Treatment Outcomes of Childhood Tuberculous Meningitis in a Real-World Retrospective Cohort, Bandung, Indonesia

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We retrospectively evaluated clinical features and outcomes in children treated for tuberculous meningitis (TBM) at Hasan Sadikin Hospital, Bandung, Indonesia, during 2011–2020. Among 283 patients, 153 (54.1%) were <5 years of age, and 226 (79.9%) had stage II or III TBM. Predictors of in-hospital death (n = 44 [15.5%]) were stage III TBM, hydrocephalus, male sex, low-income parents, seizures at admission, and lack of bacillus Calmette-Guérin vaccination. Predictors of postdischarge death (n = 18 [6.4%]) were hydrocephalus, tuberculoma, and lack of bacillus Calmette-Guérin vaccination. At treatment completion, 91 (32.1%) patients were documented to have survived, of whom 33 (36.3%) had severe neurologic sequelae and 118 (41.7%) had unknown outcomes. Predictors of severe neurologic sequelae were baseline temperature ≥38°C, stage III TBM, and baseline motor deficit. Despite treatment, childhood TBM in Indonesia causes substantial neurologic sequelae and death, highlighting the importance of improved early diagnosis, better tuberculosis prevention, and optimized TBM management strategies.

Tuberculosis (TB) is a major global health problem, and an estimated 1.2 million new pediatric cases and 230,000 deaths occurred in children <15 years of age in 2019 (*1*). Tuberculous meningitis (TBM) is the most severe manifestation of TB, leading to high rates of childhood TBM mortality, at an average of 19%, and neurodisability in >50% of survivors, even when treatment is provided (*2*). After infection with *Mycobacterium tuberculosis*, children <2 years of age are at the highest risk for progression to miliary TB and TBM, most likely because of their immature immune systems (*3*). Childhood and adolescent TB has historically been neglected (*4*,*5*); however, recently this condition has begun to gain priority as a focus of global collaborative efforts toward ending TB in children and adolescents (*6*).

The most important predictors of favorable outcome in childhood TBM are early diagnosis and immediate initiation of treatment (*2*). However, incomplete understanding of the pathogenesis, nonspecific symptoms, suboptimal performance of diagnostic tests, and the paucibacillary nature of the disease often result in a lengthy process of obtaining a definite diagnosis (*7*–*9*). Moreover, antimicrobial therapy as currently recommended by the World Health Organization (WHO) for the management of childhood TBM remains suboptimal (*9*,*10*) and most likely contributes to poor outcomes. Summary estimates of neurologic sequelae and death associated with childhood TBM have been described in a meta-analysis, but predictors of these poor outcomes other than diagnosis in the most advanced disease stage were reported to have high heterogeneities across studies (*2*). Data on clinical features and treatment outcomes of childhood TBM from large cohorts of children outside of South Africa are limited (*11*–*13*). In settings in Indonesia, a few small studies have reported clinical outcomes of childhood TBM (*14*–*16*), but none have explored factors associated with the outcomes. This characterization is clinically relevant, enabling early and targeted interventions to optimize care

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DOI: https://doi.org/10.3201/eid2803.212230

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in this vulnerable population. In this context, our study aimed to assess clinical features of childhood TBM and to evaluate factors associated with poor outcomes, including in-hospital death, postdischarge death, and neurologic sequelae.

Methods

Patients and Setting

This real-world retrospective cohort study consecutively included children <15 years of age treated for TBM at the Department of Child Health of Hasan Sadikin Hospital, a national tertiary teaching hospital in Bandung, Indonesia, during January 2011–December 2020. The study was approved by the Independent Ethics Committee of Hasan Sadikin Hospital (approval no. LB.02.01/X.6.5/91/2021). Because of the retrospective nature of the study design, the Ethics Committee waived the need for written informed consent.

Diagnosis

We established TBM diagnosis on the basis of clinical, laboratory, and radiologic findings (*17*), combining medical history, physical and clinical examinations, tuberculin skin test, chest radiography, cerebrospinal fluid (CSF) analysis, and neuroimaging by using computed tomography (CT) scan. We performed microbiologic examination of CSF and non-CSF samples, including smear microscopy for acid-fast bacilli (AFB), culture for *M. tuberculosis*, and Xpert MTB/RIF assay, depending on sample availability. We assessed diagnostic certainty of definite, probable, or possible TBM by using uniform case definition criteria for TBM research (*18*) (Appendix Table 1, https://wwwnc.cdc.gov/EID/article/28/3/21-2230-App1.pdf). We presumed that patients had drug-susceptible TBM unless drug resistance was proven in Xpert MTB/RIF or drug-susceptibility testing. We excluded TBM patients with drug-resistant TB from the study.

Treatment

We based treatment regimens on the 2010 WHO guidelines in accordance with the Indonesian Paediatric Society guidelines for TBM treatment in children, consisting of daily isoniazid at 10 mg/kg (range 7–15 mg/kg), rifampin at 15 mg/kg (range 10–20 mg/kg), pyrazinamide at 35 mg/kg (range 30–40 mg/kg), and ethambutol at 20 mg/kg (range 15–25 mg/kg) for a 2-month intensive phase, followed by a 10-month continuation phase with isoniazid and rifampin at the same doses (*17*,*19*). We administered all anti-TB drugs orally as fixed-dose combination or single-drug formulation tablets, where available. Patients received facility-based directly observed therapy (DOT) during hospitalization. After discharge, patients received home-based DOT under the supervision of parents or other family members. Most patients received adjunctive oral prednisone (2–4 mg/kg/d) for the first 4–8 weeks, tapered according to the national guidelines (*17*). We treated patients with increased intracranial pressure with hypertonic saline or mannitol 20% (0.5–1 g/kg) every 8 hours. We performed ventriculoperitoneal shunt or extraventricular drain placements in patients with obstructive hydrocephalus, at the discretion of the neurosurgical team.

Data Collection

We collected individual patient data from hospital registry in a predefined form and appropriately deidentified the data before analysis. These data were demographic information (age, sex, parents' education and income, area of living, and length of hospital admission); medical history (HIV infection, bacillus Calmette-Guérin [BCG] vaccination, and TB contact history); clinical characteristics (symptoms of TBM, vital signs, nutritional status, physical and neurologic examinations, tuberculin skin test, Glasgow coma scale [GCS], and TBM staging); laboratory findings (CSF analysis, AFB microscopy, mycobacterial culture, and Xpert MTB/RIF test); radiographic findings (chest radiograph and neuroimaging); and other supporting data (corticosteroid therapy and in-hospital complications).

