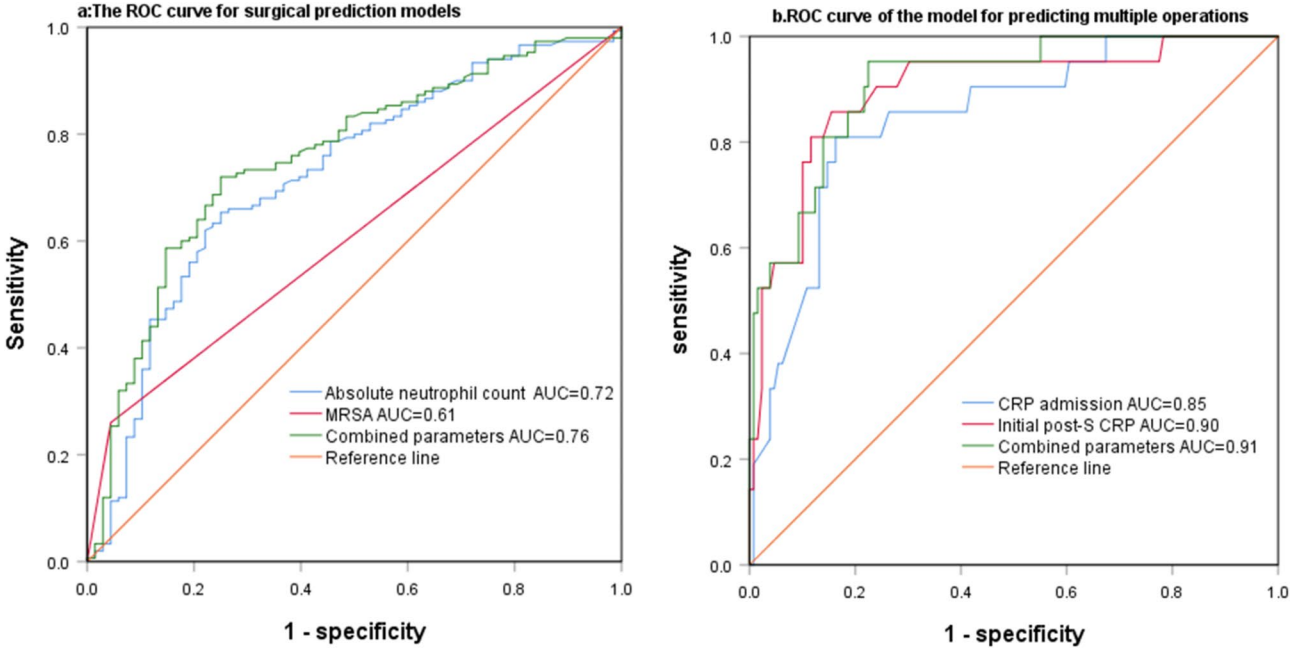

Fig. 4 Nomogram model prediction drawn in R, version 4.3.0

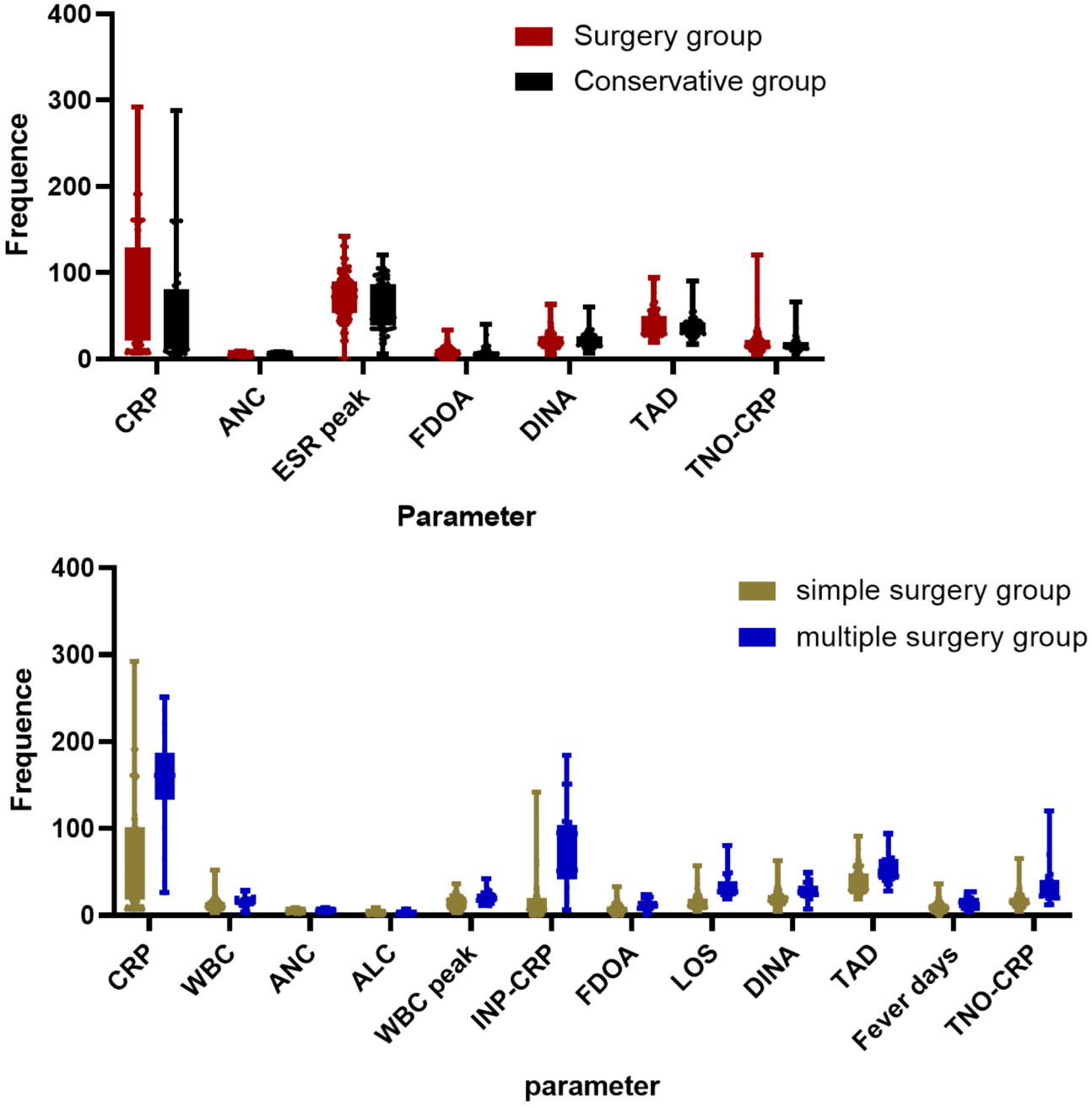

Fig. 5 Receiver operation curve and area under the curve (AUC) for the established models drawn in Statistical Package for Social Sciences (SPSS), version 25.0

children with higher ANC are at a greater risk of requiring invasive treatments [21, 22].

With advancements in pharmacology and the development of more powerful antibiotics, the administration of medications for AHO has become more efficient. However, the emergence of super drug-resistant bacteria has altered the cognition to treatment and prognosis of AHO. As illnesses get more complex and worsen quickly, more aggressive treatments are required. Lots of studies have proposed that compared with MSSA and other non-staphylococcal microorganisms, MRSA exhibited greater virulence, rendering all β-lactam antibiotics ineffective, triggered systemic inflammation and deep abscess formation, and necessitated more frequent surgical interventions [5, 23, 24]. Arnold and colleagues [4] found that 71% of MRSA patients developed subperiosteal abscesses, much greater than the MSSA group ($P = 0.02$), and 91% of MRSA patients needed surgical intervention, a far higher percentage compared to the 62% in the control group ($P < 0.001$). Tuason et al. [12] discovered that

