ORIGINAL ARTICLE

Evaluation of cerebrospinal fluid and blood parameters finding in early diagnosis and drug therapy of suspected bacterial meningitis in neonates

Huixian Li[1], Rui Xiao[2], Ruheena Javed[1], Kuanrong Li[1], Weitao Ye[3], Wei Zhou[4], Huiying Liang[1]

[1]Guangzhou Women and Children's Medical Center, Institute of Pediatrics, Guangzhou Medical University, Guangzhou, Guangdong, China, [2]Department of Respiration, Guangzhou Panyu Central Hospital, Guangzhou, Guangdong, China, [3]Public Health School, Guangzhou Medical University, Guangzhou, Guangdong, China, [4]Guangzhou Women and Children's Medical Center, Neonatal Intensive Care Unit, Guangzhou Medical University, Guangzhou, Guangdong, China

Huixian Li and Rui Xiao contributed the work equally

Background: Whether early lumbar puncture (LP) and blood indicators are suitable as diagnostic criteria and helpful to treatment strategies for newborns remains to be solved. The study was to evaluate the value of cerebrospinal fluid (CSF) at the first LP and blood indicators at the similar time in the early diagnosis and the drug therapy of neonatal bacterial meningitis. **Materials and Methods:** We conducted a retrospective observational study of 997 infants with suspected bacterial meningitis between June 2012 and June 2018. CSF and blood parameters were evaluated by three stepwise logistic models to assess their ability: to distinguish bacterial meningitis from nonbacterial meningitis, to distinguish positive CSF culture from negative, and to distinguish Gram-positive bacteria from negative. **Results:** Of the 997 neonates, 236 (23.67%) were later diagnosed as bacterial meningitis. Of the neonates with meningitis, 54 (22.88%) had positive CSF culture results. And of neonates with positive CSF culture, 27 (50%) had Gram-positive results. One or more CSF indicators were added to the three models. Only blood hypersensitive C-reactive protein and blood lactate dehydrogenase were added to the first model, while no blood parameters was added to the other two models. The areas under the effect-time curves of the three models were 0.91 (95% confidence interval [CI]: 0.89–0.92, $P < 0.001$), 0.69 (95% CI: 0.63–0.75, $P < 0.001$), and 0.86 (95% CI: 0.74–0.94, $P < 0.001$), respectively. **Conclusion:** LP was irreplaceable predictor of bacterial meningitis, and comprehensive analysis of CSF indicators can predict the offending organism, which enables refinement of therapy.

Keywords: Bacterial meningitis, cerebrospinal fluid, diagnosis, drug therapy, neonates

How to cite this article: Li H, Xiao R, Javed R, Li K, Ye W, Zhou W, *et al.* Evaluation of cerebrospinal fluid and blood parameters finding in early diagnosis and drug therapy of suspected bacterial meningitis in neonates. J Res Med Sci 2020;25:77.

INTRODUCTION

Neonatal bacterial meningitis is a rare but detrimental nervous system infection.[1] Mostly, it is a result of bacteremia and sepsis.[2] In developing countries, the annual incidence of bacterial meningitis is 0.2%–6.0% among live births and 1.4%~5% among preterm infants.[3,4] Meningitis is reported to be associated with increased neonatal mortality and morbidity and it may lead to a series of neurological sequelae in childhood, such as epileptic blindness, hearing impairment, cerebral palsy, mental retardation, autism, and so on.[5] Therefore, early diagnosis and prevention of neurologic complication after meningitis are critical.[6]

Traditionally, the diagnosis of bacterial meningitis depends on examination of cerebrospinal fluid (CSF). However, the normal range of biochemical values of CSF in neonates is larger because of gestational age and

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_470_19

Address for correspondence: Dr. Wei Zhou, Guangzhou Women and Children's Medical Center, Neonatal Intensive Care Unit, Guangzhou Medical University, No. 318 Renmin Road, Guangzhou, 510120 Guangdong, China. E-mail: zhouwei_pu002@126.com

Dr. Huiying Liang, Guangzhou Women and Children's Medical Center, Institute of Pediatrics, Guangzhou Medical University, No. 9 Jinsui Road, Guangzhou, 510623 Guangdong, China. E-mail: lianghuiying@hotmail.com

Submitted: 04-Aug-2019; **Revised:** 26-Nov-2019; **Accepted:** 18-Apr-2020; **Published:** 24-Aug-2020

birth weight.[7] CSF culture is considered the gold standard for diagnosis of bacterial meningitis, but the positive rate is low because of the use of antibiotics before lumbar puncture (LP).[8] Polymerase chain reaction is proved to be a promising test, but requires further study and adequate laboratory infrastructure.[9,10]

A number of indicators such as hypersensitive C-reactive protein (hsCRP), lactate dehydrogenase (LDH), white blood cell count (WBCs), and glucose level in CSF have been proved to be valuable in the diagnosis of bacterial meningitis. The early detection of hsCRP, LDH, and WBCs is easier in the blood. However, complete blood cell count parameter had limited value in identifying neonatal bacterial meningitis.[11] There were a few studies that have evaluated some CSF indicators with blood indicators,[12-14] and one study indicated that the serum procalcitonin (PCT) was the independent factor for bacterial etiology.[15] These studies would be limited by sample size and nonspecific inclusion criteria. This raises questions as to whether CSF at the first LP and blood parameters at the similar time are valuable in early diagnosis of neonatal bacterial meningitis and if these parameters can provide reference information for the drug therapy.

