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# Development of clinical-based scoring system to diagnose tuberculous meningitis in children

Setyo Handryastuti, Dianing Latifah, Evita Karianni Bermanshah, Hartono Gunardi, Muzal Kadim, R Adhi Teguh Perma Iskandar

Department of Child Health, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia

**Correspondence to**
Dr Dianing Latifah, Departement of Child Health, University of Indonesia, Depok, Indonesia; dlatifah@hotmail.com

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## ABSTRACT

**Objective** Diagnosing tuberculous meningitis (TBM) in children is challenging due to the low sensitivity with time delay of bacterial culture techniques and the lack of brain imaging facilities in many low- and middle-income settings. This study aims to establish and test a scoring system consisting of clinical manifestations on history and examination for diagnosing TBM in children.

**Design** A retrospective study was conducted using a diagnostic multivariable prediction model.

**Participants** 167 children diagnosed with meningitis (tuberculous, bacterial, viral and others) aged 3 months to 18 years who were hospitalised from July 2011 until November 2021 in a national tertiary hospital in Indonesia.

**Results** Eight out of the 10 statistically significant clinical characteristics were used to develop a predictive model. These resulted in good discrimination and calibration variables, which divided into systemic features with a cut-off score of ≥3 (sensitivity 78.8%; specificity 86.6%; the area under the curve (AUC) value 0.89 (95% CI 0.85 to 0.95; p<0.001)) and neurological features with a cut-off score of ≥2 (sensitivity 61.2%; specificity 75.2%; the AUC value 0.73 (95% CI 0.66 to 0.81; p<0.001)). Combined together, this scoring system predicted the diagnosis of TBM with a sensitivity, specificity and positive predictive value of 47.1%, 95.1% and 90.9%, respectively.

**Conclusion** The clinical scoring system consisting of systemic and neurological features can be used to predict the diagnosis of TBM in children with limited resource setting. The scoring system should be assessed in a prospective cohort.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tuberculous meningitis (TBM) is a severe form of tuberculosis, which causes high morbidity and mortality in children.
⇒ There are scoring systems consist of advanced parameters, such as cerebrospinal fluid (CSF) analysis and brain imaging, some routinely used to diagnose TBM in adult.
⇒ Scoring system that consist of simple parameters has not established yet, especially for children.

### WHAT THIS STUDY ADDS

⇒ This study provides demographic and clinical characteristics of children diagnosed with TBM in a referral hospital of Indonesia.
⇒ This study adds simple aid to diagnose TBM in children using basic and uncomplicated examinations as its parameters.
⇒ This study's scoring system might be useful in a setting with lack of clinical resource like in developing countries, such as Indonesia with its geographical challenge.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Further research comparing this study's scoring system with culture or Xpert MTB/RIF of cerebrospinal fluid in larger sample could be conducted to optimise the power.
⇒ Since this scoring system needs thorough anamnesis and examination specifically neurological signs, clinical practitioner may diagnose TBM earlier to prevent its mortality and/or morbidity.
⇒ This study might advocate government to supply basic or even advanced clinical test to diagnose childhood TBM in rural/remote area.

## INTRODUCTION

Globally, children with tuberculous meningitis (TBM) are estimated to account for 1–2% of all active tuberculosis (TB) cases. This severe form of TB causes high morbidity and mortality in children.[1 2] There are substantial challenges in managing TBM, including the poorly understood pathogenesis of the disease and diagnostic difficulties. Fast, sensitive and affordable tools to diagnose TBM are unavailable. There are varied methods used in many clinical trials of the TBM therapy.[2 3] The gold standard for diagnosing TBM is based on the culture of *Mycobacterium tuberculosis* from cerebrospinal fluid (CSF).[3] However, not every health facility has culture examination, and there are time delays and low sensitivity, and in many health facilities rapid molecular tests (GeneXpert) to test CSF are also as yet unavailable, and these too have limited sensitivity. It is often necessary to send specimens to higher facilities with advanced laboratory equipment and inevitably extend the time to diagnose or ruling out TBM.

Several studies developed scoring systems, including the Thwaites,[3] Lancet consensus[1] and Modified Kenneth Jones Scoring Criteria (MKJSC),[4] designed to diagnose TBM. These scoring systems require advanced examination, such as CSF analysis, culture and brain imaging. Our study aimed to create a scoring system based on clinical symptoms and simple examination. It can be used in peripheral areas with no advanced laboratory facilities to



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diagnose TBM faster, provide appropriate therapy and potentially improve the outcomes for children.