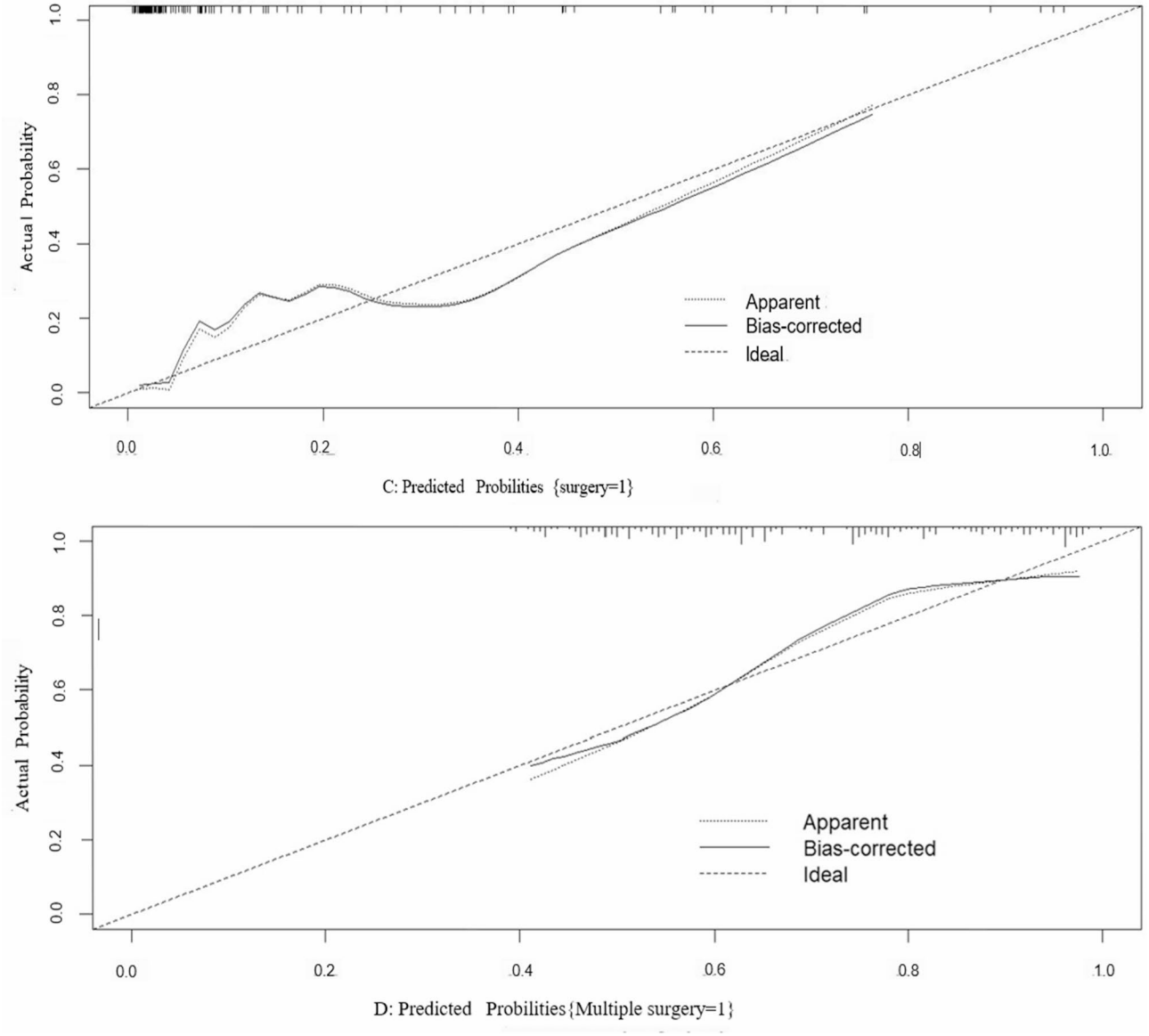

Fig. 6 Calibration curve for the established models drawn in R, version 4.3.0

in a cohort of 16 patients with co-infection with MRSA, 15 were found to have abscesses on MRI and underwent surgical debridement. Our investigation revealed comparable clinical observations. Of the 218 enrolled patients, 42 cases had MRSA-positive cultures, and 39 (93%) patients showed local abscess formation on MRI or B ultrasonography and underwent thorough debridement. The MRSA infection rate was significantly higher in multiple surgeries (55%), suggesting a direct link to disease complexity. Regarding surgical prediction, its positive predictive value reached 92.8%, accounting for a weight of 35 points in the nomogram, which needs to be paid attention to by clinicians.

Despite variations in research populations and time frames, CRP is highly valuable in predicting disease complexity. The severity of illness score developed by Copley et al. [25] could help predict the incidence of surgery and multiple procedures, and CRP levels measured over consecutive periods are remarkable parameters. Similar findings were reported in our research that CRP values were independent risk factors for multiple surgeries, with an increase of each 20 mg/L after the initial surgery adding 10 points to the risk weight. When a patient has a CRP level of 200 mg/L on admission and fails to decrease to 100 mg/L within 3 to 5 days post the original surgery, the probability of requiring multiple surgical debridement exceeds 70% according to our nomogram analysis. Roine [26] suggested that high CRP levels at 4, 6, and 7 days after admission were related to extensive radiographic changes, most probably predictive of

