

RESEARCH ARTICLE

A sequential guide to identify neonates with low bacterial meningitis risk: a multicenter study

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Introduction

Bacterial meningitis (BM) occurs more commonly in neonates than in any other age group¹ and is associated with substantial morbidity and mortality.² The definitive diagnosis of meningitis relies on the investigation of

Abstract

Objective: To derive and validate a predictive algorithm integrating clinical and laboratory parameters to stratify a full-term neonate's risk level of having bacterial meningitis (BM). **Methods:** A multicentered dataset was categorized into derivation (689 full-term neonates aged ≤ 28 days with a lumbar puncture [LP]) and external validation (383 neonates) datasets. A sequential algorithm with risk stratification for neonatal BM was constructed. **Results:** In the derivation dataset, 102 neonates had BM (14.8%). Using stepwise regression analysis, fever, infection source absence, neurological manifestation, C-reactive protein (CRP), and procalcitonin were selected as optimal predictive sets for neonatal BM and introduced to a sequential algorithm. Based on the algorithm, 96.1% of BM cases (98 of 102) were identified, and 50.7% of the neonates (349 of 689) were classified as low risk. The algorithm's sensitivity and negative predictive value (NPV) in identifying neonates at low risk of BM were 96.2% (95% CI 91.7%–98.9%) and 98.9% (95% CI 97.6%–99.6%), respectively. In the validation dataset, sensitivity and NPV were 95.9% (95% CI 91.0%–100%) and 98.8% (95% CI 97.7%–100%). **Interpretation:** The sequential algorithm can risk stratify neonates for BM with excellent predictive performance and prove helpful to clinicians in LP-related decision-making.

cerebrospinal fluid (CSF), samples of which are collected via lumbar puncture (LP)—an invasive procedure associated with clinical risk. Neonates with BM are often underinvestigated, deferred in those with cardiorespiratory instability, or due to limited resources, diagnostic technology, and access to health care.³ Additionally, up to

35% of LP procedures in children are unsuccessful or traumatic in the first attempt.⁴

At present, the indication of LP in neonates is still unclear. Most scholars think that the major indication is a suspicion of sepsis.⁵ However, up to 38% of infants with confirmed meningitis have negative blood culture.⁶ LP procedure is suggested to perform prior to the antibiotic treatment whenever possible.³ Therefore, even if positive blood culture is available in 2–3 days, the guiding role to who needs LP is restricted as antibiotics will have been started. Fever is a strong risk factor for sepsis in older infants, but its strength is diminished in at least half of neonatal BM cases without fever.⁷ Some clinical manifestations of bacterial infection, such as apnea, vomiting, poor feeding, and hyperbilirubinemia, are non-specific and may present in non-infectious conditions.⁸ Thus, LP should be performed at the clinicians' experience and discretion.

As predictors of some auxiliary tests (complete blood count [CBC], C-reactive protein [CRP], and procalcitonin [PCT] testing) individually have limited value owing to low sensitivity, many investigators are devoted to developing predictive models for the identification of young infants at low risk of invasive bacterial infection (IBI), including meningitis, using rapidly available biomarkers. However, most existing models were derived from infants with fever and/or across a wide age range, which may not have applicability in the neonatal population, especially afebrile newborns.^{9–11} There is currently no widespread consensus on the LP indication for neonates.

We aimed to develop a new sequential algorithm for the risk stratification of neonatal BM and help clinicians in LP-related decision-making.¹² For easy use, a handy online calculator based on the algorithm was further explored.

Methods

Design and setting

This is an ambispective cohort study comprised of the derivation and external validation datasets. Neonates with gestational age ≥ 37 weeks and ≤ 28 days of age were enrolled. All subjects had a diagnosis of sepsis based on the bacterial investigation or non-bacteremic clinical sepsis (negative blood culture) and in whom the LP procedure was administered. Patients admitted from January 2010 to December 2017 in the neonatal department of four tertiary university children's hospitals constituted the derivation set. To test the predictive performance of the algorithm, we further enrolled a prospective cohort in eight tertiary hospitals from January 2018 to August 2019, which comprised the external validation set (Table S1).

All eligible hospitals should meet the following criteria: adequate research abilities and facilities to conduct the study, including neonatal wards, laboratory facilities, ability to identify and manage neonatal BM, and investigators being willing to devote time to the research. This study received institutional review board approval from each hospital in 2017, with permission for data sharing (Approval number: XHEC-C-2017-084). Written informed consent of LP procedure was acquired from all guardians in both derivation and validation sets.