## METHODS

This was a retrospective study using a multivariable prediction model approach. Inclusion criteria were paediatric patients aged 3 months to 18 years hospitalised with a diagnosis of TBM or non-TBM from history, physical examination, blood work, chest X-ray imaging, CSF analysis and head CT/MRI examination. The exclusion criteria were patients with congenital hydrocephalus, leg paresis due to hypokalemia, other brain parenchymal lesions such as tumours, vascular malformation or intracranial haemorrhage, and history of trauma.

Using the inclusion criteria, the medical record data were accessed through an electronic database using the keyword meningitis G00-09 based on the ICD-10 administration coding. The subjects were recruited using consecutive purposive sampling from 1 July 2011 to 30 October 2021 in a national tertiary hospital. Subsequently, their medical records were open to collect the data. The demographic, illness symptoms and neurological examination were recorded from the patients' medical record.

Laboratory data, including complete blood count, electrolyte levels, erythrocyte sedimentation rate (ESR) and chest radiograph, were obtained from medical record data. Meanwhile, CSF analysis, gram stain and culture, with the contrasting head CT scan/MRI, were the diagnostic standards of subjects. The variables proposed to differentiate TBM and non-TBM were the length of the prodromal illness, systemic symptoms of TB (prolonged fever, recurrent or chronic cough, anorexia, weight loss), vomiting, headache, seizures, contact with adult TB, BCG unvaccinated, immunocompromised status, decrease of consciousness, bulging fontanelle, presence of meningeal sign, cranial nerve palsy, hemiparesis, involuntary movement, hyponatremia and pulmonary TB finding in a chest X-ray. These 16 variables were taken from several published studies[5–8] that identified TBM features in a cohort of patients.

The rule-of-thumb formula was used since there are no accepted approaches to estimating the sample size requirements for development and validation studies of diagnostic prediction models. The rule suggests to have at least 10 outcome events per parameter or variables tested.[9] From 16 variables proposed to have some relationship with TBM, the minimum sample size was estimated as 160. The data were analysed with the Statistical Package for the Social Sciences (SPSS) V.22 statistical programme, while the clinical parameters and examinations were calculated using bivariate analysis. All variables having $p<0.25$ proceeded in multivariate analysis using multiple logistic regression. Variables with p value $<0.05$ were included as independent diagnostic predictors in the scoring parameters. The score for each parameter is determined based on the value of t-statistic (resulted from regression β coefficient divided with SE, with values rounded to the nearest whole number). The cut-off point for the total score determined the optimal value of the scoring system's sensitivity and specificity. Finally, the area under the curve (AUC) was calculated to measure the discrimination or predictive value.

## RESULTS

A total of 229 patients were diagnosed with meningitis in this study. Several subjects were excluded because 28 had an inappropriate final diagnosis, 33 had incomplete medical record data and 1 was a duplicated subject. Criteria to determine TBM from head CT scan were the presence of basal meningeal enhancement and/or hydrocephalus. Since the culture of TB from CSF sample was not done regularly in every patient, low CSF glucose and/or low CSF-serum glucose ratio with predominant mononuclear (MN) cells of CSF used as the criteria to determine TBM. Therefore, the subjects analysed were 167, with the distribution of characteristics seen in table 1.

