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Review Article

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A Differential Diagnostic Model for Tuberculous and Bacterial Meningitis based on Clinical and Laboratory Tests

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Abstract

Tuberculous meningitis (TBM) is a severe infectious disease in the Central Nervous System (CNS). It's elusive to differentially diagnose TBM with Bacterial Meningitis (BM). Traditional diagnosis of TBM is based on clinical features, etiological examination, and the biochemistry analysis of cerebrospinal fluid. These conventional methods are time consuming and insensitive, which could lead to a delay in TBM diagnosis. The aim of our study is to develop a diagnosis model which could distinguish TBM from BM rapidly and accurately. A retrospective review of all 191 CNS patients was conducted to determine the differences between TBM (n=145) and BM (n=46) based on clinical and laboratory tests. Logistic regression was used to identify the parameters independently predicting TBM and to develop a diagnosis model. A receiver operator characteristic curve was used to determine the best cutoff for the diagnostic model. Seven parameters were found predictive: Coma, ESR30, FIB, Monocytes%, Lymphocytes%, Neutrophils%, and EOS%. Application of the above seven parameters revealed 89.0% sensitivity and 93.5% specificity. This diagnostic model can help improve the accuracy of the early diagnosis of TBM.

Keywords: Diagnosis model • Tuberculous meningitis • Bacterial meningitis • Differential diagnosis

Introduction

Tuberculous meningitis (TBM) is a global disease which is caused by *Mycobacterium Tuberculosis*. TBM is the most severe form of tuberculosis, and a high incidence is reported annually with approximately 50% of death or severe disability [1,2]. Failure to diagnose TBM at an early stage is one of the primary causes of TBM [3]. The diagnosis of TBM is mainly based on laboratory tests and clinical features [4]. However, the initial presentation of TBM is similar to Bacterial Meningitis (BM), including headache, fever, and vomiting. The smear test and cultures for TBM detection usually require a long time, with an accuracy lower than 50% [5,6]. Next generation sequencing (NGS) is currently a new method for diagnosing TBM by identifying the sequences of *Mycobacterium Tuberculosis* in cerebrospinal fluid (CSF) [7,8]. Due to the high cost, NGS is not widely used. Unfortunately, TBM patients are usually diagnosed with a delay that will result in a worse prognosis [9]. Thus, an accurate and rapid model for TBM diagnosis is warranted. To address this issue, we attempted to develop a model for the differential diagnosis between TBM and BM. Based on our new diagnosis model, we used a few clinical and laboratory parameters to diagnose TBM with a specificity of 93.5%. Our model could serve as an early indicator for TBM diagnosis and improve the outcome.

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Methods

Patients

This study was conducted at Shenzhen Third People's Hospital, China. A total of 191 patients diagnosed with a central nervous system infection from 2018 to 2021 were enrolled in this study. Patients' ages range from 24 to 51 years old. These patients were divided into two sub-groups, including a TBM group (145 cases) and a BM group (46 cases). The clinical and laboratory data from all the patients were collected, and the study was approved by the Shenzhen Third People's Hospital ethics committee (No. K2021001). A total of 211 patients diagnosed with LSCC treated with surgery were admitted to the Third Affiliated Hospital of Harbin Medical University. All patients and their families provided written informed consent regarding this study, and ethical approval for the study was obtained from the Ethics Committee of Harbin Medical University.

Procedures

A lumber puncture was performed on all the patients. The CSF from each patient was collected and used for further tests including glucose, chloride, adenosine deaminase (ADA), white blood cell (WBC) count, lymphocytes percentage, and Pandy test. The blood test parameters measured the WBC count, C-reactive protein (CRP), procalcitonin, platelet count (PLT), platelet cubic measure distributing width (PCT) disseminated intravascular coagulation (DIC), eosinophilic granulocytes (EOS) percentage, basophilic granulocytes (BASO) percentage, and erythrocyte sedimentation rate (ESR30). The clinical and demographic parameters included age, sex, the duration of illness, headache, fever, coma before admission, night sweats, and cough.