In the present study, we retrospectively analyzed the level of hsCRP, LDH, and WBCs in both CSF and blood to evaluate their reference value in the early diagnosis and drug therapy of neonatal bacterial meningitis, and the value of glucose in CSF and PCT in blood was studied at the same time. All the indicators were derived from the first LP or the blood test at the similar time.

MATERIALS AND METHODS

Study design

The retrospective observational study patients were derived from the "Infection mediated brain injury specific disease cohort" (ChiCTR1800014597), which was conducted at the Guangzhou Women and Children's Medical Center, the largest tertiary class A referral pediatric hospital of Southern China. The study protocol was approved by the institutional ethics committee (Ethical approval number: 07600) and was carried out in accordance with the Declaration of Helsinki for experiments involving humans. The requirement to obtain informed consent was waived because of the retrospective nature of the study.

Participants

We collected data of 1138 infants with the inclusion criteria: (1) the neonates who underwent LP from June 2012 to June 2018; (2) age of diagnosis is ≤28 days from birth for full-term newborns, or <40 weeks postmenstrual age for premature infants. Patients with a history of traumatic brain injury, brain tumors, cerebral palsy, epilepsy, ventricular shunt, and neurosurgery (n = 128) or patients with more than 50% data loss (n = 13) were excluded.

Diagnostic criteria and classification criteria

Two senior doctors made a definite diagnosis based on the following clinical manifestations and laboratory test results:

Meningitis: (1) Neonates with positive CSF culture; (2) neonates with negative CSF culture, but with abnormal CSF indicators, or/and with clear clinical manifestations. Nonmeningitis: Neonates with negative CSF culture and absence of clinical manifestations. Patients with meningitis and CSF culture results were grouped into two groups: positive CSF culture and negative CSF culture. Patients with positive CSF culture were also further grouped into two groups: Gram positive and Gram negative.

The clinical manifestations of neonatal meningitis are often indistinguishable from those of neonatal sepsis without meningitis. The most frequently reported clinical manifestations are as follows: (1) unstable body temperature – anal temperature >38°C (fever) or <36°C (hypothermia); (2) nervous system manifestation – irritability, lethargy, hypotonia, tremor or twitching, and seizures;[16] (3) other manifestations – feeding difficulties/vomiting, respiratory distress (tachypnea, purr, alar agitation, three depression sign, and reduced breath sounds), apnea, and diarrhea.[17,18]

Abnormal cerebrospinal fluid indicators

WBCs count >20 × 10^6/L, protein >1.5 g/L in the premature, protein >1.0 g/L in the full-term, glucose concentration lower than 50% of peripheral blood sugar, full-term glucose <1.7 mmol/L, or premature glucose <1.1 mmol/L.

Variables and measurement

The data of neonates with suspected bacterial meningitis who met the inclusion criteria, such as data on sex, gestational age, birth weight, age of onset, age of diagnosis, and results of the first LP of CSF and concurrent blood routine results, were derived from the clinical data repository. Tto reduce bias in the collection of information, another data analyst checked 5% of the data set against the original medical record data. According to the onset time of the bacterial meningitis, neonates were divided into early-onset infection (0–7 days after birth) and late-onset infection (8–28 days after birth).

Statistical analysis

Numeric variables were tested for normality using the Kolmogorov–Smirnov test. All the numeric variables were not normally distributed and were presented as the median (interquartile range). The categorical variables

were presented as numbers (percentages). The differences between groups were compared with Mann–Whitney U-test for numeric variables and with Chi-square tests or Fisher's exact test for categorical variables. There were no missing data in the sex, gestational age, birth weight, and age of onset and age of diagnosis. The proportion of missing data of CSF and concurrent blood routine results was 0.6%–1.91% and we replaced the missing value with their median. Assessment of the diagnostic performance of hsCRP, LDH, WBCs, and glucose level in CSF and hsCRP, LDH, WBCs, and PCT level in blood was preceded in two steps. First, receiver operating characteristic (ROC) curve analysis and the area under the ROC curve (AUC) were used.[19] The optimal cutoff values for defining specific group were calculated by maximizing the sum of the sensitivity and specificity of each index. Second, all the collected variables were used in the stepwise logistic regression analyses with option SLENTRY = 0.20 and SLSTAY = 0.10 to determine the optimal combination for predicting the specific group. Comparison of the AUCs from ROC curve analysis was performed with Hanley tests. The selected variables in models were also presented with odds ratio [OR], 95% confidence interval [CI]. Power analysis was performed using NCSS PASS-11. All probability values were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using SAS 9.4 Windows software (SAS Institute, Inc., Cary, NC, USA, 2015).