**Table 1** Characteristics of the study subjects

| Variables | TBM (n=85) | Non-TBM (n=82) |
|---|---|---|
| Age, n (%) | | |
| <5 years | 54 (63.5) | 55 (67.1) |
| 5–12 years | 16 (18.9) | 16 (19.5) |
| 12–18 years | 15 (17.6) | 11 (13.4) |
| Gender n (%) | | |
| Male | 44 (51.7) | 52 (63.4) |
| Female | 41 (48.3) | 30 (36.6) |
| Complete blood count | | |
| Haemoglobin, mean±SD | 10.9 ± 1.9 | 11 ± 2.3 |
| Leucocytes, median (range) | 13 100 (1730–32 990) | 14 575 (1700–47290) |
| Neutrophils, mean±SD | 67.2 ± 17.3 | 64.2 ± 17.2 |
| Erythrocyte sedimentation rate, n (%) | 11 (12.9) | 10 (12.2) |
| Electrolyte levels | | |
| Sodium, median (range) | 131.5 (117–146) | 135 (106–152) |
| Potassium, median (range) | 4.2 (2.3–6.6) | 4.1 (1.7–7.6) |
| Chloride, median (range) | 98.1 (81.1–116) | 102 (7.9–129) |
| CSF analysis | | |
| Clear CSF fluid, n (%) | 52 (68.4) | 40 (65.6) |
| CSF cells count, median (range) | 101.5 (1–1800) | 39 (1–7772) |
| CSF PMN cells, median (range) | 28.5 (0–1209) | 10 (0–5209) |
| CSF MN cells, median (range) | 57 (0–1620) | 22 (0–4537) |
| CSF protein, median (range) | 117 (5–3190) | 52.5 (2–2340) |
| CSF glucose, median (range) | 43 (6–124) | 68 (2–377) |
| Head imaging, n (%) | | |
| Brain infarct | 16 (20.3) | 2 (8.6) |
| Hydrocephalus | 52 (65.0) | 5 (14.3) |
| Enhancement of basal cistern | 53 (66.3) | 9 (25.7) |
| Tuberculoma | 8 (10.1) | 0 (0) |
| Outcome, n (%) | | |
| Alive | 62 (72.9) | 69 (84.1) |
| Dead | 23 (27.1) | 13 (15.9) |

CSF, cerebrospinal fluid; MN, mononuclear; PMN, polymorphonuclear; TBM, tuberculous meningitis.

A total of 16 clinical variables were recorded from the history and physical examination, and simple investigations were performed using bivariate analysis to determine their relationship with TBM. Bivariate analysis on continuous data used the independent t-test technique, while the categorical data used the $\chi^2$ technique. The bivariate analysis of symptom variables from the anamnesis, as seen in table 2, showed that TB systemic symptoms, prodromal duration ≥10 days, presence of TB contact and absence of BCG vaccine were the variables related to TBM occurrence ($OR>1$; $p<0.05$). Meanwhile, the bivariate analysis of the physical examination variables in table 3 shows that the low Glasgow Coma Scale (GCS) score, positive meningeal excitatory signs, cranial nerve palsy and hemiparesis were related to TBM occurrence ($OR>1$; $p<0.05$). The ESR analysis could not be performed because many subjects were not tested. Based on

**Table 2** Bivariate analysis of symptoms/anamnesis

| Variables | TBM (n=85) | Non-TBM (n=82) | P value | OR (95% CI min to max) |
|---|---|---|---|---|
| Prodromal duration ≥10 days, n (%) | 62 (72.9) | 22 (26.8) | <0.001 | 7.35 (3.71 to 14.57) |
| Systemic symptoms of TB, n (%) | 73 (85.9) | 21 (25.6) | <0.001 | 17.7 (8.05 to 38.8) |
| Vomiting, n (%) | 40 (47.1) | 34 (41.5) | 0.46 | 1.25 (0.68 to 2.231) |
| Cephalgia, n (%) | 34 (40) | 27 (32.9) | 0.34 | 0.72 (0.73 to 2.55) |
| Seizure, n (%) | 55 (64.7) | 67 (81.7) | 0.013 | 0.41 (0.2 to 0.84) |
| Presence of TB contacts, n (%) | 32 (37.6) | 4 (4.9) | <0.001 | 11.77 (3.93 to 35.24) |
| No BCG vaccinated, n (%) | 26 (32.9) | 10 (12.7) | 0.002 | 3.05 (1.45 to 6.38) |
| Immunocompromise, n (%) | 5 (5.9) | 2 (2.4) | 0.27 | 2.5 (0.47 to 13.26) |

TB, tuberculosis; TBM, tuberculous meningitis.

**Table 3** Bivariate analysis of physical signs/examination

| Variables | TBM (n=85) | Non-TBM (n=82) | P value | OR (95% CI min to max) |
|---|---|---|---|---|
| Moderate-severe level in the decrease of consciousness, n (%) | 50 (58.8) | 30 (36.6) | 0.004 | 2.47 (1.33 to 4.62) |
| Bulging fontanelle, n (%) | 11 (12.9) | 13 (15.9) | 0.59 | 0.79 (0.33 to 1.87) |
| Positive sign of meningeal stimulation, n (%) | 52 (61.2) | 28 (34.1) | <0.001 | 3.04 (1.62 to 5.71) |
| Cranial nerve palsy, n (%) | 23 (27.1) | 6 (7.3) | 0.001 | 4.7 (1.8 to 12.6) |
| Hemiparesis, n (%) | 20 (23.5) | 8 (9.8) | 0.017 | 2.85 (1.18 to 6.89) |
| Involuntary movements, n (%) | 10 (11.8) | 10 (12.2) | 0.93 | 0.96 (0.37 to 2.44) |

TBM, tuberculous meningitis.

bivariate analysis, leucocytosis and hyponatremia were variables related to TBM occurrence (p<0.05). The diagnostic examination of chest X-ray was significant with TBM (OR 31.9 (95% CI 4.2 to 242.1), p<0.001) (table 4).

