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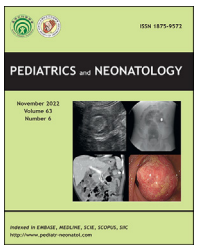

Original Article

A nomogram for predicting the development of serious bacterial infections in febrile term neonates: A single medical center experience in Southern Taiwan

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Background: Serious bacterial infections (SBIs) could lead to mortality or severe long-term sequelae in neonates and infants aged <3 months. Accordingly, the aim of this study was to develop a quantitative and accurate assessment tool for predicting the risk of SBIs in febrile neonates.
Methods: This retrospective study enrolled 131 febrile term neonates (aged <30 days) who were hospitalized at Kaohsiung Veterans General Hospital between January 2005 and December 2020. These neonates were classified into SBI and nonbacterial infection (NBI) groups on the basis of microbiological laboratory reports. The clinical characteristics and routine blood tests of both groups at the time of admission were analyzed. Stepwise logistic regression was applied to create and validate the nomogram for SBI prediction.
Results: Among the 131 febrile neonates, 38 and 93 developed SBIs and NBIs, respectively. At the time of admission, ill clinical appearance, serum myelocyte/metamyelocyte presence, C-reactive protein (CRP) > 2.5 mg/dL, and pyuria were associated with an increased risk of SBIs. Accordingly, these four factors were used to develop a nomogram for SBI prediction, which

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exhibited significantly high performance (area under curve = 0.848, $p < 0.001$) in predicting SBI risk.
Conclusion: We developed a nomogram combining clinical appearance, serum myelocyte/metamyelocyte presence, CRP, and pyuria for predicting SBI risk in febrile neonates. This tool can assist clinicians in making early diagnoses and delivering the appropriate treatment.

1. Introduction

Serious bacterial infections (SBIs) occur commonly in neonates and infants aged <3 months. The incidence of SBIs is 5%—10% and is relatively high in the neonatal population.[1–3] Although urinary tract infections (UTIs) are the most common SBIs observed in infants,[4,5] bacteremia and bacterial meningitis are considered the most invasive bacterial infections (IBIs) among all SBIs.[4,6] An early identification of SBIs might result in favorable treatment outcomes. However, if left untreated, the infections can develop into severe long-term sequelae.[3] The neonatal population is considered a high-risk group owing to its relatively poorly developed immune system. Globally, more than 1.4 million neonatal deaths caused by invasive infections occur per year.[7] Furthermore, few considerable clinical symptoms and signs could indicate SBIs in young infants, especially neonates.[8] The characterization and differentiation of SBIs from other self-limiting diseases are extremely difficult tasks. Therefore, some studies suggested the execution of a full sepsis workup for febrile neonates.[9,10] Although several criteria and protocols have been established for risk evaluation over the past decades, no definite consensus exists regarding accurate disease risk characterization. Moreover, existing evaluation tools are less precise and practical in neonates.[1,11] Therefore, such patients are carefully treated with empirical antibiotics due to the lack of specific predictors for SBIs.[12] Accordingly, the aim of this study was to develop an effective scoring system combining basic clinical and laboratory parameters for rapidly predicting SBIs during the neonatal period.

2. Materials and methods

By using the Kaohsiung Veterans General Hospital (KSVGH) clinical database, we extracted the data of patients who were admitted to the KSVGH between January 2005 and December 2020 and met the required inclusion criteria for primary diagnosis and age. The KSVGH clinical database protects the privacy of individuals and provides data to only researchers who have obtained ethical approval. Therefore, this study was approved by the KSVGH Institutional Review Board (KSVGH21-CT5-27).