Table 4 Clinical characteristics, treatment modalities, and prognosis of patients in each group

Group	Clinical characteristics %, (n/N)	Microorganism %, (ON)	Empirical antibiotic selection % (n/N)	Surgical indications	Poor prognosis %, (n/N)
Conservative Treatment (N = 68)	Localized symptoms:95.6(65/68);Fever:19.	MRSA: 4.4(3/68)	Vancomycin:35.3(24/68);	~	5.8 (4/68)
	1(13/68);Femur29.4(20/68);Tib ia17.6(12/68); With arthritis: 42.6(29/68)	MSSA: 33.8(23/68)	Cefazolin:29.4(20/68);		
			Ceftriaxone:25.0(17/68);et al.		
Simple surgery (N = 129)	Localized symptoms:99.2(128/129);Fever32 .6(42/129);Femur:46.5(60/129);Tibia:31.0(40 /129);With arthritis: 36.4(47/129)	MRSA: 22.0(28/129)	Vancomycin:17.1(22/129); Ertapenem: 13.2(17/129); Ceftriaxone:12.4(16/129); Cefuroxime:11.6(15/129);et al.	Bone marrow cavity abscess or periosteal elevation > 2 mm; No response to medical treatment for 3 to 4 days	15.5 (20/129)
		MSSA: 55.0(71/129)			
Multiple surgery (N = 21)	Localized symptoms 100(21/21);Fever:57.1(12/21); Femur :33.3(7/21);Humerus:28.6(6/21);With arthritis:52.4(11/21)	MRSA: 55.0(11/21)	Vancomycin:47.6(10/21); Ceftriaxone:23.8(5/21); Cefuroxime:23.8(5/21); Cefazolin:19.0(4/21); et al.	Continuous irrigation and drainage were maintained for 7 days, but purulent material remained.	50 (11/21)
		MSSA: 33.3(7/21)			