Definitions

We developed operational definitions for all variables (Appendix Table 2). We defined definite TBM as microbiologic confirmation of CSF and probable TBM as a total diagnostic score of ≥12 when neuroimaging was available or ≥10 when neuroimaging was unavailable. We defined possible TBM as a total score of 6–11 when neuroimaging was available or 6–9 when neuroimaging was unavailable (*18*). We classified TBM staging according to the modified British Medical Research Council grading system (*20*), as follows: stage I, GCS 15 without focal neurologic deficit; stage II, GCS 11–14, or 15 with focal neurologic deficit; and stage III, GCS ≤10. Patients with known BCG vaccination included those who had a documented vaccination history at hospital admission or had a BCG scar in the deltoid region of the upper arm. Motor deficits included hemiparesis, quadriparesis, and diplegia. Other neurologic deficits were signs of upper motor neuron lesion and cranial nerve palsies. We performed motor,

hearing, visual, and neurodevelopmental function assessments at treatment completion as indicated by the attending physicians (Appendix).

Outcomes

Outcomes of hospitalization were recovery (with or without disability), nonrecovery (persistent vegetative state and discharge against medical advice), and death. After 12 months of treatment, we reported the following outcomes: treatment completion, death, and lost to follow-up (LTFU; i.e., patients who stopped treatment for ≥2 consecutive months). "Not evaluated" or "unknown treatment outcome" categories were patients who were transferred back to regional public hospitals or community health clinics for follow-up after discharge. We defined survival as being alive at treatment completion and neurologic sequelae as any motor, hearing, visual, or neurodevelopmental impairment that appeared during the illness and persisted through treatment completion.

Data Analysis

We evaluated associations of patient characteristics with poor outcomes. First, we compared patients who died during hospitalization (in-hospital death) with those who had recovered at the time of discharge; this definition excluded persistent vegetative state and discharge against medical advice. Second, we compared patients who died after discharge (postdischarge death) with those who completed treatment, regardless of their sequelae status; this definition excluded LTFU and unknown outcomes. Third, we compared survivors with neurologic sequelae with those without sequelae; this definition excluded death, LTFU, and unknown outcomes.

We used Cox proportional-hazards regression analysis to assess predictors of in-hospital death. We calculated time to death on the basis of length of stay by subtracting day of admission from day of death. Most patients were discharged within 2 months of hospitalization; in this case, we assumed that recovering patients (with or without disability) discharged before 2 months were alive until the end of 2 months, and thus we censored these patients in the Cox regression analysis. Because the time to death after discharge was not recorded, we assessed associated factors with postdischarge death and neurologic sequelae by using logistic regression analysis. We adjusted our multivariate models for age, sex, and TBM staging, and completed the models with variables showing a trend toward association in univariate analysis. We selected these variables by using backward deletion, and the final models retained all additional variables with a p value <0.1. For logistic regression analysis, we evaluated the goodness-of-fit of the final models by using Hosmer-Lemeshow test and performance by the area under the receiver operating characteristic curve. For Cox regression analysis, we checked proportional hazards assumption using Kaplan-Meier curve before fitting the model, and using log-minus-log survival curve after fitting the model. We used adjusted hazard ratios (aHRs) for Cox regression models and adjusted odds ratios (aORs) for logistic regression models, as well as 95% CIs, to estimate the association between explanatory variables and outcomes. We defined statistical significance as $p<0.05$. We performed all analyses by using IBM SPSS Statistics 26.0 (https://www.ibm.com).

Results

Clinical Characteristics

During the study period (2011–2020), 286 children with TBM were treated at Hasan Sadikin Hospital; 3 patients with rifampin-resistant TB were excluded. No patients had concurrent bacterial meningitis. Among 283 included patients, 150 (53.0%) were boys, 153 (54.1%) were <5 years of age, 183 (64.7%) were malnourished, 226 (79.9%) had stage II or III TBM, and 51 (18.0%) had definite TBM. At admission, most patients had history of fever (88.3%), decreased consciousness (74.6%), and seizures (55.0%); the next most common signs and symptoms were weight loss (37.6%), persistent cough (33.7%), muscle weakness (26.3%), and severe headache (21.9%). These signs and symptoms had existed for >5 days before admission in 87.0% of patients (Table 1). We stratified manifestations by disease staging (Appendix Table 3).

In CSF analysis, most patients had pleocytosis (>10 cells/μL, 76.8%), and lymphocytic predominance (>50%, 81.8%), followed by a low CSF-to-plasma glucose ratio (<0.5, 54.8%), elevated protein level (>100 mg/dL, 51.8%), and hypoglycorrhachia (<40 mg/dL, 41.6%). *M. tuberculosis* susceptible to rifampin was identified by Xpert MTB/RIF assay in 48 (34.3%) of 140 CSF samples and in 76 (33.9%) of 224 non-CSF samples. In neuroimaging, most patients had basal meningeal enhancement (52.4%), followed by hydrocephalus (41.2%), tuberculoma (12.4%), and infarct (10.0%) (Table 2). Among 103 patients with hydrocephalus, 45 (43%) received neurosurgical intervention: 44 (97.8%) ventriculoperitoneal shunt and 1 (2.2%) extraventricular drain.

For in-hospital complications, 106 (37.5%) of the 283 patients had motor disorders, 37 (13.1%) had neurodevelopmental delay, 19 (6.7%) had epileptic

seizures, 17 (6.0%) had visual impairment, 12 (4.2%) had hearing impairment, and 27 (9.5%) had anti-TB drug-induced hepatotoxicity. Adjunctive oral corticosteroid was administered to 262 (92.6%) of patients. In addition, 1 of the patients (a 6-month-old boy with stage II TBM) had severe acute respiratory syndrome coronavirus 2 coinfection (Appendix).

In-Hospital Death

Upon discharge, 231 (81.6%) of 283 patients had recovered (with or without disability), 3 (1.1%) had a persistent vegetative state, and 5 (1.8%) were discharged against medical advice. The remaining 44 (15.5%) died; median time to death was 7 days (interquartile range 3–13 days) after admission (Table 3).