2.1. Data collection

We retrospectively screened and extracted the data of admitted term neonates (aged <30 days) according to *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnostic codes (*ICD-9*/*ICD-10*: 780.6/R50.9), as displayed in Fig. 1. We excluded patients who had used antibiotics within 48 h prior to their hospital visit, a recorded peak temperature of <38 °C, or congenital anomalies.[1] The included patients were then divided into two groups on the basis of microbiology laboratory reports: SBI and nonbacterial infection (NBI) groups. Data on the patients' detailed personal medical history, including gestational profile, age, sex, fever height, clinical appearance, and laboratory data at the time of admission, were collected. Fever height can be defined as the maximum temperature recorded within 48 h prior to a hospital visit.[13] Clinical appearance was assessed by a trained pediatrician, and we used a pediatric medical chart to extract relevant data. Patients with abnormalities in one or more components of the Pediatric Assessment Triangle were categorized as clinically ill-appearing neonates.[14] Laboratory blood tests included complete blood count (CBC), differential leukocyte count, serum glutamate pyruvate transaminase, serum sodium, and CRP levels. All infants were followed up till their discharge or death.

2.2. SBI diagnosis

The SBIs considered in this study included bacteremia, bacterial meningitis, pneumonia, UTIs, bacterial enterocolitis, or soft tissue or bone infections.[12] Bacteremia and bacterial meningitis were defined as the presence of any single bacterial pathogen in the blood and cerebrospinal fluid, respectively.[15] Pneumonia was defined as the presence of consolidation on chest radiography associated with a culture of pathogenic organisms from sputum or pleural fluid.[16] UTIs were diagnosed as a pyuria (urine white blood cell count [WBC]) level of ≥5 per high-power field (HPF) in urinalysis along with a positive urine culture (defined as the presence of ≥100,000 colony-forming units [CFU]/mL of a single organism from a midstream clean-catch collection or ≥10,000 CFU/mL of the organism from catheterization).[17] Bacterial enterocolitis was defined through the isolation of bacteria in stool,[4] and soft tissue or bone infections were defined as the presence of necrotizing fasciitis, cellulitis, osteomyelitis, or septic arthritis.

2.3. Statistical analysis

Statistical and nomogram analyses were performed using SAS software (version 9.4; SAS System for Windows) and