All variables from symptoms, signs and workup examinations with p value <0.25 were selected in multivariate analysis to obtain the final score and internal validation. Sodium levels and blood leucocytes were not included in the further analyses due to literature review and clinical considerations. This study conducted a multivariate analysis using a binary logistic regression model with the backward Wald logistic regression method. The significant variables included were prodromal illness duration ≥10 days, systemic symptoms of TB, presence of TB contacts and the pulmonary TB on chest X-ray findings (p value <0.05) shown in table 5 as the systemic components. Meanwhile, the final variables produced for neurological part were GCS score ≤12, a positive sign of meningeal stimulation, cranial nerve palsy, and hemiparesis, as shown in table 6.

To determine the validity of the scoring system, internal validity was measured by comparing the CIs from the multivariate analysis of the original and re-sampling data using the bootstrapping method. This study used the AUC (receiver operating characteristic (ROC) analysis) to analyse the discrimination ability and sought the probability intersection of the total score to assess the quality of the final model scoring system. From these calculations, the cut-off point for the total score ≥3 on the systemic scoring parameter had sensitivity and specificity values of 78.8% and 86.6%, respectively. The curve shows that the AUC value of the total systemic score as a diagnostic predictor of TBM is 0.89 (95% CI 0.85 to 0.95; p<0.001), as shown in figure 1. The cut-off point for the total score ≥2 on the neurological scoring parameter had sensitivity and specificity values of 61.2% and 75.2%, respectively. The curve shows that the AUC value of the total neurological score as a diagnostic predictor of TBM is 0.73 (95% CI 0.66 to 0.81; p<0.001), as shown in figure 2. Therefore, the final model of the scoring system can be seen in table 7.

A comparison of scoring system matrices against diagnoses on existing data (using a 2×2 probability table) was done to prove the prediction of TBM diagnosis. The systemic and neurological scores of the subject meet the minimum total score of ≥3 and ≥2, respectively. This resulted in a sensitivity of 47.1%, a specificity of 95.1%, a positive predictive value of 90.9% and a negative predictive value of 63.4%. These results showed low sensitivity but very high specificity when the scoring parts meet the threshold values.

**Table 4** Bivariate analysis of workup examination

| Variables | TBM (n=85) | Non-TBM (n=82) | P value | OR (95% CI min to max) |
|---|---|---|---|---|
| Haemoglobin, mean±SD | 10.9±1.9 | 11±2.3 | 0.87 | – |
| Leucocytes, median (range) | 13 100 (1730–32 990) | 14 575 (1700–47 290) | 0.03 | – |
| Sodium, median (range) | 131.5 (117–146) | 135 (106–152) | 0.01 | – |
| Potassium, median (range) | 4.2 (2.3–6.6) | 4.1 (1.7–7.6) | 0.23 | – |
| Positive chest X-ray findings of pulmonary TB, n (%) | 24 (28.2) | 1 (1.2) | <0.001 | 31.9 (4.2 to 242.1) |

TB, tuberculous; TBM, tuberculous meningitis.

**Table 5** TBM systemic scoring system

| Parameters | P value | β | SE | Score simplification |
|---|---|---|---|---|
| Prodromal duration ≥10 days | 0.004 | 1.340 | 0.466 | 1 |
| Systemic symptoms of TB | <0.001 | 2.301 | 0.696 | 2 |
| Presence of TB contact | 0.001 | 2.425 | 0.494 | 1 |
| Pulmonary TB chest X-ray findings | 0.005 | 3.349 | 1.203 | 1 |

TB, tuberculous; TBM, tuberculous meningitis.