The exclusion criteria were: (1) central nervous system (CNS) malformation or intracranial hemorrhage; (2) a history of invasive instrumentation of the CNS, such as placement of a ventriculoperitoneal shunt or myelomeningocele repair; (3) complex chronic conditions, including cardiac malformations, cancer, and cystic fibrosis;¹³ and (4) Apgar score at 5 min ≤ 3 . The external validation set followed a similar methodology.

Clinical management of patients

Data on CBC, CRP, PCT, and bacteriological detection in the blood and CSF (culture and/or metagenomic next-generation sequencing [mNGS]) were examined for each patient. The indication for LP was as follows: (1) without contraindications for LP;¹⁴ and (2) clinical manifestations suggesting bacterial infection, including hyperthermia or hypothermia, poor feeding, lethargy or restlessness, recurrent vomiting, apnea, cyanosis, jaundice aggravation, high-pitched cry, bulging fontanel, seizure, etc.^{3,15} Patients were hospitalized and received antibiotic treatment based on the protocol of each center. Detailed data were collected and recorded in standardized electronic forms and integrated by an experienced data administrator.

Definitions

Fever: peak temperature $>38^{\circ}\text{C}$ as measured at home, in the pediatric emergency department or outpatient clinic, or on admission.¹⁶

Neurological manifestation: presence of one or more signs, including seizure, abnormal muscle tone, irritability, and bulging anterior fontanelle.¹⁷

Ill-appearance: presence of one or more of the following symptoms: unconsciousness, lethargy, weak or highly pitched cry, hypothermia, poor feeding, apnea, recurrent cyanosis, jaundice aggravation, etc.^{3,15,17,18}

Definite sources of bacterial infection except BM: several common causes of bacterial infection in neonates, collected from diagnoses in the electronic medical histories, including impetigo, urinary tract infection, omphalitis, respiratory infection, and purulent arthritis.

Primary outcome

Neonatal BM was defined if met any criterion of the following: (1) detection of qualifying pathogenic bacteria in the CSF culture;¹⁹ or (2) identification of a microbe (species level) with a coverage rate 10-fold greater than that of any other microbes on CSF mNGS;²⁰ or (3) detection of pathogenic bacteria in the blood and CSF pleocytosis (WBC $>20 \times 10^6/L$);²¹ or (4) CSF pleocytosis (WBC $>20 \times 10^6/L$) with a predominance of polymorphonucleocytes (PMNs) ($>50\%$).²² *Escherichia coli*, Group B Streptococcus, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Enterobacter cloacae*, *Enterococcus* species, hemolytic streptococcus, *Listeria monocytogenes*, and *Enterobacter sakazakii* were considered as qualifying pathogens.^{23,24} Coagulase-negative staphylococci, *Lactobacillus*, *Bacillus non-cereus/non-anthraxis*, viridans group streptococci, diphtheroids, and *Micrococcus* were categorized as contaminants.^{23,24}

Statistical analysis

Descriptive results were analyzed using the Student's *t*-test, Wilcoxon rank-sum test, or Chi-square test, accordingly. A sequential algorithm was established based on the composite model constructed in the preceding step, in which the variables were selected by stepwise regression analysis and were the most powerful subset for meningitis prediction. The predictors were then entered into the algorithm in a sequential order based on their contributions, that is, standard regression coefficients, to discriminate BM in the composite model mentioned above. The two sets of CRP and PCT cut-off points, "25 mg/L and 2.5 ng/mL" and "50 mg/L or 30 ng/mL", were derived from those with the maximum Youden index in receiver operating characteristics (ROC) curves and 90th percentiles in the study, respectively, as well as the ease of use. The predictive performance was then tested in the external validation set. Statistical analysis was conducted using SAS statistical software version 9.4 (SAS Institute, Inc., Cary, North Carolina). In order to provide clinicians with a convenient tool in practice, a handy online calculator was instantiated to estimate the risk of BM in neonatal patients based on the sequential algorithm.

The estimated sample size was calculated by Epi-info software version 7 (Centers for Disease Control and Prevention, Atlanta, Georgia) and SAS Power and Sample Size 13.2 (SAS Institute, Inc., Cary, NC, USA) assuming the 95% CI ($\alpha = 0.05$) and 90% power ($\beta = 0.9$). Based on previous studies and our pilot study, the estimated sample size was at least 489 for the derivation set. Assuming half of the derivation set, the sample was at least 250 for the external validation set.^{25,26}

Results

In the derivation and validation sets, we excluded the 382 and 301 patients with antibiotic pretreatment before admission and before delivery (specifically for neonates of age ≤ 72 h). Patients with missing CSF white blood cell (WBC) or PMN values, or with traumatic LP within 72 h after admission were excluded ($n = 164$ and $n = 425$). Patients without information on either CRP or PCT within 24 h after admission were also excluded ($n = 301$ and $n = 121$). Totally, 689 and 383 patients were eligible for assignment to the derivation and validation sets (Fig. 1). The prevalence of BM in neonates who accepted LP procedure was 14.8% (102 of 689) and 12.5% (48 of 383), respectively.