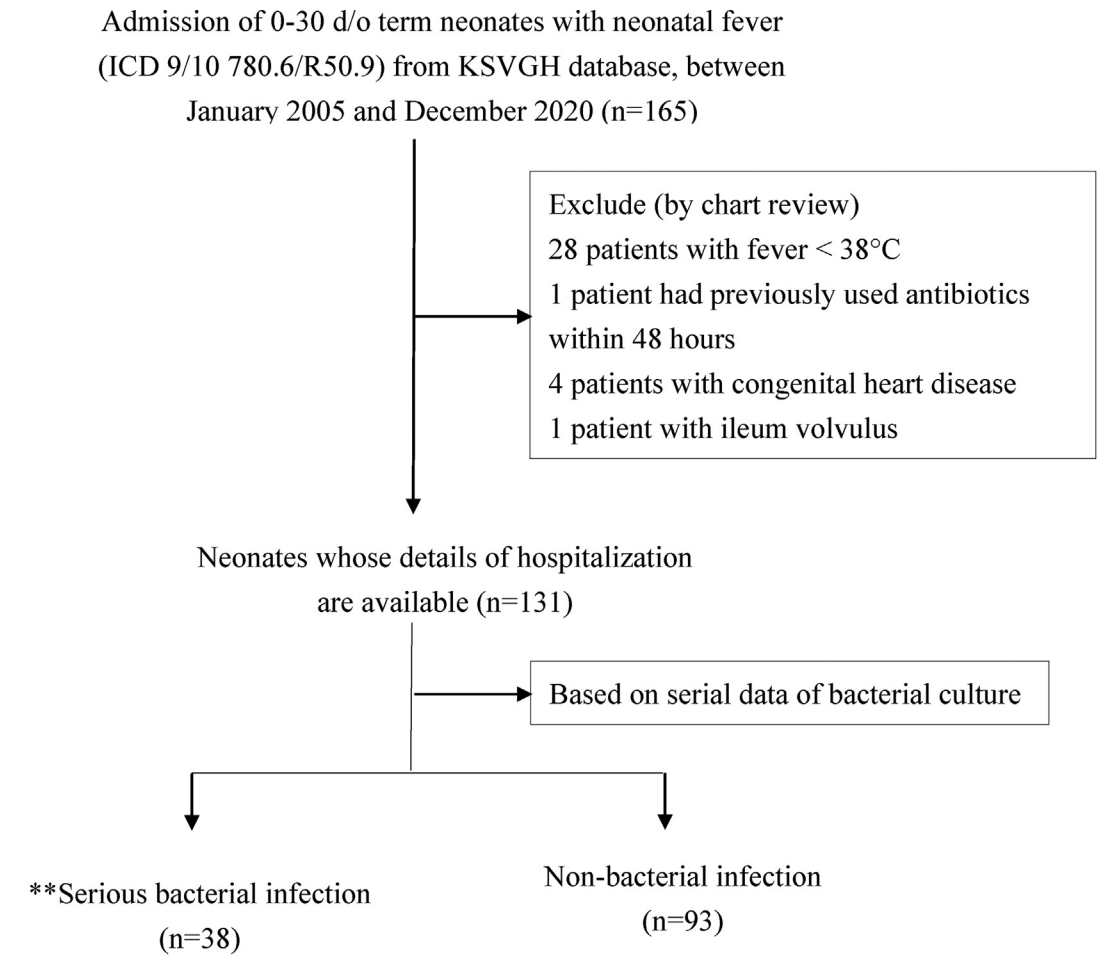

Figure 1 Flow chart of the patient selection process.

SPSS software (version 20; SPSS Inc, Chicago, IL, USA). An independent t test was used to compare continuous data, which are presented herein as mean ± standard deviation. Categorical variables were analyzed using a chi-square test and are presented herein as numbers (percentages). A p value of <0.05 was considered statistically significant. A univariate analysis was used to analyze all parameters for both study groups. Variables that were significant ($p < 0.20$) in the univariate analysis were selected as candidates for the multivariate analysis. Among potential predictive factors, influential factors were evaluated using a stepwise regression analysis. Additionally, the maximum area under the curve (AUC) value was selected to determine the optimal cutoff for each parameter in order to identify the predictive power of the factors. On the basis of the findings of the multivariate logistic regression analysis, we selected variables to establish a nomogram. A nomogram provides graphical depictions of variables and allows the direct calculation of output probabilities. The Hosmer–Lemeshow goodness-of-fit test was used to assess the overall fit of the data for performance validation.[18,19]

3. Results

We enrolled a total of 131 patients in this study, of whom 38 were assigned to the SBI group and the remaining were assigned to the NBI group. The SBI group comprised 7 cases of bacterial meningitis with bacteremia, 6 cases of bacteremia (2 of which involved urosepsis), 2 isolated cases of bacteremia meningitis, 18 cases of UTIs, 1 case of omphalitis, 1 case of necrotizing fasciitis, 2 cases of cellulitis, and 1 case of enterocolitis. The SBI and NBI groups were compared in terms of demographics, clinical characteristics, and laboratory findings, as presented in Table 1. The groups did not differ significantly in terms of body weight or delivery profiles. We noted a significant difference in clinical appearance ($p < 0.001$) and heart rate ($p = 0.006$) between the two groups. Compared with the NBI group, the SBI group had higher CRP values and band cell percentages, in addition to having a higher frequency of metamyelocyte/myelocyte presence, pyuria, and urine nitrite.

Our univariate logistic regression analysis revealed that ill clinical appearance ($p < 0.001$), heart rate > 160/min

Table 1 Baseline characteristics of febrile neonates at the time of admission during 2005–2020, $N = 131$.