We performed univariate (Appendix Table 4) and multivariate (Table 4) analyses of risk for in-hospital death. In multivariate analysis, factors associated with increased risk were stage III TBM (aHR 5.96 [95% CI 1.39–25.58]), hydrocephalus (aHR 2.32 [95% CI 1.13–4.79]), male sex (aHR 2.10 [95% CI 1.09–4.05]), low-income parents (aHR 2.59

Table 1. Demographic and clinical characteristics at admission of children with TBM treated at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020*

	Total patients		<5 y		5–14 y	
Characteristic	No.†	Value	No.†	Value	No.†	Value
Age, y , median (IQR)	283	4.0 (1.0; 10.0)	153	1.0 (0.7–2.4)	130	10.2 (8.0–12.2)
Sex						
M	283	150 (53.0)	153	74 (48.4)	130	76 (58.5)
F	283	133 (47.0)	153	79 (51.6)	130	54 (41.5)
Nutritional status‡						
WFAZ, median (IQR)	227	−2.2 (−3.0 to −1.0)	153	−1.9 (−2.9 to −0.7)	74	−2.5 (−3.2 to −1.7)
HFAZ, median (IQR)	283	−1.6 (−2.6 to −0.3)	153	−1.6 (−2.8 to −0.7)	130	−1.6 (−2.5 to −0.4)
BFAZ, median (IQR)	283	−2.1 (−3.2 to −0.4)	153	−1.7 (−2.8 to −0.2)	130	−2.6 (−3.7 to −0.5)
Moderately malnourished	283	74 (26.1)	153	44 (28.8)	130	30 (23.1)
Severely malnourished	283	109 (38.5)	153	47 (30.7)	130	62 (47.7)
Known BCG vaccination	283	223 (78.8)	153	120 (78.4)	130	103 (79.2)
Known TB contact history	283	73 (25.8)	153	36 (23.5)	130	37 (28.5)
Known HIV co-infection	283	4 (1.4)	153	0 (0.0)	130	4 (3.1)
Baseline temperature, °C, median (IQR)	282	37.0 (36.8–37.9)	153	37.2 (36.9–38.0)	129	37.0 (36.8–37.8)
Symptoms duration, d, median (IQR)§	269	8 (7–11)	145	8 (7–10)	124	9 (7–12)
Symptoms						
Fever	283	250 (88.3)	153	136 (88.9)	130	114 (87.7)
Severe headache	278	61 (21.9)	150	13 (8.7)	128	48 (37.5)
Muscle weakness	278	73 (26.3)	151	40 (26.5)	127	33 (26.0)
Altered consciousness	283	211 (74.6)	153	111 (72.5)	130	100 (76.9)
Seizures	282	155 (55.0)	153	84 (54.9)	129	71 (55.0)
Persistent cough	282	95 (33.7)	152	53 (34.9)	130	42 (32.3)
Poor weight gain or weight loss	279	105 (37.6)	151	51 (33.3)	128	54 (41.5)
Motor function						
Hemiparesis	263	51 (19.4)	142	27 (19.0)	121	24 (19.8)
Quadriparesis	263	95 (36.1)	142	59 (41.5)	121	36 (29.8)
Cranial nerve palsy	277	48 (17.3)	149	31 (20.8)	128	17 (13.3)
Signs of upper motor neuron lesion	264	188 (71.2)	143	93 (65.0)	121	95 (78.5
Signs of raised intracranial pressure	283	47 (16.6)	153	29 (19.0)	130	18 (13.8)
TBM category¶						
Definite	283	51 (18.0)	153	26 (17.0)	130	25 (19.2)
Probable	283	178 (62.9)	153	101 (66.0)	130	77 (59.2)
Possible	283	54 (19.1)	153	26 (17.0)	130	28 (21.5)
GCS, median (IQR)	283	12 (10–14)	153	12 (10–15)	130	12 (10–14)
TBM stage#						
Stage I	283	57 (20.1)	153	35 (22.9)	130	22 (16.9)
Stage II	283	131 (46.3)	153	60 (39.2)	130	71 (54.6)
Stage III	283	95 (33.6)	153	58 (37.9)	130	37 (28.5)

*Values are no. (%) or median (IQR) except as indicated. BCG, bacillus Calmette-Guérin; BFAZ, body mass index-for-age Z-score; GCS, Glasgow Coma Scale; HFAZ, height-for-age Z-score; IQR, interquartile rage; TB, tuberculosis; TBM, tuberculous meningitis; WFAZ, weight-for-age Z-score.
†Number of total patients for whom data were available (denominator).
‡In children <5 years of age, moderate malnutrition was defined as WFAZ or HFAZ ≥–3 but <–2 standard deviation (SD), and severe malnutrition as WFAZ or HFAZ <–3 SD. In children aged 5–14 y, moderate malnutrition was defined as HFAZ or BFAZ ≥–3 but <–2 SD, and severe malnutrition as HFAZ or BFAZ <–3 SD.
§Duration of symptoms before admission.
¶Diagnostic certainty was categorized as definite TBM (microbiologically proven from CSF examination), probable TBM (diagnostic score of ≥10 when neuroimaging was unavailable or ≥12 when neuroimaging was available), and possible TBM (diagnostic score of 6–9 when neuroimaging was unavailable or 6–11 when neuroimaging was available) (*18*).
#TBM staging was classified according to the modified British Medical Research Council grading system as stage I (GCS of 15 with no focal neurologic signs), stage II (GCS 11–14 or 15 with focal neurologic signs), or stage III (GCS ≤10) (*20*).

Table 2. Laboratory and radiographic findings at admission of children with tuberculous meningitis treated at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020*

Characteristic	Total patients		Age <5 y		Age 5–14 y	
	No.†	Value	No.†	Value	No.†	Value
CSF analysis, median (IQR)						
Leukocytes, cells/μL	276	44 (11–109)	149	56 (14–117)	127	40 (8–95)
Protein, mg/dL	276	107 (60–239)	151	103 (68–234)	125	120 (46–248)
MN, %	275	83 (60–96)	151	81 (60–95)	124	86 (64–98)
PMN, %	275	15 (4–37)	151	18 (5–40)	124	12 (0.2–36)
Glucose, mg/dL	269	47 (25–66)	150	42 (20–67)	119	52 (34–66)
CSF-to-plasma glucose ratio, median (IQR)	241	0.4 (0.2–0.6)	140	0.4 (0.2–0.6)	101	0.5 (0.3–0.6)
Cerebral imaging‡						
Hydrocephalus	250	103 (41.2)	136	64 (47.1)	114	39 (34.2)
Basal meningeal enhancement	250	131 (52.4)	136	74 (54.4)	114	57 (50.0)
Infarct	250	25 (10.0)	136	12 (8.8)	114	13 (11.4)
Tuberculoma	250	31 (12.4)	136	17 (12.5)	114	14 (12.3)
Chest radiography						
Miliary TB	281	19 (6.8)	152	10 (6.6)	129	9 (7.0)
Other signs of active TB	281	128 (45.6)	152	66 (43.4)	129	62 (48.1)
TST positive§	283	64 (22.6)	153	37 (24.2)	130	27 (20.8)
M. tuberculosis cultured from any source¶	267	26 (9.7)	147	15 (10.2)	120	11 (9.2)
AFB smear microscopy						
Positive from CSF	272	6 (2.2)	149	4 (2.7)	123	2 (1.6)
Positive from any non-CSF sample#	282	49 (17.4)	152	23 (15.1)	130	26 (20.0)
Xpert MTB/RIF testing**						
Positive from CSF	140	48 (34.3)	77	24 (31.2)	63	24 (38.1)
Positive from gastric lavage	212	71 (33.5)	120	43 (35.8)	92	28 (30.4)
Positive from sputum	12	5 (41.7)	2	0	10	5 (50.0)