Demographic, laboratory, and clinical characteristics

In the derivation set, no significant difference between groups with and without meningitis was found in the delivery method, birth weight, gestational age, sex, general appearance, and CBC results (Table 1). Patients who had fever, abnormal neurological manifestations, absence of infection source, positive blood culture, and higher levels of CRP and PCT were more likely to have neonatal BM. Similar results were found in the validation set (Table S2).

Development of the sequential algorithm for the prediction of neonatal BM

Using stepwise regression analysis, five predictors were selected, including fever, absence of infection source, neurological manifestation, CRP, and PCT. As shown in Table 2, neonates with fever, absence of infection source, abnormal neurological manifestation, and higher levels of CRP (>25 mg/L) and PCT (>2.5 ng/mL) had 6.3-fold (95% CI: 3.3, 12.0), 3.4-fold (95% CI: 2.0, 5.7), 7.1-fold (95% CI: 3.8, 13.1), 2.1-fold (95% CI: 1.2, 3.5), and 2.4-fold (95% CI: 1.4, 4.1) increased risks of having BM, respectively. Fever and absence of other evident sources of infection were combined as a composite index, represented a group of neonates with "fever without source" (FWS). Compared to neonates without FWS, those with FWS had the highest risk [7.2-fold (95% CI: 4.3, 11.9)] of having BM.

Figure 2 shows the prevalence of neonatal BM in the subgroups with different risk factor(s) on the application of the sequential approach. In the first step of the algorithm, FWS was employed, as having a high standard regression coefficient. The prevalence of BM was 34.6% (53 of 153) in neonates with FWS, 3.8 times higher than

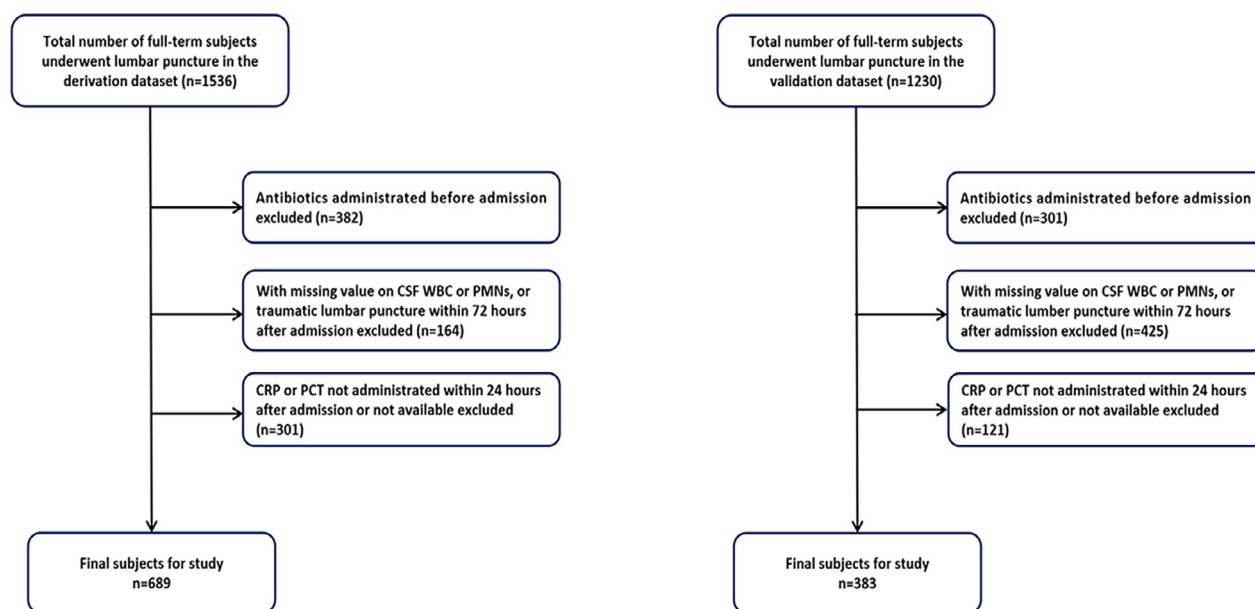


Figure 1. Study subjects' flow chart.