Variable	Total	SBI	NBI	p-value
	n = 131	n = 38 (29%)	n = 93 (71%)	
Admission age(days) (Mean ± SD)	13.8 ± 8.7	14.6 ± 9.4	13.5 ± 8.4	0.543
Bodyweight (gm), (Mean ± SD)	3412.4 ± 659.7	3503.7 ± 554.1	3375 ± 697.5	0.313
Birth gestational age(weeks) (Mean ± SD)	38.7 ± 1.0	38.7 ± 0.8	38.7 ± 1.1	0.825
Vaginal delivery	86 (66%)	24 (63%)	62 (67%)	0.701
Male	80 (61%)	25 (66%)	55 (59%)	0.479
Maternal GBS	23 (18%)	7 (18%)	16 (17%)	0.868
Clinically ill-appearing	54 (41%)	26 (68%)	28 (30%)	<0.001
Fever before visit ≥ 2 days	6 (5%)	2 (5%)	4 (4%)	1.000
Height of fever > 39°C	29 (22%)	12 (32%)	17 (18%)	0.096
Heart rate(/min), (Mean ± SD)	157.6 ± 17.8	164.2 ± 17.9	154.9 ± 17.0	0.006
Examined Lab data				
Serum				
WBC (1000/uL)	11.3 ± 5.5	11.1 ± 6.6	11.3 ± 5.0	0.850
Neutrophil (%)	52.3 ± 14.4	50.8 ± 14.8	53.0 ± 14.2	0.430
Lymphocyte (%)	33.8 ± 14.4	36.9 ± 16.4	32.6 ± 13.4	0.124
Band (%)	2.3 ± 4.9	4.6 ± 6.7	1.3 ± 3.6	0.001
Metamyelocyte/Myelocyte	24 (18%)	15 (40%)	9 (10%)	<0.001
Hgb(g/dL)	13.6 ± 2.4	13.0 ± 2.2	13.8 ± 2.4	0.092
PLT (1000/uL)	331.0 ± 133.6	305.7 ± 124.8	341.4 ± 136.2	0.166
CRP (mg/dL)	2.4 ± 3.6	5.4 ± 5.2	1.1 ± 1.4	<0.001
GPT (g/dL)	21.1 ± 13.8	16.6 ± 7.5	22.9 ± 15.3	0.016
Na (mmol/L)	138.7 ± 3.9	137.8 ± 3.5	139.0 ± 4.0	0.111
Urine				
Pyuria (urine WBC > 5/HP)	12 (9%)	9 (24%)	3 (3%)	0.001
Positive urine nitrite	4 (3%)	4 (11%)	0 (0%)	0.006
Received lumbar puncture	66 (50%)	21 (55%)	45 (48%)	0.475
LOS, d (Mean ± SD)	8.7 ± 9.3	15.8 ± 14.2	5.9 ± 3.7	<0.001

Abbreviations: CRP, C-Reactive protein; GBS, Group B streptococcus; LOS, length of stay; Na, sodium; NBI, nonbacterial infection; PLT, platelet; SBI, serious bacterial infection; WBC, the white blood cell count.

($p = 0.009$), band cell count > 2% ($p = 0.003$), metamyelocyte/myelocyte presence ($p < 0.001$), CRP > 2.5 mg/dL ($p < 0.001$), and pyuria ($p = 0.001$) were independent risk factors for SBIs (Table 2).

Our stepwise logistic regression analysis revealed that the following factors with clear cutoff values reached statistical significance: ill clinical appearance (adjusted odds ratio [aOR] = 3.67, 95% confidence interval [95% CI] = 1.30–10.32; $p = 0.014$), metamyelocyte/myelocyte presence (aOR = 5.51, 95% CI = 1.70–17.81; $p = 0.004$), CRP > 2.5 mg/dL (aOR = 5.13, 95% CI = 1.70–15.52; $p = 0.004$), and pyuria (aOR = 11.24, 95% CI = 2.11–60.00; $p < 0.001$). Furthermore, on the basis of our stepwise logistic regression analysis results, we developed a predictive nomogram for SBIs; the AUC value for the nomogram was 0.848 (0.77–0.92; Table 3). Each of the four aforementioned factors was assigned a score of 0 or 1, and the cumulative score was considered to represent the relative probability of SBIs (Fig. 2). We applied the Hosmer–Lemeshow goodness-of-fit test to examine the performance of the predictive model; the test results showed an $\chi 2$ value of 2.718 ($p = 0.437$).