*Values are no. (%) or median (IQR) except as indicated. AFB, acid-fast bacilli; CSF, cerebrospinal fluid; IQR, interquartile rage; MN, mononuclear cells; PMN, polymorphonuclear cells; TB, tuberculosis; TST, tuberculin skin test.
†Number of total patients for whom data were available (denominator).
‡Cerebral imaging results were obtained mostly from noncontrast brain computed tomography scan, or from magnetic resonance imaging, where available.
§The median size of induration (minimum–maximum range) in patients with a positive TST result was 12 (10–30) mm and in patients with a negative TST result was 0 (0–8) mm.
¶Culture of *M. tuberculosis* from CSF is rarely performed in our setting, mostly because of the limited CSF volume available from lumbar puncture. From our experience, most of the non-CSF specimens were obtained from gastric lavage, and some specimens were obtained from sputum, but our data could not further specify the type of specimens used. Mycobacterial culture were mostly performed on solid media; the use of liquid culture media (MGIT, BACTEC) has only begun in recent years.
#We could not further specify the types of non-CSF specimens used for AFB smear microscopy.
**Data on Xpert MTB/RIF testing results have only been available since 2013.

[95% CI 1.06–6.31]), seizures on admission (aHR 1.96 [95% CI 1.01–3.82]), and unknown BCG vaccination (aHR 1.97 [95% CI 1.03–3.76]). Among children <5 years of age, known history of TB contact was associated with an increased risk for in-hospital death (aHR 2.42 [95% CI 1.06–5.50]), adjusted for age, sex, and TBM staging. We charted Kaplan-Meier curves for several risk groups for in-hospital death (Figure).

Postdischarge Death

After the 12-month follow-up, 272 (96.1%) of 283 patients were evaluated for treatment outcomes, and 11 (3.9%) in ongoing treatment who started taking anti-TB drugs in late 2020 were excluded from further analysis. Among the 272 patients, 91 (33.5%) completed treatment, 1 (0.4%) was LTFU, and 62 (22.8%) died, including 18 (6.6%) who died after discharge; 118 (43.4%) had unknown outcomes (Table 3).

We performed univariate (Appendix Table 5) and multivariate (Table 5) analyses of odds for postdischarge death. Multivariate analysis identified that patients with unknown BCG vaccination status (aOR 5.38 [95% CI 1.07–27.07]) and those with clinical findings during hospitalization such as hydrocephalus (aOR 18.97 [95% CI 2.68–134.38]) and tuberculoma (aOR 8.78 [95% CI 1.10–70.39]) had increased odds of postdischarge death. Among patients with hydrocephalus, the absence of neurosurgical intervention was associated with increased odds of postdischarge death (aOR 11.06 [95% CI 1.61–76.12]), adjusted for age, sex, and TBM staging.

Neurologic Sequelae

Among 91 survivors who completed treatment, 58 (63.7%) had good recovery without neurologic sequelae and 33 (36.3%) had severe neurologic sequelae (Table 3). Of patients with severe neurologic sequelae, 22 (66.7%) had motor disorders, 9 (27.3%) had epileptic seizures, 7 (21.2%) had neurodevelopmental delay, 3 (9.1%) had visual impairment, and 3 (9.1%) had hearing impairment. Neurologic sequelae were

observed in 23% of patients diagnosed with TBM at stage I, 31% at stage II, and 58% at stage III.

We performed univariate (Appendix Table 6) and multivariate (Table 6) analyses of odds for neurologic sequelae. In multivariate analysis, factors associated with higher odds of severe neurologic sequelae were baseline temperature ≥38°C (aOR 6.68 [95% CI 1.55–28.85]), stage III TBM (aOR 5.65 [95% CI 1.21–26.43]), and motor deficits at baseline (aOR 3.64 [95% CI 1.19–11.16]).

Discussion

We present important information from Indonesia about the high rates of neurologic sequelae and death in children with TBM, even when standard therapy has been provided. In TBM, treatment response is often judged by early morbidity, mortality, and relapse rates (*21*). Our overall case-fatality rate for childhood TBM (22.8%) is within the global estimates reported in a recent meta-analysis (19.3% [95% CI 14.0%–26.1%]) (*2*) but is lower than that reported in the same setting during 2007–2010 (34.4%) (*14*). The high proportion of unknown treatment outcomes in this study (43%) is unfortunate but comparable to a previous report in our hospital during 2007–2010 (45%), even after phone calls and home visits had been made (*14*). Considering the increased likelihood of death in patients with unknown outcomes after hospital discharge, the case-fatality rate recorded is probably an underestimate.

A diagnosis of TBM alone has been associated with an increased risk for childhood death compared with other types of TB (*22*), and this risk may be exacerbated by specific risk factors identified in this study. TBM diagnosis in stage II or III, hydrocephalus, and seizures are not surprising risk factors for death because they reflect more advanced disease. Neurosurgical complications (e.g., shunt blockage or infections) may have contributed to poor outcomes, but we believe the effect was minimal because the postdischarge death rate was significantly reduced with neurosurgery. The association of tuberculoma on baseline CT with postdischarge death might be related to a paradoxical worsening of tuberculomas during treatment (*23*). For male sex and low-income parents, their associations with in-hospital death are unclear but could be related to biologic factors (particularly for sex differences) or largely attributed to socioeconomic and cultural determinants (*24*).