Table 1. Clinical and laboratory characteristics in the derivation group ($n = 689$).

Characteristics	Without meningitis, ($n = 587$)	With meningitis, ($n = 102$)	$t/\chi^2/z$	p value*
Clinical variables				
Birth weight, mean (SD), g	3389 (453)	3396 (441)	-0.2	0.878 ^a
Gestational age, mean (SD), wk	39.0 (1.1)	39.0 (1.1)	0.39	0.699 ^a
Age on admission, mean (SD), d	11.7 (8.9)	12.7 (8.0)	-1.1	0.277 ^a
Sex, No. (%)			0.3	0.578 ^b
Male	351 (59.8)	58 (56.9)		
Female	236 (40.2)	44 (43.1)		
Delivery method, No. (%)			0.1	0.931 ^b
Vaginal delivery	343 (59.1)	59 (59.6)		
Caesarean section	237 (40.9)	40 (4.4)		
Fever, No. (%) [#]	292 (49.7)	75 (73.5)	19.7	<0.001 ^b
Neurological manifestations, No. (%) [†]	76 (13.0)	37 (36.3)	34.5	<0.001 ^b
Ill-appearances, No. (%) [‡]	305 (52.0)	54 (52.9)	0.03	0.855 ^b
Absence of infection source, No. (%) [§]	235 (40.0)	69 (67.6)	26.9	<0.001 ^b
Positive blood culture, No. (%)	50 (8.5)	45 (44.1)	92.6	<0.001 ^b
Laboratory variables				
WBC, median (IQR), cells per μ L	12,700 (8700–18,400)	11,400 (7300–17,400)	-1.8	0.068 ^c
CRP, median (IQR), mg/L	8 (5–20)	11 (5–52)	3.1	0.002 ^c
NPC, median (IQR), %	58.0 (43.2–71.1)	59.7 (43.9–72.0)	0.7	0.486 ^c
ANC, median (IQR), cells per μ L	6800 (3900–11,100)	5700 (3300–11,400)	-0.9	0.361 ^c
PCT, median (IQR), ng/mL	0.4 (0.2–1.7)	1.0 (0.2–11.8)	2.9	0.004 ^c

IQR, interquartile range; NPC, neutrophil percentage; ANC, absolute neutrophil count.

^aStudent's t -test.

^bChi-square test.

^cWilcoxon rank-sum test.

*Characteristics with p values <0.05 were considered statistically significant.

[#]Peak temperature >38°C as measured at home, in the pediatric emergency department or outpatient clinic, or on admission.

[†]Seizure, abnormal muscle tone, irritability, bulging anterior fontanelle, etc.

[‡]Hypothermia, poor drink, jaundice, recurrent cyanosis, vomit, apnea, etc.

[§]Neonates did not have any of impetigo, urinary infection, omphalitis, respiratory infection, purulent arthritis, etc.

Table 2. Risk of meningitis by predictors in the derivation group (n = 689).

Predictor	Crude OR (95% CI)	Adjusted OR (95% CI) [†]	Standard β [†]	p value*
Fever [#]	2.8 (1.8–4.5)	6.3 (3.3–12.0)	0.51	<0.001
Absence of infection source [§]	3.1 (2.0–4.9)	3.4 (2.0–5.7)	0.34	<0.001
Neurological manifestations [‡]	3.8 (2.4–6.1)	7.1 (3.8–13.1)	0.40	<0.001
CRP > 25 mg/L	2.4 (1.5–3.8)	2.1 (1.2–3.5)	0.17	0.008
PCT > 2.5 ng/mL	2.5 (1.6–3.9)	2.4 (1.4–4.1)	0.21	<0.001
Fever without infection source	5.0 (3.2–7.8)	7.2 (4.3–11.9)	0.381	<0.001

*Characteristics with p values <0.05 were considered statistically significant.

[†]Adjusted for age on admission and sex, with other predictors.

[#]Peak temperature >38°C as measured at home, in the pediatric emergency department or outpatient clinic, or on admission.

[‡]Seizure, abnormal muscle tone, irritability, bulging anterior fontanelle, etc.

[§]Neonates did not have any of impetigo, urinary infection, omphalitis, respiratory infection, purulent arthritis, etc.