RESULTS

Clinical characteristics and bacterial culture data

A total of 997 neonates who were suspected of neonatal meningitis and underwent LP, including 625 (62.69%) males and 372 (37.31%) females, were eventually included in the study. Among them, 761 (76.33%) neonates were diagnosed as nonmeningitis by doctors before discharge and 236 (23.67%) were diagnosed as bacterial meningitis. 836 (83.9%) neonates had antibiotics before underwent LP. Majority of the study subjects were full-term and normal-birth-weight neonates (68.30%). A total of 54 (22.88%) neonates with confirmed bacterial meningitis were positive in CSF culture, and out of them, 27 (50%) were Gram positive [Table 1].

The top three common bacteria were *Streptococcus agalactiae* (Group B) (GBS) ($n = 13$), followed by *Escherichia coli* ($n = 13$) and *Klebsiella pneumoniae* ($n = 4$), which together accounted for 55.56% of the bacteria. The composition of bacterial pathogens is shown in Figure 1, and they differed with different characteristics except the gender. *E. coli* was mainly found in bacterial meningitis term and late-onset neonates, and *K. pneumoniae* was found in low-birth-weight (LBW), premature, and early-onset neonates. In addition, some bacteria such as *Flavobacterium meningosepticum*, *Staphylococcus epidermidis*, and *Staphylococcus haemolyticus* could be detected in normal-body-weight (NBW) and term neonates, which were lacking in LBW and premature neonates. The bacterial species in neonates with late-onset purulent meningitis was also more diverse than that in those with early-onset bacterial meningitis.

Table 1: Baseline demographic characteristics and clinical groups

	n (%)
Gender (*n*=997)	
Male	625 (62.69)
Female	372 (37.31)
Gestational age (*n*=997)	
Preterm	232 (23.27)
Term	765 (76.73)
Birth weight (*n*=997)	
LBW	278 (27.88)
NBW	719 (72.12)
Group (*n*=997)	
Nonmeningitis	761 (76.33)
Meningitis	236 (23.67)
Among meningitis (*n*=236)	
Early onset	47 (19.92)
Late onset	189 (80.08)
Among meningitis (*n*=236)	
No culture result	16 (6.78)
Negative in CSF culture	166 (70.34)
Positive in CSF culture	54 (22.88)
Among positive in CSF culture (*n*=54)	
Gram negative	27 (50.00)
Gram positive	27 (50.00)

LBW=Low birth weight; NBW=Normal birth weight; CSF=Cerebrospinal fluid

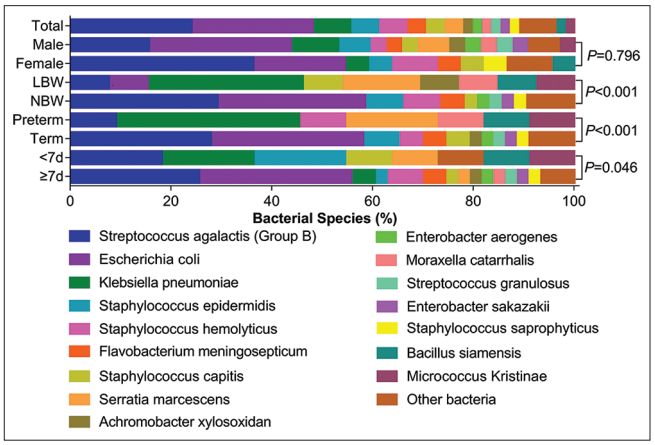

Figure 1: Distribution of bacterial pathogens detected in cerebrospinal fluid culture

Distinguish meningitis from nonbacterial meningitis

All the CSF indicators showed statistically significant difference between bacterial meningitis patients and nonbacterial patients as presented in Supplementary Table 1, while among the blood indicators, a statistically significant difference was observed only for hsCRP and LDH but not for

WBCs and PCT. The frequency of LBW was also significantly different between bacterial patients and nonpatients. Gender and gestational age showed no significant difference of distribution between the two groups. The areas under the effect-time curves (AUCs) of CSF indicators were 0.87 (95% CI: 0.85–0.89, $P < 0.001$), 0.84 (95% CI: 0.81–0.86, $P < 0.001$), 0.77 (95% CI: 0.74–0.79, $P < 0.001$), and 0.70 (95% CI: 0.67–0.73, $P < 0.001$) for WBCs, glucose, LDH, and hsCRP, respectively. For blood indicators, the AUCs were 0.64 (95% CI: 0.61–0.67, $P < 0.001$) for both hsCRP and LDH [Figure 2]. Stepwise logistic regression showed that the combination of the gender (OR = 0.60, 95% CI: 0.38–0.92, $P = 0.021$), birth weight (OR = 0.41, 95% CI: 0.25–0.67, $P = 0.003$), level of glucoses in CSF (OR = 0.18, 95% CI: 0.13–0.25, $P < 0.001$), count of WBCs in CSF (OR = 1.01, 95% CI: 1.00–1.01, $P < 0.001$), hsCRP level in blood (OR = 1.00, 95% CI: 1.00–1.01, $P = 0.022$), and LDH level in blood (OR = 1.00, 95% CI: 1.00–1.00, $P = 0.006$) had an AUC value 0.91 (95% CI: 0.89–0.92). The model showed a sensitivity of 52.97% and a specificity of 96.98% with the positive predictive value of 84.46% and negative predictive value of 86.93%.