4. Discussion

This study established a four-factor nomogram for precisely predicting SBIs in febrile neonates. Early diagnosis and appropriate treatment are essential for achieving favorable outcomes in febrile neonates. Huang et al. and Weiss et al. have conducted retrospective studies and reported that the early use of antibiotics led to shortened hospital stays and decreased mortality in pediatric patients with severe sepsis, respectively.[20,21] Several studies have focused on the development of accurate screening tools for identifying the risk of SBIs in low-risk febrile infants.[22–24] Owing to differences in epidemiological and pathogenic features between infants, the study populations were mostly limited to infants aged >1 month.[22,23] Moreover, clinical manifestations and adaptive immune system responses in term infants are quite distinct from those in preterm infants.[25]

The clinical manifestations of neonatal sepsis are nonspecific and vague.[26] Therefore, aggressive diagnostic and therapeutic modalities have been suggested for neonates with fever,[27] even in well-appearing patients in our clinical practice. The Pediatric Assessment Triangle is

Table 2 Univariate logistic regression analysis for SBIs with febrile neonates, $N = 131$.

Variables	Beta	OR (95% CI)	p value
Admission age(days)	0.014	1.01 (0.97–1.06)	0.540
Birth gestational age (weeks)	0.042	1.04 (0.72–1.51)	0.823
Vaginal delivery	−0.154	0.86 (0.39–1.88)	0.701
Male	0.284	1.33 (0.61–2.92)	0.479
Maternal GBS	0.083	1.09 (0.41–2.90)	0.868
Bodyweight (g)	0.000	1.00 (1.00–1.00)	1.000
Clinically ill-appearing	1.615	5.03 (2.23–11.36)	<0.001
Fever before visit ≥ 2 days	0.212	1.24 (0.22–7.05)	0.811
Fever height > 39′C	0.773	2.17 (0.96–4.91)	0.064
Heart rate>160 (/min)	1.044	2.84 (1.30–6.21)	0.009
Examined Lab data			
Serum			
WBC > 11 (1000/uL)	−0.297	0.74 (0.35–1.59)	0.445
Neutrophil (%) > 50	−0.622	0.54 (0.25–1.16)	0.113
Lymphocyte (%) < 32	−0.405	0.68 (0.31–1.42)	0.295
Band(%) > 2	1.303	3.68 (1.55–8.73)	0.003
Metamyelocyte/Myelocyte > 0	1.801	6.09 (2.36–15.68)	<0.001
Hgb < 13 (g/dL)	0.581	1.79 (0.84–3.83)	0.135
PLT < 330 (1000/uL)	0.127	1.14 (0.53–2.42)	0.742
CRP > 2.5 (mg/dL)	2.445	11.53 (4.51–29.48)	<0.001
GPT > 20 (g/dL)	−0.573	0.56 (0.25–1.27)	0.168
Na < 140 (mmol/L)	0.615	1.85 (0.80–4.26)	0.148
Urine			
Pyuria (urine WBC > 5/HP)	2.231	9.31 (2.36–36.71)	0.001

Abbreviations: CI, confidence interval; CRP, C-Reactive protein; GBS, Group B streptococcus; Na, sodium; NBI, non-bacterial infection; OR, odds ratio; PLT, platelet; SBI, serious bacterial infection; WBC, the white blood cell count.

frequently used for evaluating clinical appearance. Studies have demonstrated that ill-appearing patients with fever were at a higher risk of bacterial infections, particularly infants aged <3 months[28] and children aged <5 years.[16] Accordingly, developing a tool for SBI identification is imperative. On the basis of the classic Rochester, Philadelphia, Boston criteria and a step-by-step approach,[22–24,29] we considered clinical appearance as the first factor for risk stratification regarding bacterial infections in our tool. Additionally, increased microbial resistance, higher therapeutic costs, and adverse effects of antibiotics due to irrational overuse of prescriptions should be considered in tool development.[30] In our study, clinical appearance was assessed by senior and trained pediatricians, and we categorized terms such as "lethargic," "toxic," or "sick-appearing" as ill clinical appearance. Nevertheless, the process of identifying a patient's clinical appearance remains subjective. The categorization should be interpreted with caution.