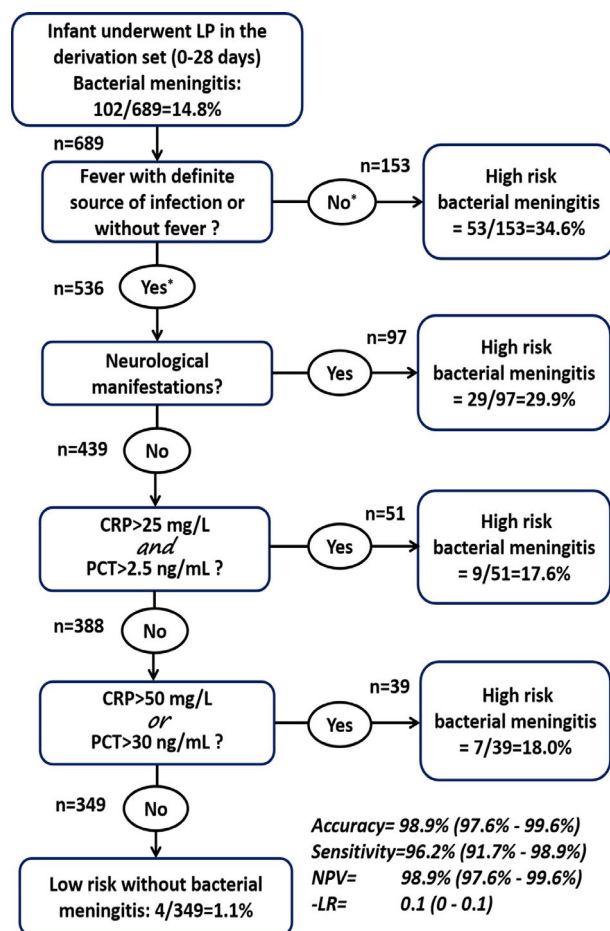


Figure 2. Prevalence of neonatal bacterial meningitis in different risk subgroups in the derivation set (0–28 days). –LR, Negative likelihood ratio; NPV, Negative predictive value. Neurological manifestation: Including seizure, abnormal muscle tone, irritability, bulging anterior fontanelle, etc. Fever with definite source of infection or without fever? No*: With fever but absence of infection source; Yes*: With fever and definite source of infection, or without fever.

it in neonates without FWS (9.1%, 49 of 536). FWS was an independent risk factor for neonatal BM. However, of the 689 included neonates, 102 were diagnosed with BM, of whom only half (52.0%, 53 of 102) had FWS. In the second step, the neurological evaluation identified 28.4% of neonatal BM cases (29 of 102). Considering CRP and PCT, we further identified a subgroup of 50.7% (349 of 689) of low-risk neonates with a BM prevalence of only 1.1% (4 of 349). Ultimately, in the derivation set, we identified 96.1% neonatal BM cases (98 of 102) and 50.7% low-risk BM cases (349 of 689). Due to the high physiological level of PCT and CRP in full-term babies in the first few days after birth,^{27,28} we also performed sensitivity analyses to test the diagnostic performance of the algorithm in patients within 3 days after birth and obtained similar results (Fig. S1).

In the derivation set, the algorithm provided the highest diagnostic performance, superior to that of the composite model integrated with the same five predictors in sensitivity (96.2% vs. 84.1%), negative predictive value (NPV) (98.9% vs. 95.1%), negative likelihood ratio (–LR) (0.1 vs. 0.2), and accuracy (98.9% vs. 95.1%) for identifying neonates at low risk of BM (Table S3). Table S4 reveals the characteristics of the four neonates in the derivation set who would have been classified as low-risk patients but were finally diagnosed with BM.

The risk stratification in the external validation set was illustrated in Figure 3. The diagnostic performance was 95.9% in sensitivity and 98.8% in NPV (Table S3). The characteristics of the two misclassified BM neonates in the external validation set are also presented in Table S4. The sensitivity analysis for neonates aged 0–3 days is presented in Figure S2.

Based on the sequential algorithm, a user-friendly online calculator was constructed to provide clinicians with a convenient way to estimate the risk of neonatal