Distinguish positive from negative in cerebrospinal fluid culture in confirmed bacterial meningitis

The distributions of gender, birth weight, gestational age, and age of onset were similar between positive CSF culture group and negative CSF culture group [Supplementary Table 2]. However, the levels of hsCRP in both blood and CSF in positive CSF culture group were significantly higher than those in the negative culture group. Furthermore, CSF glucose was statistically significantly lower in the positive CSF culture group than that in the negative group, while the results of other biochemical tests were similar in the two groups. There were only CSF hsCRP, blood hsCRP, and CSF glucose provided significant discriminatory information, with an AUC of 0.69 (95% CI: 0.63–0.75, $P < 0.001$), 0.65 (95% CI: 0.59–0.72, $P < 0.001$), and 0.59 (95% CI: 0.52–0.66, $P = 0.034$), respectively [Figure 3]. Stepwise binary logistic regression showed that only CSF hsCRP (OR = 1.23, 95% CI: 1.11–1.37, $P < 0.001$) was added to the model and the model had the same AUC of 0.69 (95% CI: 0.63–0.75, $P < 0.001$) as single CSF hsCRP do. The model showed a sensitivity of 20.37% and a specificity of 96.39% with the positive predictive value of 64.71% and negative predictive value of 78.82%.

Distinguish Gram positive from Gram negative in confirmed bacterial meningitis with positive cerebrospinal fluid culture

Distribution of Gram-positive bacteria and Gram-negative bacteria was similar in different gestational age and age of onset group. Male neonates and LBW had significantly higher proportion of Gram-negative cases than female and NBW (62.50% vs. 31.82%; 76.92% vs. 41.46%). Gram-positive group was significantly associated with lower CSF hsCRP and higher CSF glucose (all $P < 0.05$), while the other biochemical parameters were similar to the negative CSF culture group [Supplementary Table 3]. There were only CSF hsCRP and CSF glucose provided significant discriminatory information. CSF glucose had the similar diagnostic value in terms of predicting positive Gram's stain (AUC: 0.71, 95% CI: 0.57–0.83, $P = 0.003$) with CSF hsCRP (AUC: 0.68, 95% CI: 0.54–0.80, $P = 0.015$) [Figure 4]. Stepwise binary logistic regression analysis showed that only BW (OR = 0.02, 95% CI: 0.00–0.23, $P = 0.002$) and CSF glucose (OR = 4.34, 95% CI: 1.79–10.56, $P = 0.001$) were showed up into the model and the model had a c-statistic of 0.86 (95% CI: 0.74–0.94, $P < 0.001$). The model showed a sensitivity of 66.67% and a specificity of 88.89% with the positive predictive value of 85.71% and negative predictive value of 72.73%.

Power analysis

The value of AUC under the null hypothesis was 0.50, and the significance level (alpha) was 0.05 in the power

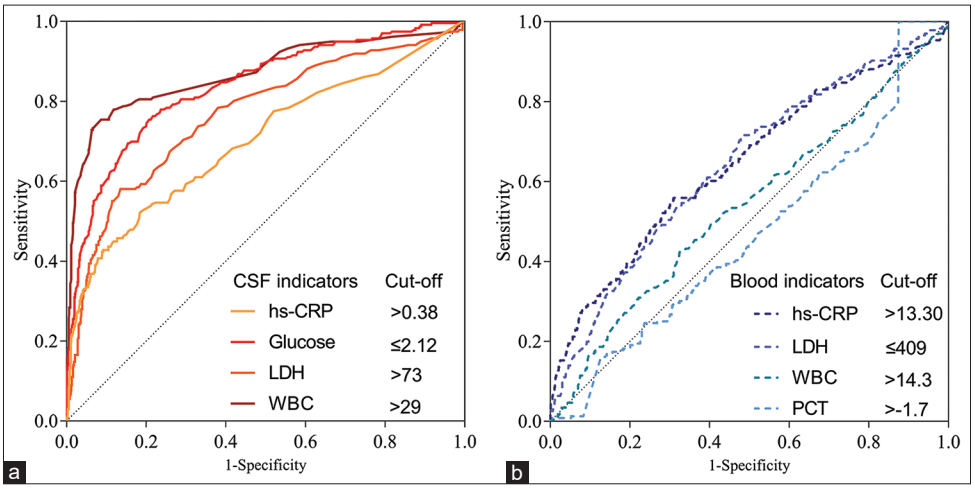

Figure 2: Cerebrospinal fluid and blood indicators' receiver operating characteristic curves for discriminating meningitis from nonmeningitis