Statistical analysis

Comparisons between TBM and BM on the 34 clinical and laboratory parameters were analyzed using Mann-Whitney U-test for continuous variables and the chi-square test for categorical variables. The categorical

variables are shown as frequency and percentage, while the continuous variables are presented as the mean and interquartile range (IQR). The receiver operating characteristic (ROC) curve was used to analyze the best cutoff values evaluating the specificity and sensitivity of the differential diagnosis between TBM and BM. The diagnostic model was built by logistic regression. P<0.05 was considered significant. All analyses were performed by SPSS.

Results

A total of 191 patients were enrolled in this study, including 145 patients (76%) diagnosed with TBM and 46 patients (24%) diagnosed with BM. All enrolled patients were HIV negative. 145 TBM patients had their diagnosis confirmed by *Mycobacterium tuberculosis* cultures from CSF or NGS. The comparisons between TBM and BM patients in clinical and laboratory parameters are shown in Table 1. Significant differences were found in the following parameters: Coma, Cough, FIB, DIC, ESR30, CRP, Pandy test, WBCBF, PMN, PMN%, ADA, glucose, chloride, CSF protein, WBC, Neutrophils%, Lymphocytes%, BASO%, PLT, and PCT. According to the CSF results, the levels of glucose and chloride were significantly lower in TBM patients than those in BM patients. In contrast, TBM patients had significantly higher levels of total protein and ADA than the BM patients (Figure 1). Multivariable analysis was performed to determine the independent parameters. The result showed 7 variables (Coma, ESR30, FIB, Monocytes %, Lymphocytes %, Neutrophils %, and EOS %) independently correlated with the diagnosis of TBM (Table 2). A ROC curve was performed to analyze the best cutoff for the 7 parameters to diagnose TBM. As showed in Figure 2, when the cutoff value was 0.928, the diagnostic model revealed 93.5% specificity and 89.0% sensitivity.

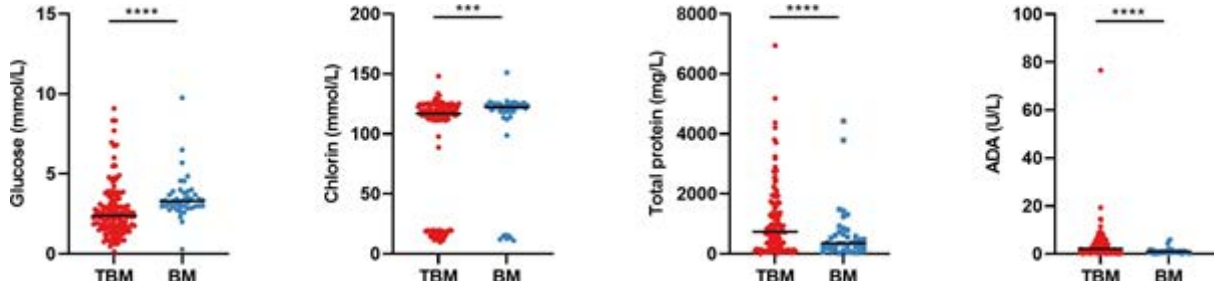

Figure 1. Scatter plots showing the levels of CSF indicators in TBM and BM patients.

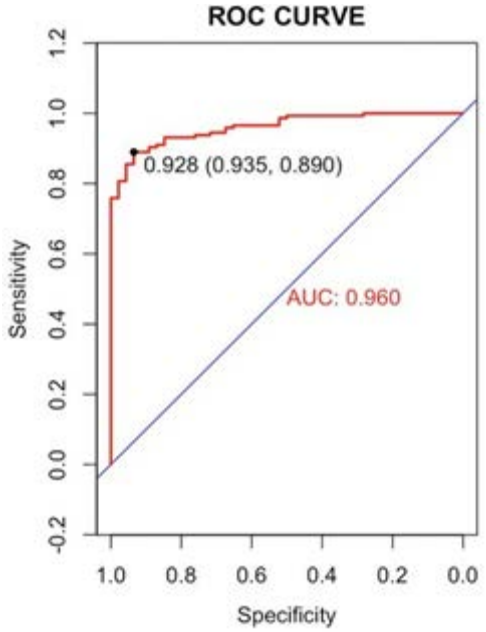

Figure 2. Receiver operating characteristic (ROC) curve for the logistic regression model.