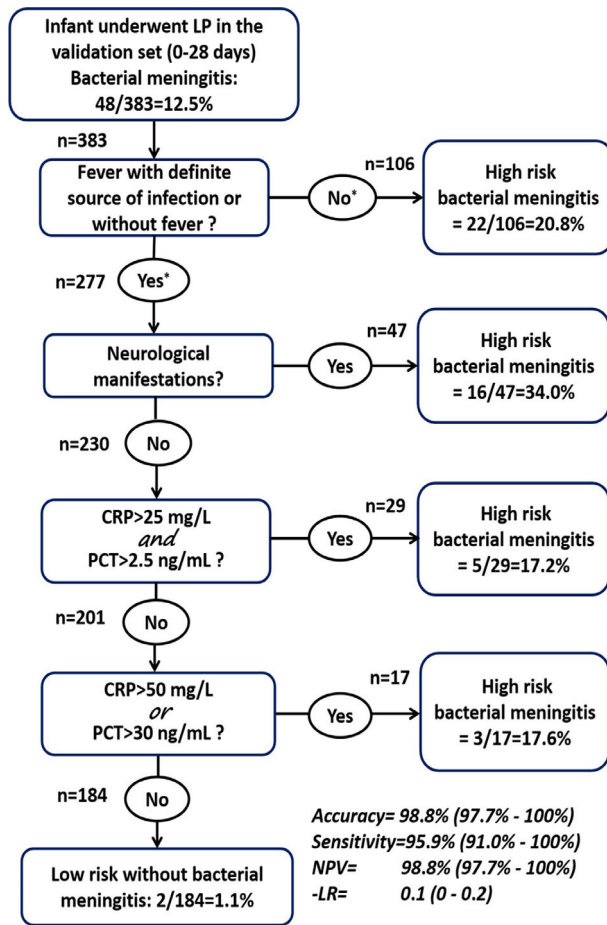


Figure 3. Prevalence of neonatal bacterial meningitis in different risk subgroups in the validation set (0–28 days). NPV: Negative predictive value; –LR: Negative likelihood ratio. Fever with definite source of infection or without fever? No*: With fever but absence of infection source; Yes*: With fever and definite source of infection, or without fever.

BM. The calculator can be accessed at <http://infantsmc.com/RISK/> (Fig. 4).

Discussion

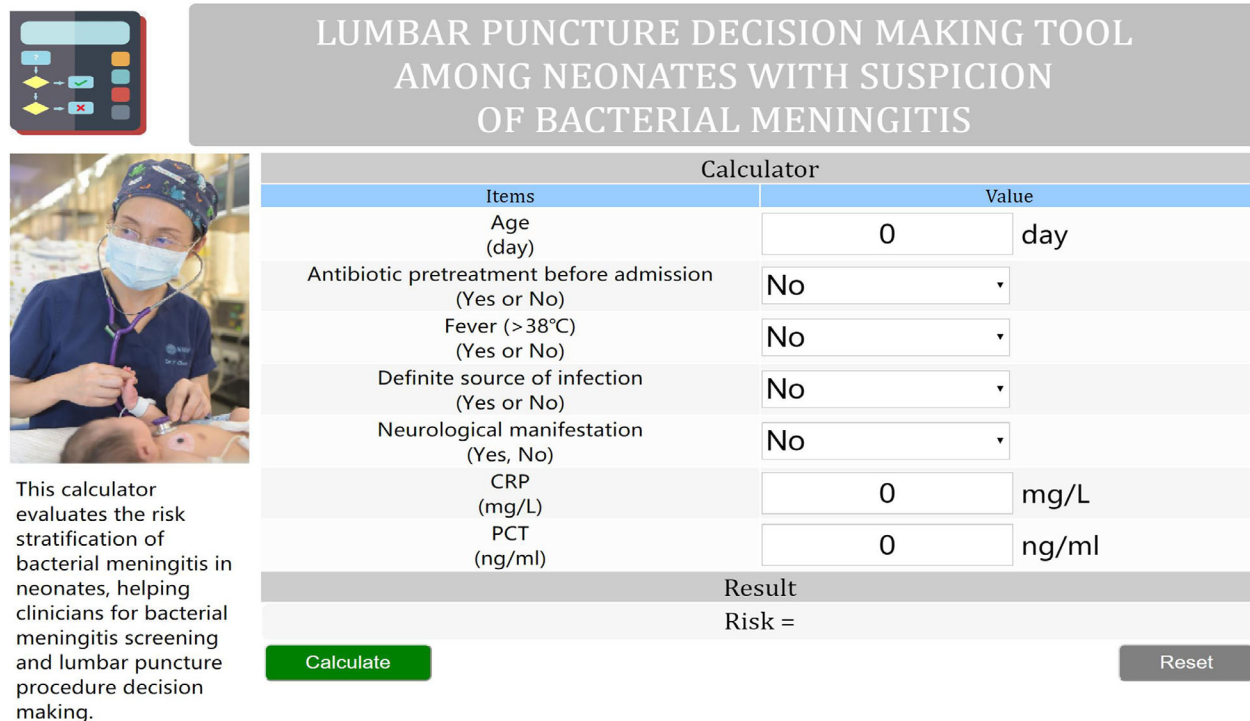
In this large multicenter study, an accurate predictive sequential algorithm was derived and validated for identification of BM across two risk levels in full-term neonates. It comprised five predictors, data on which were readily available. Based on the algorithm, 96.1% of neonatal BM cases and 50.7% of low-risk neonatal BM patients could be identified. The algorithm’s sensitivity was 96.2%, NPV was 98.9%, –LR was 0.1, and accuracy for identifying neonates at low risk of BM was 98.9%, all values that were superior to those obtained in the multivariable regression model with the same predictors.