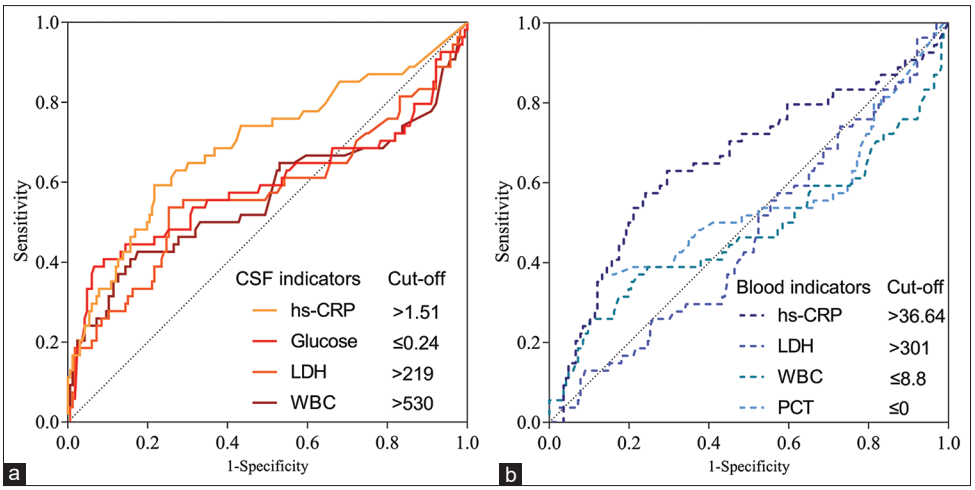

Figure 3: Cerebrospinal fluid and blood indicators' receiver operating characteristic curves for discriminating positive cerebrospinal fluid culture from negative

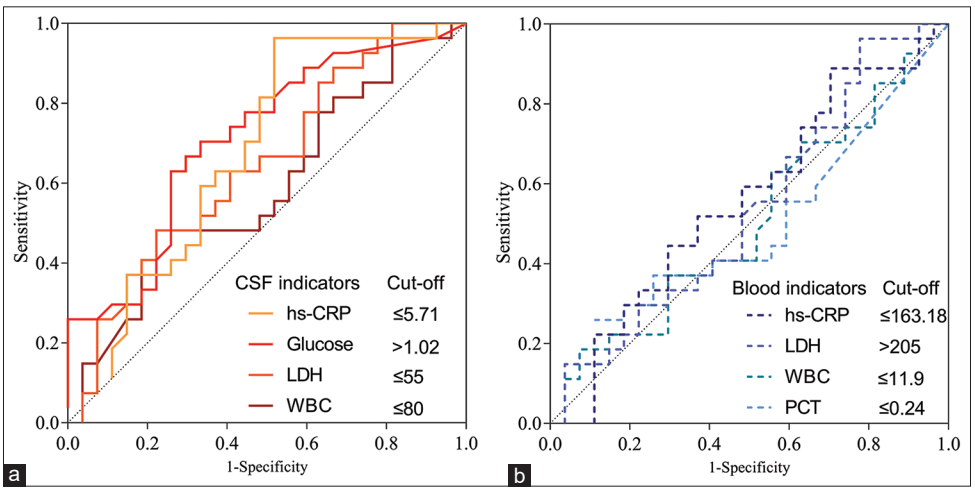

Figure 4: Cerebrospinal fluid and blood indicators' receiver operating characteristic curves for discriminating Gram-positive from negative. Color should be used for all the four figures in print

analysis. The differences between null hypothesis and alternative hypothesis were tested by two-sided *z*-test. In classification model to distinguish bacterial meningitis from nonbacterial meningitis, a sample size of 997 (positive = 236, negative = 761) yields 100% power to detect a difference of 0.41 between the null hypothesis and the alternative hypothesis (AUC = 0.91). In classification model to distinguish positive CSF culture from negative, a sample size of 220 (positive = 54, negative = 166) yields 99% power to detect a difference of 0.19 between the null hypothesis and the alternative hypothesis (AUC = 0.69). In classification model to distinguish Gram-positive bacteria from negative, a sample size of 54 (positive = 27, negative = 27) yields 100% power to detect a difference of 0.36 between the null hypothesis and the alternative hypothesis (AUC = 0.86).

DISCUSSION

CSF culture remains to be the gold standard method for diagnosis of neonatal bacterial meningitis, while infants with bacterial meningitis had high intracranial pressure and were at high risk of herniation during LP.[20] Many doctors performed LP to reduce missed diagnosis even some of them are not required. In our study, we evaluated the value of CSF and blood indicators in the early diagnosis and the drug therapy of neonatal bacterial meningitis.