Table 1. Univariate analysis for the comparison of parameters between TBM and BM.

	BM (n=46)	TBM (n=145)	P
	n (%) or Median (IQR)	n (%) or Median (IQR)	
Age	32.5 (24-50)	34 (27-51)	0.250
Male sex	28 (60.9)	98 (67.6)	0.510
Fever	33 (71.7)	116 (80.0)	0.330
Headache	33 (71.7)	106 (73.1)	1.000
Coma	11 (23.9)	60 (41.4)	0.050
Tic	6 (13.0)	12 (8.3)	0.500
Sweat	2 (4.3)	12 (8.3)	0.571
Cough	5 (10.9)	46 (31.7)	0.009
Emesis	19 (41.3)	50 (34.5)	0.507
Pandy test	19 (41.3)	111 (76.6)	<0.001
CSF color	1(2.2)	32(22.1)	0.004
CSF clear	44(95.7)	123(84.8)	0.094
FIB (g/L)	3.38 (2.74-4.22)	4.00 (3.14-4.85)	0.008
DIC (g/mL)	0.41 (0.24-1.13)	1.18 (0.54-2.01)	<0.001
ESR30	12.00 (5.00-29.25)	42.00 (20.00-60.00)	<0.001
CRP (mg/L)	6.15 (1.19-13.13)	14.70 (3.42-51.94)	0.001
Procalcitonin (ng/mL)	0.05 (0.03-0.19)	0.06 (0.04-0.16)	0.054
LDH (U/L)	155.00 (0.00-199.25)	199.00 (0.00-358.00)	0.052
WBCBF (106/L)	37.00 (6.00-144.00)	142.00 (27.00-374.00)	0.222
PMN (106/L)	89.60 (66.70-94.38)	67.90 (31.60-87.80)	<0.001
PMN%	10.40 (5.62-33.30)	32.10 (11.80-68.00)	<0.001
ADA	0.80 (0.20-1.30)	2.20 (0.60-5.40)	<0.001
Glucose (mmol/L)	3.13 (2.88-3.65)	2.25 (1.60-3.06)	<0.001
Chlorin (mmol/L)	122.10 (118.35-124.33)	116.90 (109.60-122.30)	0.006
CSF protein (mg/L)	502.00 (271.50-836.50)	1054.00 (737.00-1750.00)	<0.001
WBC (109/L)	6.16 (5.20-9.30)	7.77 (5.88-10.71)	0.028

Neutrophils%	64.63 (55.95-73.10)	78.30 (66.70-85.50)	<0.001
Lymphocytes%	22.65 (17.10-29.58)	11.30 (7.40-20.90)	<0.001
Monocytes%	9.42 (6.80-11.75)	7.90 (5.60-10.30)	0.067
EOS%	0.70 (0.10-1.67)	0.30 (0.00-1.00)	0.080
BASO%	0.30 (0.20-0.48)	0.20 (0.10-0.40)	0.029
PLT (109/L)	210.00 (168.00-252.75)	279.00 (210.00-334.00)	<0.001
PCT	0.22 (0.19-0.27)	0.27 (0.22-0.32)	<0.001
IQR: Interquartile range.			

Table 2. Multivariate logistic regression analysis to distinguish TBM from BM.