*Poor prognosis was define as treatment failure, deformity, limb length discrepancy, growth arrest, osteonecrosis, chronic osteomyelitis, pathological fracture, chondrolysis, and recurrence

debridement and drainage. However, due to the retrospective design of this study, we could not set a specific time to monitor CRP following disease onset and surgery, potentially leading to variations in results. For instance, the disparity in CRP levels observed between patients evaluated at 2 days versus those assessed at 14 days after disease onset could have been influenced by antibiotic treatment timing. Upon admission, the acute inflammatory phase may have subsided, resulting in significantly lower CRP values than the initial level. This discrepancy may explain why it was not identified as an independent risk factor for predicting a single operation. Additionally, how long postoperative CRP can truly reflect the outcome of treatment is also a question that needs to be further explored, because the operation itself also could lead to an increase in CRP. According to Hunter et al. [27], failure of CRP levels to decrease by 50% on the fourth or fifth day after anti-inflammatory treatment may predict acute complications (including the need for ≥ 2 operations). We choose CRP levels from 3 to 5 days after surgery, primarily considering that CRP is a non-specific acute-phase reactant with a half-life of 24 to 48 h and normalizes within 7 days [26]. After 2 days of standard drug treatment, CRP did not decrease significantly, indicating that the high-intensity inflammatory reaction continues. At this time, it is necessary to be alert to whether there is local abscess formation at or near the infection site. Most academics agree that persistent fever or non-decreasing CRP levels despite appropriate antibiotic treatment for several days indicate unresolved infection processes and serve as risk factors for complicated AHO [27–28].

As mentioned in the methods, the decision on whether surgical intervention is needed for children with AHO is mainly based on their general condition and local symptoms (persistent fever and local abscess formation). The clinical significance of our study lies in incorporating more objective laboratory indicators for selecting children who need surgical intervention, including multiple surgeries, and providing valuable predictive probabilities for decision-making. These findings do not imply that all high-risk individuals should undergo surgical treatment. Rather, the focus is on raising the awareness of clinicians and ensuring a rational allocation of medical resources. Currently, relevant research in this area is relatively limited, Table 5. Tuasion's research [12] mentions that children followed first surgical debridement should be continuously monitored with repeated ESR and CRP every 48 h. If the child continues to have fever or if there is no improvement in CRP within 96 h post-surgery, they will be considered for additional surgery. Our predictive model aligns with this conclusion, suggesting that for patients whose CRP levels fail to decrease below 29.5 mg/L within 3–5 days after initial surgery, or who continue to present with localized symptoms and high fever, an ultrasound examination or MRI should be performed again to assess for subperiosteal abscesses. However, no studies have found a correlation between MRSA co-infection and absolute neutrophil count with surgical intervention. Although most literatures mention

Table 5 Summary of research on surgical treatment for AHO in children

Study/Model	Poulation (region, age, number)	Methodology	Key findings	Limitations
Copley 2014	America, 7.1y (0.1 ~ 16.5y), 56	Retrospective; Logistic regression analysis	The triage respiratory rate and the CRP value admission predict surgery (≥ 1);	Loss to follow-up in outpatient clinics;
			2 or more febrile days on antibiotics and the CRP values at admission, 48 hours and 96 hours predict multiple surgery (≥ 2).	Insufficient number of ICU admissions; Small sample size.
Tuason 2014	America, 6.8y, 57	Retrospective; Logistic regression analysis	Swollen extremity, admission CRP, respiratory rate predict surgery (≥ 1);	Lack of preestablished indications or criteria for surgery; Small sample size.
			Febrile days on antibiotics; admission CRP; CRP 48 h postsurgery; CRP 96 h postsurgery predict multiple surgery (≥ 2).	
Upasani 2022	America, 8.1y, 1003	Retrospective; Logistic regression analysis	Institution, ability to bear weight, multifocal infection, elevated CRP, elevated platelet count, and anatomic location predict surgery (≥ 1).	Differences in surgical techniques, institutional practices, and study populations.
Hartman 2022	America, 7.0y (3.0–13.Oy), 111	Retrospective; Correlation analysis	CRP demonstrated the highest correlation between AHO and subperiosteal abscess (r = 0.51; cutoff value = 10.3 mg/dL, with a sensitivity of 67.7% and a specificity of 77.6%)	Small sample size; Regression analysis was not conducted; Missing data.

that MRSA co-infection usually indicates a more severe disease, its virulence and epidemiology may exhibit regional differences. At least in China, clinical practitioners need to identify high-risk groups early (e.g., those with ANC > $6.9*10^9$/L combined with MRSA-positive status) to prioritize surgical interventions and potentially modify preoperative screening protocols to include ANC and MRSA testing for these groups. Our next step is to conduct multicenter external validation of the model to verify its generalization performance in independent and diverse populations.