The rate of positive CSF culture in the neonates with meningitis was 22.9%, which was consistent with Stoll *et al*.'s study (20%–30%).[21] In developed countries, early-onset infections are mainly caused by GBS, *E. coli*, and *Listeria*, while late-onset infections are mainly caused by *Staphylococcus, G-bacillus*, and GBS.[22] A French study including 363 children with meningococcal meningitis demonstrated that the infection rate of GBS was significantly higher than that of *E. coli* (59% vs. 28%), while the infection rate of *E. coli* was higher than that of GBS (45% vs. 32%) in premature infants and LBW infants.[23] Our study results showed no difference in pathogenic bacteria by sex. However, the diversity of pathogenic bacteria was more obvious in

neonates with late-onset infections, whose main bacteria were *E. coli* and GBS. In early-onset cases, GBS was the main pathogenic bacteria. No *E. coli* was observed in premature infants, which may be a result of maternal antibiotics use. As an opportunistic pathogen, *K. pneumoniae* were found in premature, LBW, and early-onset infants. However, they were very rare in NBW and full-term infants. The difference may due to the former's immature immune system, weak neutrophil and monocyte phagocytosis, insufficient complement and antibody secretion.[24] In a meta-analysis in 2016, there was no significant difference between glycerol and dexamethasone in the prevention of neurologic complication after meningitis, irrespective of the cause.[6] However, dexamethasone may have different effects in bacterial meningitis caused by different pathogens. In our study, neonates in different groups had different pathogen compositions. It was important to identify pathogen before using dexamethasone in neonates.[25]

Our model for distinguishing meningitis from nonmeningitis included sex, birth weight, and age at admission, level of glucoses and count of WBCs in CSF, hsCRP and LDH level in blood had an AUC of value 0.91. However, the overall missed diagnosis rate was 47.03% (the missed diagnosis rate was calculated by 100% minus the model's sensitivity), which suggests lower accuracy to correctly identify those with of bacterial meningitis, whereas specificity of 96.98% suggests higher accuracy to correctly identify those without the disease. It suggests that clinicians need to consider more objective indicators to improve the model's sensitivity.

Chadwick *et al.*'s study found CSF WBCs >21 × 10^6/L as diagnostic criteria for BM, with a sensitivity of 79% and a specificity of 81%.[26] Our study showed that the cutoff value for WBCs was 29 × 10^6/L and the sensitivity was 75.4%, which is lower than other studies. It is hard to clearly diagnose the meningitis only based on LP results, and it often requires repeated puncture.[27] We further compared the first model in distinguishing nonbacterial meningitis from bacterial meningitis with single CSF WBCs. The Δ AUC was 0.03 (95% CI, 0.00–0.07, $P = 0.020$), which suggested that there was only a limited improvement in diagnosis with combination of multiple indicators compared with single CSF WBCs. This was consistent with Huang *et al.*'s study.[28]

As CSF culture positive rate was low, we emphasized to enucleate weather is there any indicator which could help indicate the positive culture rate. The overall missed diagnosis rate was 79.69% (100–20.31), and the overall accuracy was related to a lower level of 0.69. None of the factors except hsCRP in CSF we considered could improve the accuracy in distinguishing negative culture from positive culture cases, it may be related to small sample size of CSF culture positive cases which suggest to investigate the multi-center, large sample studies data to better understand the differences between positive and negative culture in the future.

Early identification of Gram-negative or Gram-positive neonatal suppurative meningitis, selection of correct antibiotics, and early evaluation of prognosis are very important to reduce the sequelae of infants. The present study found that Gram-negative bacterial infections were more common in men and LBW infants, and CSF hsCRP increased significantly, and glucose levels in CSF decreased significantly. Our predicted model suggested the overall missed diagnosis rate 33.33% (100–66.67), the misdiagnosis rate 11.11% (100%–88.89%), and the overall accuracy 0.86, which suggested to be of good value to guide clinicians in early empirical drug therapy.

Limitations

There were some limitations of this study. First, as a retrospective cohort study, there was inevitable bias when collecting data and we only included the objective measures to reduce the recall bias. Second, glucose in blood and PCT in CSF were not routine tests and we could not adequately evaluate all the indicators in pairs. Third, only neonates who underwent LP were included and mild cases might be missed, which would cause an underestimate of the diagnostic cutoff values.

CONCLUSION

The testing of CSF in the prediction of neonatal bacterial meningitis is still irreplaceable. Early diagnosis and early pathogen identification of bacterial meningitis will contribute to personalized treatment of neonates with suspected meningitis in the early stage. More prospective research is needed to better explore the impacts of early diagnosis and early pathogen identification on prognosis.

Acknowledgments

We thank friendly help from colleagues of Clinical Laboratory Department and the Ethics Committee (Ethical approval number: 07600) of Guangzhou Women and Children's Medical Center.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. van de Beek D. Progress and challenges in bacterial meningitis. Lancet 2012;380:1623-4.
2. Baud O, Aujard Y. Neonatal bacterial meningitis. Handb Clin