## DISCUSSION

This study showed that the proposed new scoring system could predict the diagnosis of TBM in children. From subject characteristics, the age group <5 years had the highest number with 109 (65.3%) patients, while those aged >12 years had the smallest at 26 (15.5%) patients, with a similar proportion between two groups. These data were comparable with other studies by Dodd *et al*[10] and Daniel *et al*,[11] which showed that children <5 years old were vulnerable to meningitis. In post-hospitalisation outcomes, 36 patients died, with the highest mortality over 23 (27%, n=85) in the TBM group. High mortality rate in TBM group was expected because this study was conducted in a national tertiary hospital, which often received referral patient with advanced stage presentations of the ongoing disease. Another systematic review also showed treatment outcome in 1636 children with TBM-resulted estimation at 19.3% mortality.[12]

This study analysed the relationship of the variables with the diagnosis using bivariate analysis and resulted in 12 as potential predictors of TBM. Bang *et al*[13] found potential predictors of mortality and neurological sequelae, such as convulsion, decreased consciousness and focal neurological deficit. Since this study aimed to devise a clinical scoring system that relied on thorough history taking and physical examination, also reflect on Indonesia peripheral areas which have limited resource mostly just routine blood count and X-ray available, potential predictor hyponatremia from laboratory examination was dropped. Studies showed various results of leucocyte count between TBM and non-TBM, mostly normal or slightly increased due to the increased polymorphonuclear leucocyte and macrophage as a part of immune defence mechanism.[3 7 14] Therefore, leucocytosis was removed from the potential predictors list. After undergoing multivariate analysis, the scoring system final model was validated using the bootstrapping method. Divided into two parts, systemic and neurological, the score variables are expected to assist clinicians finding specific signs and symptoms from the first examination of the patients.

There are widely known scoring systems used in adults to diagnose TBM. An early score was devised by Marais *et al*[1] known as the uniform case definition. Besides the clinical manifestations of symptoms and signs, it included advanced workup examination such as CSF criteria from a lumbar puncture, head imaging criteria in the form of contrast CT/MRI also CT/MRI/ultrasound evidence for TB outside the CNS. The second scoring system was a study by Thwaites *et al*[3] designed to distinguish TBM and bacterial meningitis, which comprised clinical manifestations of symptoms and signs, component of CSF analysis workup, without the need for head imaging.

**Table 6** TBM neurological scoring system

| Parameters | P value | β | SE | Score simplification |
|---|---|---|---|---|
| GCS score ≤12 (moderate-severe) | 0.012 | 0.855 | 0.349 | 1 |
| Positive sign of meningeal stimulation | 0.013 | 0.774 | 0.348 | 1 |
| Cranial nerve palsy | 0.007 | 1.387 | 0.518 | 2 |
| Hemiparesis | 0.068 | 0.869 | 0.489 | 1 |

TBM, tuberculous meningitis.

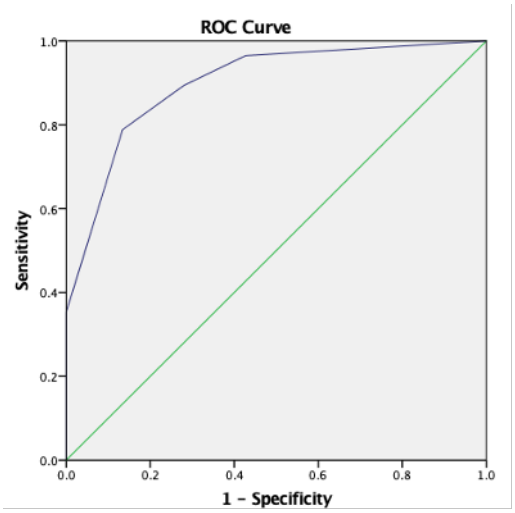


**Figure 1** The final model ROC curve of the systemic scoring part.

Several studies built scoring system to identify or manage TBM in children. The MKJSC criteria were used to diagnose pulmonary TB in children and studied by Anwar *et al*.[4] Even though the sensitivity and specificity of MKJSC were calculated to be 93.6% and 88.6%, the scoring criteria lacked neurological parameters of TBM. The study by Lee *et al*[14], designed to differentiate TBM and viral meningitis, constructed a weighted scoring system with predictive factors comprised of hyponatremia, CSF lactate dehydrogenase (LDH)>70 µ/L, CSF protein >160 mg/dL, cranial nerve palsy, voiding difficulty and convulsion. Saitoh *et al*[15] developed a novel TBM acute neurological scoring system that predicted severe neurological sequelae only using weighted scores on the variables without proceeded in univariate and multivariate analysis, therefore the quality of the assessed variables are subject to observer bias. The scoring system by Marais *et al*[1] has been applied and analysed in paediatric patients by Solomons *et al*.[16] The uniform case definition performed well