A review article on neonatal sepsis[31] included several common biomarkers, with CRP and procalcitonin (PCT) being the most common. However, to date, no single ideal marker for neonatal sepsis is available. CRP is an extensively used laboratory biomarker for evaluating the presence of an inflammatory process and tissue damage. Several studies have reported a correlation between CRP levels and bacterial infections in febrile infants and that the AUC for serum CRP was approximately 0.74–0.8 ($p < 0.001$, p 0.07), with the optimal cutoff values being 25 and 20 mg/L, respectively.[1,32] Another earlier prospective cohort study conducted on febrile children aged between 7 days and 36 months revealed that the use of serum CRP values with a cutoff of 40 mg/L for predicting SBIs achieved

Table 3 Stepwise logistic regression analysis for SBIs with febrile neonates, $N = 131$.

Variables	Beta	aOR (95% CI)	p value
Clinical ill appearing	1.299	3.67 (1.30–10.32)	0.014
Examined Lab data			
Metamyelocyte/Myelocyte > 0	1.636	5.51 (1.70–17.81)	0.004
CRP > 2.5 mg/dL	1.706	5.13 (1.70–15.52)	0.004
Pyuria (urine WBC > 5/HP)	2.420	11.24 (2.11–60.00)	0.020
c-statistic		0.848 (0.77–0.92)	<0.001
Hosmer–Lemeshow test		$\chi^2 = 2.718$	0.437

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; CRP, C-Reactive protein; SBI, serious bacterial infection.

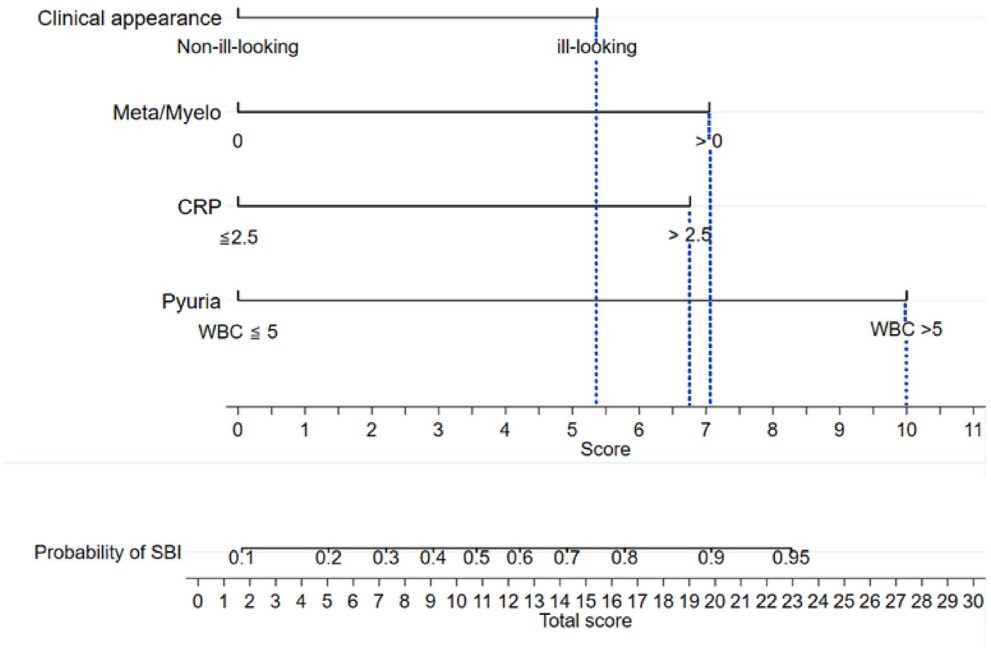

Figure 2 Nomogram plot for predicting SBIs. For an individual patient, each variable corresponds to a point in the fifth row (score). The total score was derived by summing all points, as indicated in the sixth row (bottom row). Drawing a vertical line from a total point to the fifth row can indicate the corresponding probability of SBIs. For example, for an ill-appearing patient (5.4 points) with metamyelocyte/myelocyte presence (7 points) and CRP $>$ 2.5 mg/dL (6.7 points), the total score can be determined to be 19.1. The probability of SBIs can be determined to be approximately 90%, according to the total score axis.
Abbreviations: CRP, C-reactive protein; Meta/Myelo, metamyelocytes/myelocytes; SBI, serious bacterial infection; WBC, the white blood cell count.