This study confirms that TBM mainly affects young children (*8*), illustrated by 54% of our patients being <5 years of age. The high proportions of altered consciousness and seizures at admission suggest that these symptoms are the main reasons for clinicians to suspect childhood TBM. This finding raises important issues about training of healthcare

Table 3. Hospitalization and end of treatment outcome, stratified by disease staging, in children with tuberculous meningitis treated at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020*

Variable	Total	Stage I†	Stage II†	Stage III†
Outcome of hospitalization‡				
Cases, no.	283	57	131	95
Recovered	231 (81.6)	54 (94.7)	111 (84.7)	66 (69.5)
Not recovered	8 (2.8)	1 (1.8)	5 (3.8)	2 (2.1)
Died	44 (15.5)	2 (3.5)§	15 (11.5)	27 (28.4)
Length of hospital stay, d, median (IQR)	10 (7–17)	9 (7–14)	10 (7–14)	15 (8–25)
Time to death, d, median (IQR)	7 (3–13)	(4–14)¶	6 (2–8)	8 (3–16)
Outcome at treatment completion‡#				
Cases, no.	272	56	122	94
Completed treatment	91 (33.5)	22 (39.3)	45 (36.9)	24 (25.5)
Without neurologic sequelae**	58 (63.7)	17 (77.3)	31 (68.9)	10 (41.7)
With neurologic sequelae**	33 (36.3)	5 (22.7)	14 (31.1)	14 (58.3)
Died	62 (22.8)	2 (3.6)	22 (18.0)	38 (40.4)
Died after hospital discharge	18 (6.6)	0 (0.0)	7 (5.7)	11 (11.7)
Lost to follow-up	1 (0.4)	0 (0.0)	1 (0.8)	0 (0.0)
Unknown treatment outcome	118 (43.4)	32 (57.1)	54 (44.3)	32 (34.0)

*Values are no. (%) except as indicated. IQR, interquartile rage.
†Stage I was defined as Glasgow Coma Scale (GCS) of 15 with no focal neurologic signs, stage II as GCS of 11–14 or 15 with focal neurologic signs, and stage III as GCS ≤10 (*20*).
‡On hospital discharge, recovering patients were those who had clinical improvement (with or without disability), whereas non-recovering patients were those who had persistent vegetative state or discharged against medical advice. Treatment completion included patients who completed 12 mo of TBM therapy. Lost to follow-up included patients who stopped treatment for two consecutive months or more. Unknown treatment outcome included patients who were transferred back to regional public hospitals or community health clinics for follow-up after discharge. Neurologic sequelae were defined as any motor, hearing, visual, or neurodevelopmental impairment that appeared during the illness and persisted through treatment completion.
§The causes of death in two patients with stage I TBM were hospital acquired pneumonia + thalassemia major (n = 1), and intracranial metastases of Burkitt lymphoma + increased intracranial pressure (n = 1).
¶Minimum–maximum range.
#Excluding 11 patients who were still in ongoing treatment.
**Percentages were calculated only in patients who completed 12 mo of treatment.

Table 4. Multivariate Cox proportional-hazards regression model for factors associated with in-hospital death in children treated for TBM at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020*

Variable	Died†‡	Alive†	Crude HR (95% CI)	p value	aHR (95% CI)	p value
No. cases	44	231				
Age, y						
<2	13 (29.5)	78 (33.8)	0.78 (0.37–1.67)	0.527	0.78 (0.36–1.68)	0.522
2–4	11 (25.0)	47 (20.3)	1.04 (0.47–2.29)	0.992	0.93 (0.41–2.12)	0.867
5–9	6 (13.6)	43 (18.6)	0.65 (0.25–1.70)	0.384	0.41 (0.15–1.11)	0.079
10–14	14 (31.8)	63 (27.3)	Referent		Referent	
Sex						
M	29 (65.9)	118 (51.1)	1.72 (0.92–3.20)	0.089	2.10 (1.09–4.05)	0.027
F	15 (34.1)	113 (48.9)	Referent		Referent	
TBM stage§,¶						
Stage I	2 (4.5)	54 (23.4)	Referent		Referent	
Stage II	15 (34.1)	111 (48.1)	3.53 (0.81–15.44)	0.094	2.57 (0.58–11.41)	0.214
Stage III	27 (61.4)	66 (28.6)	9.16 (2.18–38.51)	0.003	5.96 (1.39–25.58)	0.016
Parents' monthly income#						
USD ≤140	33 (75.0)	136 (58.9)	2.79 (1.17–6.67)	0.021	2.59 (1.06–6.31)	0.036
USD >140	6 (13.6)	74 (32.0)	Referent		Referent	
Unknown	5 (11.4)	21 (9.1)	2.73 (0.83–8.95)	0.097	2.04 (0.59–7.02)	0.261
Known BCG vaccination						
No	15 (34.1)	44 (19.0)	2.01 (1.08–3.76)	0.028	1.97 (1.03–3.76)	0.040
Yes	29 (65.9)	187 (81.0)	Referent		Referent	
Hydrocephalus on CT¶						
No	12 (27.3)	133 (57.6)	Referent		Referent	
Yes**	22 (50.0)	76 (32.9)	3.00 (1.48–6.05)	0.002	2.32 (1.13–4.79)	0.022
Unknown	10 (22.7)	22 (9.5)	4.38 (1.89–10.13)	0.001	4.21 (1.77–10.01)	0.001
Seizures on admission¶						
No	13 (29.5)	112 (49.5)	Referent		Referent	
Yes	31 (70.5)	119 (51.5)	2.09 (1.09–3.99)	0.026	1.96 (1.01–3.82)	0.048

*Values are no. (%) except as indicated. aHR, adjusted hazard ratio; BCG, bacillus Calmette-Guérin; CT, computed tomography; GCS, Glasgow Coma Scale; IDR, Indonesian Rupiah; TBM, tuberculous meningitis.
†Including patients who died or had recovered (with or without disability) on hospital discharge, and excluding patients who had persistent vegetative state or discharged against medical advice.
‡Signs of upper motor neuron lesion was associated with an increased risk of in-hospital death in univariate analysis, but did not remain significant in multivariate analysis. Signs of raised intracranial pressure with hydrocephalus as well as GCS score with TBM stage had the likelihood of collinearity; therefore, only hydrocephalus and TBM staging were included in the final multivariate model. For HIV coinfection, although it was significantly associated with in-hospital death in univariate analysis, we did not include this variable in multivariate analysis due to the selective HIV testing and a very low number of patients with HIV positive (n = 4).
§Stage I TBM was defined as GCS of 15 with no focal neurologic signs, stage II TBM as GCS of 11–14 or 15 with focal neurologic signs, and stage III TBM as GCS ≤10 (*20*).
¶TBM staging might interact with hydrocephalus and seizures on admission; however, due to the low number of patients with stage I TBM who died during hospitalization (n = 2), these potential interactions could not be assessed in the Cox regression model.
#Parents' monthly income was estimated based on the current provincial minimum wage for West Java (IDR 1.810.350,00, rounded up to IDR 2.000.000,00, equal to approximately USD 140).
**In-hospital death among children with hydrocephalus was not significantly different between those who received neurosurgical intervention and who did not receive neurosurgical intervention (p = 0.604).

providers to improve their ability to recognize and diagnose the disease (*25*). In addition, increasing community awareness of the signs and symptoms of TBM by including enhanced messaging in existing TB advocacy materials has the potential to improve early recognition of childhood TBM (*25*).