In this study, all subjects included had probable meningitis, with proven or suspected sepsis, and underwent LP

procedure. This may explain the higher prevalence of BM in this study than it was reported in febrile young infants presenting to the emergency department, 14.8% versus 0.5–0.7%.^{29,30} The prevalence of BM in symptomless cases, even in neonates, is very low.¹⁵ In the first two steps, the identification of FWS and neurological manifestation aided in the identification of 80.4% of BM patients. About 5–10% of infants with FWS were reported having a high risk of serious bacterial infections, including BM.³¹ In this study, we reaffirmed that FWS was an independent high-risk factor for neonatal BM, with the risk shown to be about 3.8 times stronger than in neonates without FWS. Presentations of seizure and neurological signs were considered to be relatively objective predictors. In the United Kingdom and Ireland cohorts, young infants (aged ≤ 90 days) with BM had some clinical features suggestive of BM, particularly seizure, apnea, and bulging fontanelle.⁷ Additionally, the patient’s ill-appearance was not introduced in the algorithm as it was not selected by the stepwise regression analysis, presumably for its non-specific characteristics.

In the next two steps, CRP and PCT, both of which are employed as rapidly available screening tools for neonates with bacterial infections in current practice, were identified as reliable biomarkers. Previous studies have indicated that CRP and PCT, in combination, are often associated with a higher area under the curve, sensitivity, but lower –LR values than individual predictors.³² In practice, however, we occasionally may run into a kind of patients with infectious conditions who have single significantly high-level predictor (either PCT or CRP), since the increasing trajectories of CRP and PCT may differ in inflammatory response. In the fourth step, we took a high level of either CRP or PCT as a predictor for high BM risk, with 50 and 30 ng/mL as the cutoffs, respectively, to prevent from missing the BM neonates with single high-level predictor. Additionally, in terms of physiological status, the levels of CRP and PCT in healthy full-term infants may be transiently high and revert to normal quickly by about 72 h of life.^{27,28} Despite the physiological elevation, our sequential algorithm was still confirmed to exhibit robust predictive ability in this subgroup. We inferred that the consequence of the acute inflammatory response induced by BM might overwhelm the early physiological elevation of CRP and PCT.

In this algorithm, we identified half of all the neonates with a low risk of neonatal BM, indicating that LP should be administered at the clinician’s discretion in these patients. The algorithm also yielded a higher detection rate of BM (96.1%, 98 of 102), superior to the value obtained with the currently used LP indications (fever [73.5%, 75 of 102] and sepsis with positive blood culture [44.1%, 45 of 102]). Meanwhile, although the American



LUMBAR PUNCTURE DECISION MAKING TOOL AMONG NEONATES WITH SUSPICION OF BACTERIAL MENINGITIS

Calculator	
Items	Value
Age (day)	0 day
Antibiotic pretreatment before admission (Yes or No)	No
Fever (>38°C) (Yes or No)	No
Definite source of infection (Yes or No)	No
Neurological manifestation (Yes, No)	No
CRP (mg/L)	0 mg/L
PCT (ng/ml)	0 ng/ml
Result	
Risk =	

Calculate **Reset**

This calculator evaluates the risk stratification of bacterial meningitis in neonates, helping clinicians for bacterial meningitis screening and lumbar puncture procedure decision making.

Figure 4. Web tool calculator.

Academy of Pediatrics guidelines recommended the performance of LP in infants with signs of sepsis,¹⁵ there is still controversy surrounding if it should be used in routine diagnosis. The sequential algorithm may provide a prudent and evidence-based suggestion in neonatal BM screening and LP-related decision-making. We further designed a free handy online calculator for the risk stratification of BM based on the sequential algorithm.

There were four patients in the derivation set who were finally diagnosed as neonatal herpes simplex virus (HSV) encephalitis confirmed by CSF mNGS. All of them were classified as having high risk of BM by the predictive algorithm. Two of them presented at least one abnormal neurological manifestations, such as seizure, abnormal muscle tone, and irritability, while the other two had FWS. None of them had a high level of CRP or PCT. Accordingly, it may be necessary to complete CSF viral investigation in neonates at high risk of BM but without high level of CRP or PCT.