	β-coefficient	Odds ratio (95% CI)	P
ESR30	3.211	1.100 (1.047-1.178)	0.001
FIB	-2.498	0.207 (0.051-0.633)	0.012
Monocytes%	-2.440	0.383 (0.137-0.719)	0.015
Coma	2.290	7.752 (1.493-52.91)	0.022
Lymphocytes%	-2.162	0.437 (0.163-0.812)	0.031
Neutrophils%	-2.097	0.456 (0.172-0.840)	0.036
EOS%	-1.960	0.404 (0.135-0.915)	0.049

Discussion

The diagnosis of TBM is still a challenge that needs to be solved [3,10]. Early diagnosis of TBM can improve the prognosis and reduce disability [11]. Nevertheless, the traditional diagnosis for TBM relies mostly on initial clinical features and subsequent tuberculosis diagnosis from CSF. Certain features of TBM such as the longer duration of symptoms (>6 days), moderate CSF pleocytosis, and low glucose will increase the probability of TBM [12]. However, even with these specific features, it was impossible to diagnose patients without a definitive microbiological test. The detection of *Mycobacterium Tuberculosis* has been considered the gold standard for TBM diagnosis [13]. Due to the low expression level of *Mycobacterium tuberculosis* in CSF, a large volume of CSF is usually required for laboratory tests [14]. Moreover, the sensitivity of microbiologic detection is lower than 40% [15-17]. Although some studies showed the acid-fast stain had a better performance for *Mycobacterium tuberculosis* detection with around 80% sensitivity, the detection was highly associated with the sample volume [18-20]. The traditional laboratory detection methods of *Mycobacterium tuberculosis* are time consuming. With the development of techniques, NGS has been used for TBM diagnosis [7,8,21]. The NGS detection only requires a small volume of CSF and can identify the sequences of *Mycobacterium tuberculosis* with a higher sensitivity [22]. However, NGS detection is expensive, and it usually takes more than 15 days to get the results. Thus, the diagnosis of TBM is difficult and patients cannot be diagnosed in time which will cause a poor prognosis [23]. A new method that is sensitive, low cost, and rapid is urgently needed for the diagnosis of TBM.

More and more studies have tried to distinguish TBM from BM based on clinical and laboratory features. Thwaites. et al performed a study that enrolled 251 patients to build a diagnosis formula for TBM diagnosis. In this study, five parameters (age, neutrophil percentage in CSF, blood white cell count, total CSF white cell count, and disease course) were included in the diagnosis model showing 97% sensitivity and 91% specificity respectively [24]. This diagnostic model was further validated by studies in different countries and showed different performances to distinguish TBM from BM [25-27]. However, the diagnostic model was less effective at diagnosing patients who had been treated [28]. Depending on the region and population, the diagnostic results may differ. Hence, we would like to develop a model using our patients' data to aid in TBM diagnosis in southern of China.

In this study, we compared 145 TBM patients with 46 BM patients on 35 clinical and laboratory features. We found TBM patients had higher levels of DIC, ESR30, CRP, WBCBF, PMN%, ADA, CSF protein, PLT and lower levels of glucose, chloride, and Lymphocytes%. The low level of glucose is a characteristic CSF finding in TBM [3,29]. By using logistic regression, we identified 7 independent parameters for TBM diagnosis, including Coma, ESR30, FIB, Monocytes%, Lymphocytes%, Neutrophils%, and EOS%. The TBM diagnostic model was developed with the above 7 parameters: TDI=DI(ESR30)+DI(Coma)+DI(FIB)+DI(Lymphocytes%)+DI(Monocytes%)+DI(Neutrophils%)+DI(EOS%). We further used a ROC curve to find the best cutoff and the cutoff value of 0.928 revealed the greatest sensitivity (89.0%) and with acceptable specificity (93.5%). The diagnostic model we developed in this study may serve as an indicator for TBM diagnosis.

Conclusion

Therefore, the diagnostic model developed in this study can be used to distinguish TBM patients from BM patients simply and rapidly. This model can be widely used even with limited microbiological facilities. Further validation with patients from different regions will be needed to improve the diagnostic model.

Acknowledgment

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Conflict of Interest

It is declared that there is no conflict of interest.

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