The difficulty of early diagnosis is confirmed by the fact that nearly 80% of our patients had stage II or III TBM at admission. This high proportion of patients with advanced disease at admission is supported by various studies from high TB incidence countries in Asia and Africa (*11*,*14*,*26*,*27*), and only slightly reduced in low TB incidence countries in Europe, where 66% of the patients have stage II or III TBM at admission (*28*). In many cases, nonspecific symptoms such as fever, headache, and vomiting are often wrongly interpreted, and other systemic symptoms such as cough, weight loss, and night sweats may be suggestive of TB but are also nonspecific (*18*).

The high risk for death in patients with unknown BCG vaccination status highlights the importance of better TB prevention. In young children, BCG vaccination has consistently shown protection against miliary TB and TBM (*29*–*31*) for ≥10 years after vaccination (*29*). The global shortage of BCG vaccine since 2013, particularly in countries where it was procured through UNICEF (*32*), has led to an alarming increase in the number of hospital admissions for childhood TBM (*33*). In Indonesia, where BCG vaccine is recommended at birth for all infants and annual coverage has been an estimated ≈90% since 2011 (*34*), this shortage has also been experienced, although the vaccine supply depends largely on domestic production by Biofarma, a state-owned vaccine manufacturer

(*32*). In addition, among children with prolonged exposure to *M. tuberculosis*, protection with BCG vaccination alone is unlikely to be sufficient. Without early initiation of preventive therapy, the risk for TB disease development among exposed young children and infants is very high (*35*), but data on preventive treatment in our patients with known TB contact history were unavailable. Taken together, aside from improving BCG vaccination coverage, it is important to reduce TB transmission in children through contact investigation, coupled with preventive therapy among exposed children.

Neurologic sequelae occurred mostly in our patients who had stage III TBM at admission (58%), a higher rate than for those in stage I (23%) and II (31%). A meta-analysis in children with TBM confirms this upward trend with pooled estimates of 27% in stage I, 41% in stage II, and 70% in stage III (*2*). Recent studies also reported an increase in neurologic sequelae among children with stage II or III TBM (*36*,*37*). In children in South Africa with TBM, severe neurologic sequelae and death were significantly associated with cerebral infarctions (*11*); we did not find this association in our study. A high proportion of patients had hemiparesis or quadriparesis at admission in this study (55%), comparable to that reported in South Africa (62.1%) (*11*), but few patients had cerebral infarcts on brain CT (10%). This finding is difficult to explain but is likely attributable to the low sensitivity of early infarct detection with noncontrast CT as commonly used in the study.

Given the substantial levels of neurologic sequelae and death associated with childhood TBM, the current standard care for childhood TBM clearly remains suboptimal. New diagnostic strategies should be tested in future clinical trials because of the poor sensitivity, specificity, or both of available laboratory and clinical diagnostic tools (*38*). For TBM treatment, future research should explore the use of intensified antimicrobial therapy that contains high-dose

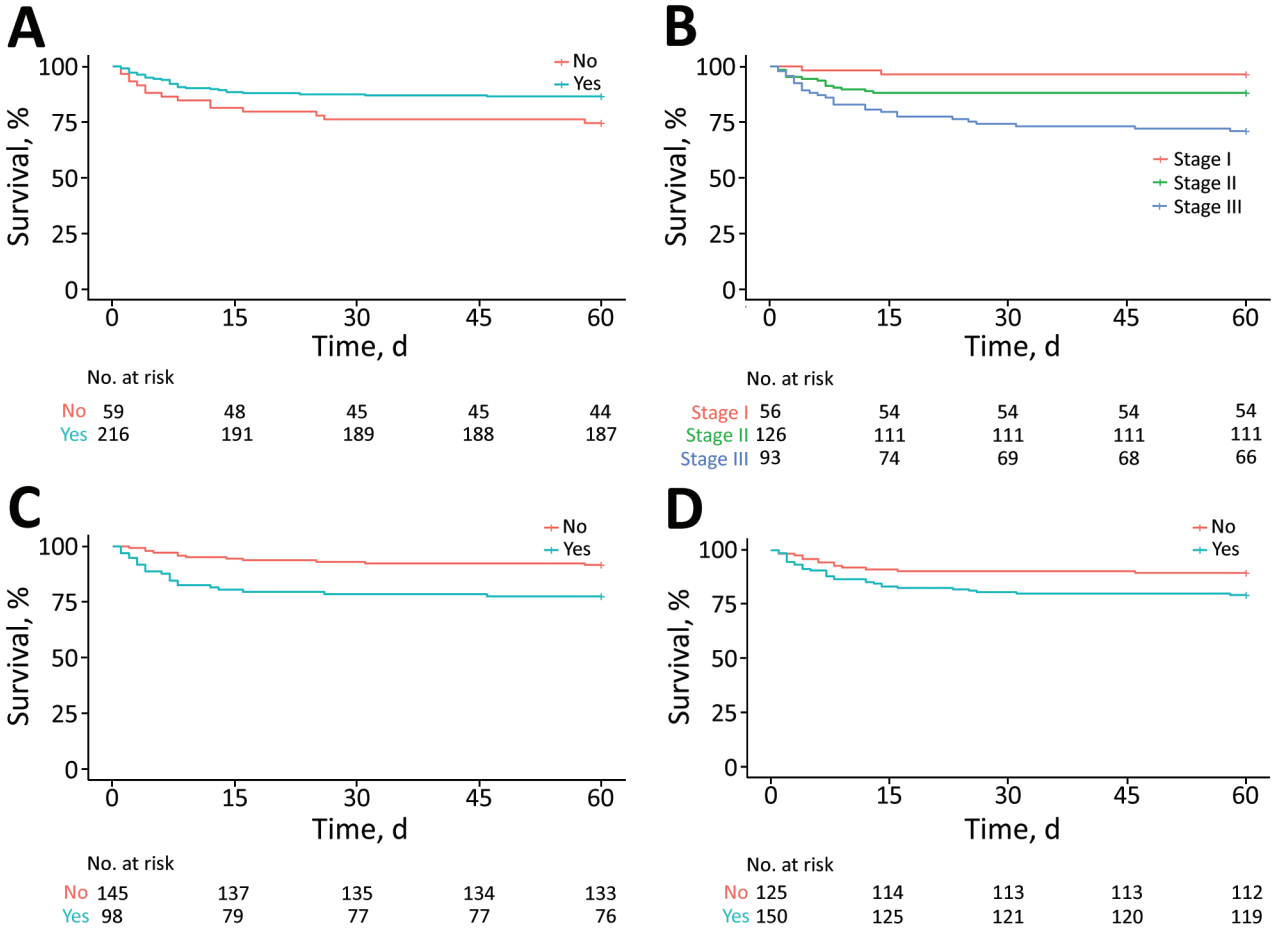

Figure. Survival curves for in-hospital death in children treated for tuberculous meningitis at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020. A) Known bacillus Calmette-Guérin (BCG) vaccination status (yes/no); B) tuberculous meningitis stage (I–III); C) radiographic evidence of hydrocephalus (yes/no); D) presence of seizures at hospital admission (yes/no).