moderate accuracy (OR = 7.8; sensitivity = 81%; specificity = 76%).[33] Because serum CRP peaks within 10—12 h, it might be unreliable for identifying patients who require immediate medical intervention. For such patients, serial measurements were suggested to be a relevant strategy; such measurements could also provide valid parameters for predicting therapeutic response.[31] In our study, we used CRP as one of the predictive factors and set its cutoff to 25 mg/dL, which is consistent with those in the aforementioned studies. However, the predictive capability of this factor increased significantly (AUC = 0.848) after we combined it with the three other factors.

The precise roles of white blood cell counts (WBC), absolute neutrophil counts (ANC), and immature to total leukocyte ratio (I/T ratio) in the diagnosis of bacterial infections vary and are limited. Cruz et al. reported that complete blood cell count (CBC) exhibited low performance in predicting SBI risk in febrile infants (aged 0—60 days); they used the following factors for prediction in their study: WBC $\geq$ 11600/uL (AUC = 0.57), ANC $\geq$ 4100/uL (AUC = 0.7), and platelet count $\leq 362 \times 10^3$/uL (AUC = 0.61).[15] Moreover, De et al. found similar results in predicting SBI risk in febrile children (AUC = 0.65 for WBC; AUC = 0.64 for ANC).[34] Although an I/T ratio of $>$0.2 was reported to show high specificity for neonatal sepsis, it was easily influenced by adverse perinatal conditions.[31] Similarly, we observed that CBC lacked predictive accuracy in our study. Few studies have considered that myelocyte/metamyelocyte presence in peripheral blood could be a predictor of SBIs; myelocyte/metamyelocyte presence is associated with SBIs because it suggests that circulating blood does not have sufficient segmented and band neutrophils for controlling such infections.[35] Considering its specificity and statistical significance, we selected myelocyte/metamyelocyte presence as one of the predictive factors in our nomogram.

UTIs are the most frequent SBIs in febrile infants. Our study revealed that the incidence of UTIs was 13.7% (18/131), which is consistent with the incidence reported by a previous study,[1] in which the most common isolated pathogen was *Escherichia coli* (11/18, 61%). Moreover, a study indicated that young infants had a relatively high risk of bacteremia secondary to UTIs.[28] A multicenter prospective study involving 747 infants with UTIs (mean age = 46.6 days) revealed that the leukocyte esterase test exhibited remarkable accuracy in diagnosing UTIs in young infants (sensitivity = 82.1%; specificity = 92.4%).[36] These findings thus demonstrate that leukocyturia exhibits sufficient distinction for diagnosing UTIs. However, its diagnostic accuracy for other SBIs remains ambiguous.

Our study has some limitations. First, we collected data from and performed this study in a single medical center. Therefore, some of the laboratory data might have been lost in distant cases, and the results may not be generalizable to other settings. Second, a PCT assay is not extensively used in our study group, considering the difficulty of blood sampling and larger volume of blood samples necessary for the assay. Nevertheless, the PCT assay is currently used as a more discriminative assay for predicting SBIs and IBIs.[1] Therefore,

the lack of a PCT assay renders further validation of our tool with other risk stratification tools impractical.

5. Conclusions

Our retrospective study revealed that ill clinical appearance, myelocyte/metamyelocyte presence in peripheral blood, CRP $\geq$ 2.5 mg/dL, and pyuria (urine WBC $>$ 5/HPF) were associated with SBIs in febrile neonates. Therefore, we combined these factors to develop a four-factor nomogram with high predictive performance (AUC = 0.848, $p < 0.001$). This tool can assist clinicians in decision-making and choosing appropriate therapeutic modalities.

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Declaration of competing interest

The authors declare that they have no potential conflicts of interest.

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