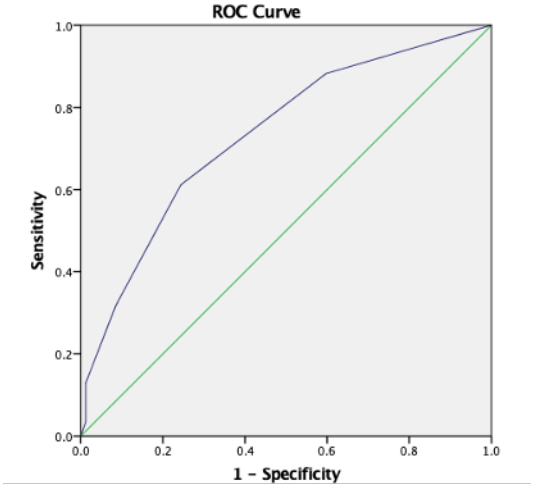


**Figure 2** The final model ROC curve of the neurological scoring part.

**Table 7** The final model of the scoring system

| Criteria | Score |
|---|---|
| Systemic | |
| Prodromal duration ≥10 days | 1 |
| Systemic symptoms of TB | 2 |
| Presence of TB contact | 1 |
| Pulmonary TB chest X-ray findings | 1 |
| Neurological | |
| GCS score ≤12 (moderate-severe) | 1 |
| Positive sign of meningeal stimulation | 1 |
| Cranial nerve palsy | 2 |
| Hemiparesis | 1 |

TB, tuberculous.

when using a 'probable' TBM score to differentiate childhood TBM and bacterial meningitis. However, using these scoring systems will be challenging because of more complex workup components required. Most small hospitals and health centres lack medical personnel with expertise of lumbar puncture in children, laboratory capabilities in CSF analysis and culture is limited or non-existent, as are imaging facilities such as CT scan or head MRI with contrast.

In order to use the scoring system we developed, the minimum total score of systemic ≥3 and neurological ≥2 must be fulfilled separately. The total overall score was not useful for this scoring system because it may cause bias if the total score reached from one part only, whether systemic or neurological. The lower sensitivity in this study can be a challenge to its usage in larger population. But with high specificity, patients whose score meets the criteria were expected to initiate TBM treatment in time, with additional corticosteroid treatment to potentially reduce mortality and neurological sequelae.[17 18] Then patients can be referred to advanced facilities to confirm their TBM diagnosis, while continuing the treatment. This strategy is suitable in Indonesia where an uneven distribution of general paediatricians is present in a dispersed archipelago country.

Concerning the limitations of this study, CSF culture to obtain *M. tuberculosis* has not been routinely performed on every working diagnosis of TBM. This gold standard cannot be compared with the constructed scoring system. This study used a retrospective study design which creates a possibility of bias in the accuracy of recording medical records and the possibilities of under-reported clinical features. Continuing this study, the external validity work still in ongoing progress using multicentre hospital and larger subjects to evaluate the scoring system in a prospective cohort. Further analyses using the microbiological gold standard from CSF samples to diagnose TBM and non-TBM using larger sample and prospective design to determine higher power of the scoring system are still needed.

From the pathophysiology specifically produced by *M. tuberculosis* infection, a good history and physical examination, particularly neurological, can be performed to establish a distinct working diagnosis. A high specificity is needed for a tool in diagnosing disease. This study was the first to analyse clinical parameters resulting in a scoring system model to identify TBM in children. This scoring system is expected to be a stepping point in diagnosing TBM in low-resource setting.

## CONCLUSION

The scoring system can predict the diagnosis of TBM in children with a sensitivity and specificity of 47.1% and 95.1%, respectively. The systemic and neurological scoring has a cut-off point score of ≥3 and ≥2, respectively. The scoring system is easy and simple to use and may benefit in a setting with lack of clinical resource.

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**Patient consent for publication** Not applicable.

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**Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary information.



**ORCID iDs**
Dianing Latifah http://orcid.org/0000-0003-4922-5764
R Adhi Teguh Perma Iskandar http://orcid.org/0000-0002-5776-9692

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