rifampin and other anti-TB drugs with better CSF penetration and bactericidal activity (*39*). On the basis of observational data among children in South Africa, a 6-month intensified TBM treatment regimen with isoniazid, rifampin, and ethionamide at 20 mg/kg/day and pyrazinamide at 40 mg/kg/day was reported to be safe and effective, with lower case-fatality rates ranging from 4%–14% (*11*,*12*,*40*). This short-course, high-dose therapy has recently been added by WHO as an alternative treatment option for childhood TBM (*41*). Suboptimal plasma and CSF concentrations with standard doses of oral rifampin at 10–20 mg/kg/day in children with TBM have also been reported in recent pharmacokinetic studies (*42*,*43*), advocating the use of higher rifampin doses with further efficacy and safety evaluations.

Minimizing damaging immunologic responses leading to neurologic complications by using anti-inflammatory drugs such as aspirin, thalidomide, and specific tumor necrosis factor α antibodies (e.g., infliximab) also warrants further investigations (*10*,*44*–*46*), particularly for paradoxical TBM reactions and potentially also for TBM in general. There is no evidence that corticosteroids (the mainstay of host-directed therapy) reduce neurologic sequelae although they do improve the TBM survival rate (*47*). Therefore, optimization of anti-TB drug dosing and consideration of immunomodulatory therapy beyond corticosteroids are required to improve childhood TBM treatment outcomes (*9*,*46*). Moreover, understanding the disease pathogenesis pathways of childhood TBM, particularly in the cerebral inflammatory response, is likely to offer valuable insights into potential targets for new treatment interventions (*48*,*49*).

The main limitation of our study is that, although most of the essential information recommended for TBM research was available (*50*), the retrospective nature of the study did not provide us with complete records on all key variables, especially longer-term outcome. Our dataset did not contain information on the drug-susceptibility pattern of the source case and was

Table 5. Multivariate logistic regression model for predictors of postdischarge death, tracked until the end of treatment in children treated for TBM at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020*†

Variable	Died‡§	Alive‡	Crude OR (95% CI)	p value	aOR (95% CI)	p value
No. cases	18	91				
Age group, y						
<2	3 (16.7)	26 (28.6)	0.65 (0.15–2.86)	0.573	0.13 (0.01–1.12)	0.064
2–4	6 (33.3)	9 (9.9)	3.78 (0.98–14.56)	0.054	1.60 (0.26–9.86)	0.610
5–9	3 (16.7)	22 (24.2)	0.77 (0.17–3.41)	0.734	0.23 (0.03–1.75)	0.156
10–14	6 (33.3)	34 (37.4)	Referent		Referent	
Sex						
M	10 (55.6)	39 (42.9)	1.67 (0.60–4.61)	0.325	3.43 (0.76–15.45)	0.109
F	8 (44.4)	52 (57.1)	Referent		Referent	
TBM stage¶						
Stage I or II	7 (38.9)	67 (73.6)	Referent		Referent	
Stage III	11 (61.1)	24 (26.4)	4.39 (1.53–12.6)	0.006	2.31 (0.56–9.54)	0.247
Known BCG vaccination						
No	7 (38.9)	15 (16.5)	3.22 (1.08–9.66)	0.037	5.38 (1.07–27.07)	0.041
Yes	11 (61.1)	76 (83.5)	Referent		Referent	
Hydrocephalus on CT						
No	3 (16.7)	66 (72.5)	Referent		Referent	
Yes	13 (72.2)	23 (25.3)	12.43 (3.25–47.59)	<0.001	18.97 (2.68–134.38)	0.003
Unknown	2 (11.1)	2 (2.2)	22.00 (2.26–214.23)	0.008	17.85 (1.30–245.49)	0.031
Tuberculoma on CT#						
No	12 (66.7)	85 (93.4)	Referent		Referent	
Yes	4 (22.2)	4 (4.4)	7.08 (1.56–32.13)	0.011	8.78 (1.10–70.39)	0.041
Positive TST						
No	10 (55.6)	76 (83.5)	Referent		Referent	
Yes	8 (44.4)	15 (16.5)	4.05 (1.37–11.96)	0.011	4.79 (0.96–24.05)	0.057

*Data are no. (%) except as indicated. aOR, adjusted odds ratio; BCG, bacillus Calmette-Guérin; CT, computed tomography; GCS, Glasgow Coma Scale; TBM, tuberculous meningitis; TST, tuberculin skin test.
†The goodness-of-fit of the model using Hosmer-Lemeshow test was p = 0.877. The performance of the model using the area under the receiver operating characteristic curve was 0.91 (95% CI 0.85–0.97).
‡Including patients who were tracked until death or treatment completion, and excluding patients who were lost to follow-up and with unknown treatment outcomes.
§Positive TST and motor disorders were associated with higher odds of postdischarge death in univariate analysis but did not remain significant in multivariate analysis. Signs of raised intracranial pressure with hydrocephalus as well as GCS score with TBM staging had the likelihood of collinearity; therefore, only hydrocephalus and TBM staging were included in the final multivariate model. In our subgroup analysis among children aged <5 y, no additional independent predictors of postdischarge death were observed.
¶Stage I TBM was defined as GCS of 15 with no focal neurologic signs, stage II TBM as GCS of 11–14 or 15 with focal neurologic signs, and stage III TBM as GCS ≤10 (*20*). Patients with stages I and II TBM were combined in the analysis because there were no patients with TBM stage I died after hospital discharge.
#Because of the redundancy with the variable "unknown status of hydrocephalus," the degree of freedom for the variable "unknown status of tuberculoma" was reduced.