Neurol 2013;112:1109-13.
3. Softić I, Tahirović H, Hasanhodžić M. Neonatal bacterial meningitis: Results from a cross-sectional hospital based study. Acta Med Acad 2015;44:117-23.
4. Hasbun R, Wootton SH, Rosenthal N, Balada-Llasat JM, Chung J, Duff S, *et al*. Epidemiology of meningitis and encephalitis in infants and children in the United States, 2011-2014. Pediatr Infect Dis J 2019;38:37-41.
5. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, *et al*. ESCMID guideline: Diagnosis and treatment of acute bacterial meningitis. Clin Microbiol Infect 2016;22 Suppl 3:S37-62.
6. Vaziri S, Mansouri F, Sayad B, Ghadiri K, Torkashvand E, Rezaei M, *et al*. Meta-analysis of studies comparing adjuvant dexamethasone to glycerol to improve clinical outcome of bacterial meningitis. J Res Med Sci 2016;21:22.
7. Srinivasan L, Harris MC, Shah SS. Lumbar puncture in the neonate: Challenges in decision making and interpretation. Semin Perinatol 2012;36:445-53.
8. Du B, Hua C, Xia Y, Li J, Xie Y, Tao Y, *et al*. Evaluation of the BioFire FilmArray meningitis/encephalitis panel for the detection of bacteria and yeast in Chinese children. Ann Transl Med 2019;7:437.
9. Hou Y, Zhang X, Hou X, Wu R, Wang Y, He X, *et al*. Rapid pathogen identification using a novel microarray-based assay with purulent meningitis in cerebrospinal fluid. Sci Rep 2018;8:15965.
10. Ramasamy R, Willis L, Kadambari S, Kelly DF, Heath PT, Nadel S, *et al*. Management of suspected paediatric meningitis: A multicentre prospective cohort study. Arch Dis Child 2018;103:1114-8.
11. Cruz AT, Mahajan P, Bonsu BK, Bennett JE, Levine DA, Alpern ER, *et al*. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. JAMA Pediatr 2017;171:e172927.
12. Cao W, Jian C, Zhang H, Xu S. Comparison of clinical features and prognostic factors of cryptococcal meningitis caused by cryptococcus neoformans in patients with and without pulmonary nodules. Mycopathologia 2019;184:73-80.
13. Ibrahim KA, Abdel-Wahab AA, Ibrahim AS. Diagnostic value of serum procalcitonin levels in children with meningitis: A comparison with blood leukocyte count and C-reactive protein. J Pak Med Assoc 2011;61:346-51.
14. Sanaei Dashti A, Alizadeh S, Karimi A, Khalifeh M, Shoja SA. Diagnostic value of lactate, procalcitonin, ferritin, serum-C-reactive protein, and other biomarkers in bacterial and viral meningitis: A cross-sectional study. Medicine (Baltimore) 2017;96:e7637.
15. Julián-Jiménez A, Morales-Casado MI. Usefulness of blood and cerebrospinal fluid laboratory testing to predict bacterial meningitis in the emergency department. Neurologia 2019;34:105-13.
16. Pong A, Bradley JS. Bacterial meningitis and the newborn infant. Infect Dis Clin North Am 1999;13:711-33, viii.
17. Weisman LE, Stoll BJ, Cruess DF, Hall RT, Merenstein GB, Hemming VG, *et al*. Early-onset group B streptococcal sepsis: A current assessment. J Pediatr 1992;121:428-33.
18. Nizet V, JO K. Bacterial sepsis and meningitis [JJ. In: Remington JS, Klein JO, Wilson CB, editors, *et al*. Infectious Diseases of the Fetus and Newborn Infant. 7th ed. Philadelphia: Elsevier Saunders; 2016. p. 217.
19. Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. Circulation 2007;115:654-7.
20. Srinivasan L, Shah SS, Padula MA, Abbasi S, McGowan KL, Harris MC. Cerebrospinal fluid reference ranges in term and preterm infants in the neonatal intensive care unit. J Pediatr 2012;161:729-34.
21. Stoll BJ, Hansen NI, Sánchez PJ, Faix RG, Poindexter BB, Van Meurs KP, *et al*. Early onset neonatal sepsis: The burden of group B Streptococcal and *E. coli* disease continues. Pediatrics 2011;127:817-26.
22. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, *et al*. Bacterial meningitis in the United States, 1998-2007. N Engl J Med 2011;364:2016-25.
23. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. Clin Microbiol Rev 2010;23:467-92.
24. Heath PT, Okike IO. Neonatal bacterial meningitis: An update. Paediatrics Child Health 2010;20:526-30.
25. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2013;6:CD004405.
26. Chadwick SL, Wilson JW, Levin JE, Martin JM. Cerebrospinal fluid characteristics of infants who present to the emergency department with fever: Establishing normal values by week of age. Pediatr Infect Dis J 2011;30:e63-7.
27. Greenberg RG, Smith PB, Cotten CM, Moody MA, Clark RH, Benjamin DK Jr., Traumatic lumbar punctures in neonates: Test performance of the cerebrospinal fluid white blood cell count. Pediatr Infect Dis J 2008;27:1047-51.
28. Huang H, Tan J, Gong X, Li J, Wang L, Xu M, *et al*. Comparing single vs. Combined cerebrospinal fluid parameters for diagnosing full-term neonatal bacterial meningitis. Front Neurol 2019;10:12.