Regarding the inclusion and exclusion criteria for this study, we provide the following clarifications: The immune system of newborns is not fully mature, exhibiting weaker immune responses. Their clinical manifestations and therapeutic profiles significantly differ from those of older children. Furthermore, in China, universal BCG vaccination has been mandatory since 1954 under the National Immunization Program, administered intradermally within 24 h of birth. To exclude the confounding influence of BCG-related osteomyelitis, we have selected patients aged between 1 month and 18 years. For the exclusion criteria, we primarily consider five aspects: Firstly, autoimmune responses in patients. To ensure consistency among study subjects, we require all patients to exhibit normal immune responses to bacterial infections. Secondly, rheumatic and immune diseases, which present with clinical symptoms similar to those of osteomyelitis and affect the child's inflammatory indicators (such as CRP and ESR), thus complicating the assessment of inflammatory recovery in osteomyelitis patients. Thirdly, the child's history of related surgeries at other hospitals, as a diagnosis of osteomyelitis and subsequent surgical treatment elsewhere can also impact the homogeneity of the patient population (due to variations in surgical techniques, antibacterial treatment protocols, and timing for reassessing inflammatory indicators). Fourthly, the mechanism of infection, excluding cases with a history of penetrating trauma. Fifthly, the completeness of the data.

In addition to the limitations of the retrospective study mentioned above, this study still has four shortcomings. Firstly, not all patients underwent PCT and D-dimer monitoring, which prevented their inclusion in the multivariate regression analysis, the related differences may still lead to decision variability. Secondly, this study is based on single-center retrospective data to construct a clinical prediction model, which requires multi-center prospective validation before it can be generalized. Thirdly, most bacterial culture results were not available before surgical intervention, with only 12 cases (30.8%) being diagnosed with MRSA infection prior to surgery, this limits the clinical utility value. When using this model, it is necessary to combine rapid molecular diagnostic techniques (such as PCR) or preoperative pus/blood culture results to clarify the MRSA status. Besides, in some regions, the MRSA infection rate is extremely low, which results in the single-operation model having very little reference. Fourth, As much as possible to minimize the dropout rate, concomitant suppurative arthritis as a criterion for exclusion is not recommended. Therefore, whether the presence of this group significantly impacts the predictive efficacy of the model remains uncertain. Finally, for patients who underwent multiple surgical interventions, we were unable to determine which initial debridements were ineffective.

Conclusions

The superior performance of these models in internal validation highlights their potential to complement clinical assessments for surgical decision-making. Future

prospective multicenter studies are imperative to confirm their generalizability across diverse populations and healthcare settings.

Abbreviations

AHO	Acute hematogenous osteomyelitis
MRSA	Methicillin-resistant Staphylococcus aureus
MSSA	Methicillin-sensitive Staphylococcus aureus
ROC	Receiver operating characteristic
AUC	Area under the curve

Supplementary Information

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Supplementary Material 1

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Author contributions

JL.G. and Q.W. designed this study. BJ.S, W.F, and DJ.Z. conducted surgery and follow-up visits. YW.W. provided the data and methods guidelines. JL.G. wrote this manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study received approval from the Ethics Committee of Beijing Children's Hospital Affiliated with Capital Medical University (approval number: [2024]-E-132-R). All patients provided written informed consent from a parent and/or legal guardian for study participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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