Of note, the lower bound of the 95% CI for sensitivity was 91.7%, which meant at most 1 in 12 neonates with BM may still have a risk of misdiagnosis. In reality, totally six neonates with BM were misclassified as having low risks of BM by this method. Each of them had at least one non-specific ill-appearance possibly implying central nervous impairment, including poor feeding, jaundice aggravation, recurrent cyanosis, lethargy, or high-pitched

cry. Although these non-specific appearances were not identified as independent risk factors in the algorithm, in practice, LP procedure must be reassessed if a low-risk neonate with appearances above possibly suggesting central nervous diseases or has a poor improvement after initial antibiotic therapy. Additionally, our algorithm had a low specificity, positive predictive value, and positive likelihood ratio (+LR), indicating a high false-positive rate, that is, many neonates who underwent LP did not have BM. This high false-positive rate may be acceptable as BM was a serious diagnosis. Accurate LP decision-making is a crucial step in neonatal BM management.

This was a large multicenter clinical research study that had a sufficient sample size for analysis. Although we confirmed that FWS was highly associated with neonatal BM, about half of the BM cases were still identified in neonates without it. To this end, our algorithm was derived from neonates suspected of having meningitis regardless of the presence of fever. Likewise, our algorithm was also verified as having applicability in neonates aged 0–3 days. Few studies on predictive models for neonatal BM in such settings have been reported.

This study also had several limitations. First, our algorithm cannot be applied to neonates who have received antibiotics, as well as those with underlying conditions. In particular, neonates with immunodeficiencies (e.g., SCID) could have BM without the corresponding values that

would be stratified as high risk in this algorithm. Second, concerning the low rate of positive culture, we applied additional criteria on CSF pleocytosis (WBC count $> 20 \times 10^6/L$) with a predominance of PMNs (PMNs $> 50\%$) to eliminate the interference of false-negative CSF cytology. About 54.7% (82 of 150) of neonates from the derivation and validation sets were diagnosed as BM using this criterion. Some researchers argued that more than 10% of BM cases would have an initial lymphocytic predominance, while viral meningitis may initially be dominated by neutrophils,³³ which may lead to BM overdiagnosis. Given the high morbidity and mortality of neonatal BM, the benefits of our study design may outweigh the costs. Last, about 22.1% (196 of 885) of subjects had missing data of CRP and PCT, CSF analysis due to traumatic LP, or time of these tests. Table S5 implied that there was no significant difference in the prevalence of meningitis between the groups with and without complete information, as well as key variables in the algorithm, except fever. Subjects with missing information were more likely to be afebrile, presumably due to the higher proportion of neonates aged 0–3 days. As our algorithm was applicable for neonates aged 0–3 days and both fever and infection sources were considered in the first step, it may have a limited effect on our results.

Conclusions

In summary, the sequential algorithm was a valuable screening tool in risk stratification of BM in full-term neonates, which may help clinicians in the estimation of neonates with a low risk of BM, in whom LP is not necessary. On the other hand, as the algorithm is not 100% sensitive for neonatal BM, the LP procedure must be considered repeatedly if a low-risk neonate exhibiting signs possibly suggesting central nervous diseases or has a poor improvement after initial antibiotic therapy.

Acknowledgments

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Conflict of Interest

The authors have no conflict of interest to declare.

Author Contributions

Y. Chen conceptualized and designed the study, developed the model, constructed the tables and figures, and reviewed and revised the manuscript. Z. Yin cleared the

data, drafted the initial manuscript, and reviewed and revised the manuscript. X. Gong, J. Li, W. Zhong, L. Shan, X. Lei, Q. Zhang, Q. Zhou, Y. Zhao, and C. Chen collected data, and reviewed and revised the manuscript. Y. Zhang conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Prevalence of neonatal bacterial meningitis in different risk subgroups in the derivation set (0–3 days).

Figure S2. Prevalence of neonatal bacterial meningitis in different risk subgroups in the validation set (0–3 days).

Table S1. Hospitals in derivation set and validation set.

Table S2. Clinical and laboratory characteristics in the validation group ($n = 383$).

Table S3. Diagnostic performance for BM by predictive models and sequential algorithm in the derivation group ($n = 689$) and validation cohort ($n = 383$).

Table S4. Characteristics of neonates classified as low-risk patients according to the sequential algorithm who had a diagnosis of bacterial meningitis.

Table S5. Clinical characteristics between neonates with and without complete information in the derivation group.