Supplementary Table 1: Clinical characteristic for neonates by meningitis and nonmeningitis

Indicators, *n* (row %) or as shown	Nonmeningitis, (*n*=761)	Meningitis (*n*=236)	χ^2/Z	*P*
Gender				
Male	468 (74.88)	157 (25.12)	1.95	0.16
Female	293 (78.76)	79 (21.24)		
Gestational age				
Preterm	188 (81.03)	44 (18.97)	3.71	0.05
Term	573 (74.90)	192 (25.10)		
Birth weight				
LBW	229 (82.37)	49 (17.63)	7.80	0.01
NBW	532 (73.99)	187 (26.01)		
CSF, median (IQR)				
hsCRP	0.08 (0.01-0.29)	0.40 (0.08-2.18)	9.41	<0.001
LDH	43 (33-58)	85.5 (50-327)	12.38	<0.001
WBC	8 (3-10)	100 (30-500)	17.28	<0.001
Glucose	2.55 (2.21-2.97)	1.65 (0.76-2.12)	−15.63	<0.001
Blood, median (IQR)				
hsCRP	3.21 (0.49-22.14)	18.06 (1.74-81.70)	6.68	<0.001
LDH	416 (310-578)	325 (259-450)	−6.57	<0.001
WBC	11.8 (8.9-16.0)	12.8 (8.8-18.05)	1.78	0.08
PCT	0.61 (0.17-8.20)	0.50 (0.10-6.13)	−1.48	0.14

LBW=Low birth weight; NBW=Normal birth weight; CSF=Cerebrospinal fluid; LDH=Lactate dehydrogenase; WBC=White blood cell count; PCT=Procalcitonin; hsCRP=Hypersensitive C-reactive protein; IQR=Interquartile range

Supplementary Table 2: Clinical characteristic for neonates by cerebrospinal fluid culture results

Indicators, *n* (row %) or as shown	Negative (*n*=166)	Positive (*n*=54)	χ^2/Z	*P*
Gender				
Male	113 (77.93)	32 (22.07)	1.41	0.24
Female	53 (70.67)	22 (29.33)		
Gestational age				
Preterm	30 (73.17)	11 (26.83)	0.14	0.71
Term	136 (75.98)	43 (26.83)		
Birth weight				
LBW	34 (72.34)	13 (27.66)	0.31	0.58
NBW	132 (76.30)	41 (23.70)		
Onset type				
Early onset	34 (75.56)	11 (24.44)	0.00	0.99
Late onset	132 (75.43)	43 (24.57)		
CSF, median (IQR)				
hsCRP	0.27 (0.07-1.19)	1.79 (0.25-5.77)	4.27	<0.001
LDH	83 (51-252)	236 (49-676)	1.57	0.12
WBC	100 (32-330)	160 (10-1340)	1.42	0.16
Glucose	1.68 (1.02-2.1)	1.27 (0.04-2.37)	−2.01	0.05
Blood, median (IQR)				
hsCRP	13.63 (1.45-54.73)	70.95 (5.02-135.57)	3.40	<0.001
LDH	319.5 (253-449)	330 (259-456)	0.65	0.51
WBC	13 (9.5-17.1)	11.5 (7.7-22.5)	−0.43	0.67
PCT	0.5 (0.12-4.04)	0.38 (0-10.96)	−0.55	0.58

LBW=Low birth weight; NBW=Normal birth weight; CSF=Cerebrospinal fluid; LDH=Lactate dehydrogenase; WBC=White blood cell count; PCT=Procalcitonin; hsCRP=Hypersensitive C-reactive protein; IQR=Interquartile range

Supplementary Table 3: Clinical characteristic for neonates by Gram stain

Indicators, *n* (row %) or as shown	Gram negative (*n*=27)	Gram positive (*n*=27)	χ^2/Z	*P*
Gender				
Male	20 (62.50)	12 (37.50)	4.91	0.03
Female	7 (31.82)	15 (68.18)		
Gestational age				
Preterm	8 (72.73)	3 (27.27)	2.85	0.09
Term	19 (44.19)	24 (55.81)		
Birth weight				
LBW	10 (76.92)	3 (23.08)	4.96	0.03
NBW	17 (41.46)	24 (58.54)		
Onset type				
Early onset	4 (36.36)	7 (63.64)	1.03	0.31
Late onset	23 (53.49)	20 (46.51)		
CSF, median (IQR)				
hsCRP	3.56 (0.41-10.78)	1.53 (0.10-3.06)	−2.23	0.03
LDH	266 (58-1560)	80 (38-412)	−1.84	0.07
WBC	190 (96-2330)	130 (8-1010)	−1.13	0.26
Glucose	0.15 (0.01-1.94)	1.76 (0.34-2.62)	2.65	0.01
Blood, median (IQR)				
hsCRP	77.78 (14.80-183.70)	57.92 (4.13-112.10)	−0.74	0.46
LDH	329 (252-424)	331 (259-488)	0.45	0.65
WBC	13.2 (7.7-22.5)	11.3 (6.9-19.6)	0.09	0.93
PCT	1.65 (0-10.48)	0.21 (0-25)	−0.07	0.94

LBW=Low birth weight; NBW=Normal birth weight; CSF=Cerebrospinal fluid; LDH=Lactate dehydrogenase; WBC=White blood cell count; PCT=Procalcitonin; hsCRP=Hypersensitive C-reactive protein; IQR=Interquartile range