Table 6. Multivariate logistic regression model for predictors of severe neurologic sequelae at treatment completion in children treated for TBM at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020*†

Variable	Neurologic sequelae		Crude OR (95% CI)	p value	aOR (95% CI)	p value
	Yes‡§	No‡				
Cases, no.	33	58				
Age group, y						
<2	13 (39.4)	13 (22.4)	2.78 (0.94–8.20)	0.064	2.59 (0.67–10.00)	0.166
2–4	2 (6.1)	7 (12.1)	0.79 (0.14–4.55)	0.795	0.97 (0.13–7.28)	0.974
5–9	9 (27.3)	13 (22.4)	1.92 (0.61–6.02)	0.261	1.32 (0.34–5.07)	0.684
10–14	9 (27.3)	25 (43.1)	Referent		Referent	
Sex						
M	12 (36.4)	27 (46.6)	0.66 (0.27–1.58)	0.346	0.48 (0.16–1.45)	0.191
F	21 (63.6)	31 (53.4)	Referent		Referent	
TBM stage¶						
Stage I	5 (15.2)	17 (29.3)	Referent		Referent	
Stage II	14 (42.4)	31 (53.4)	1.53 (0.47–5.00)	0.476	1.83 (0.43–7.75)	0.410
Stage III	14 (42.4)	10 (17.2)	4.76 (1.32–17.22)	0.017	5.65 (1.21–26.43)	0.028
Baseline temperature ≥38°C						
No	23 (69.7)	53 (91.4)	Referent		Referent	
Yes	10 (30.3)	5 (8.6)	4.61 (1.42–14.99)	0.011	6.68 (1.55–28.85)	0.011
Motor deficit at baseline						
No	8 (24.2)	27 (46.6)	Referent		Referent	
Yes	24 (72.7)	23 (39.7)	3.52 (1.33–9.33)	0.011	3.64 (1.19–11.16)	0.024
Unknown	1 (3.0)	8 (13.8)	0.42 (0.05–3.90)	0.447	0.39 (0.03–4.58)	0.452

*Values are no. (%) except as indicated. aOR, adjusted odds ratio; TB, tuberculosis; TBM, tuberculous meningitis.
†The goodness-of-fit of the model using Hosmer-Lemeshow test was p = 0.473. The performance of the model using the area under the receiver operating characteristic curve was 0.80 (95% CI 0.70–0.90).
‡Including patients who were tracked until treatment completion, and excluding those who died, who were lost to follow-up and with unknown treatment outcomes (which represents a large percentage of the cohort (n = 118, 43.3%). Neurologic sequelae were defined as any motor, hearing, visual or neurodevelopmental impairment that appeared during the illness and persisted through treatment completion.
§Suggestive TB through chest radiography was associated with an increased odd of neurologic sequelae in univariate analysis but did not remain significant in multivariate analysis. In our subgroup analysis among children aged <5 y, no additional independent predictors for neurologic sequelae were found.
¶Stage I TBM was defined as Glasgow Coma Scale (GCS) of 15 with no focal neurologic signs, stage II TBM as GCS of 11–14 or 15 with focal neurologic signs, and stage III TBM as GCS ≤10 (*20*).

unable to reliably distinguish a contact history with an infectious drug-susceptible or drug-resistant TB case. This limitation may have led to underdiagnosis of drug-resistant TB disease, resulting in inappropriate antimicrobial therapy that may have contributed to poor outcomes. However, drug-resistance rates are not known to be high in the study population, an estimated 2.4% of multidrug-resistant TB among new cases in Indonesia (*1*), limiting the likely effect of inappropriate treatment of drug-resistant disease. In addition, the frequency of total neurologic sequelae at treatment completion might be underestimated in this study, given that mild to moderate sequelae were not tested or recorded in the database. Despite its limitations, this study provides one of the largest child TBM cohorts ever described globally outside of South Africa (*11*), and includes a wide range of variables in the analysis.

In conclusion, childhood TBM in Indonesia causes substantial neurologic sequelae and death, despite standard treatment. Several predictors of in-hospital death, postdischarge death, and neurologic sequelae have been identified for further development of early and tailored interventions to optimize care in this population. This study emphasizes the importance of improved early diagnosis, better TB prevention beyond BCG vaccination, and optimizing TBM management strategies, including antimicrobial and supportive therapy.

Acknowledgments

We thank the director of Hasan Sadikin Hospital and head of the Department of Child Health of Hasan Sadikin Hospital for accommodating the study. We also thank Raisa Moeis for helping with data checking.

This work was supported by the Academic Leadership Grant of the Universitas Padjadjaran (grant no. 4851/UN6.C/LT/2018) awarded to H.M.N. The funding organization was in no way involved in study design or conception, writing or reviewing of the manuscript, and decision to submit the manuscript for publication.

H.M.N. was the principal investigator. H.M.N., R.R., N.A.R., and F.G. contributed to conception and design of the study. H.M.N. contributed to data collection, whereas H.M.N. and F.G. contributed to data cleaning. F.G. performed data analysis and created tables and figures. H.M.N., F.G., N.A.R., D.A.W., S.S., B.J.M., J.S., J.W.C.A., and R.R. interpreted the results. F.G. drafted the manuscript under the supervision of H.M.N. and J.W.C.A. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript before submission for publication.

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Article DOI: https://doi.org/10.3201/eid2803.212230

Treatment Outcomes of Childhood Tuberculous Meningitis in a Real-World Retrospective Cohort, Bandung, Indonesia

Appendix

Assessments of neurologic sequelae in children with tuberculous meningitis at treatment completion

In this study, neurologic sequelae were defined as any motor, hearing, visual or neurodevelopmental impairment that appeared during the illness and persisted through treatment completion. Only severe neurologic sequelae were recorded in the database. Mild to moderate sequelae were not routinely tested or recorded, and complete assessments were only performed if indicated or requested by the attending physicians. Generally, hearing function was assessed using the Brainstem Auditory Evoked Response (BAER) method. Degree of hearing loss was determined based on the Pure Tone Average (PTA). Visual examinations consisted of a visual acuity test using Cardiff Acuity Cards or the Snellen Chart, an extraocular muscle examination test, the anterior segment of the eyeball examination test using a slit lamp or a loop/magnifier 3D and a penlight, and the posterior segment of the eyeball/fundus examination test using direct and indirect ophthalmoscope. Neurodevelopmental function in children aged ≤8 years was assessed using the Griffiths General Developmental Quotient. In children aged >8 years, neurodevelopmental function was assessed using the Wechsler Intelligence Scale for Children (WISC). Gross motor function was assessed using the Growth Motor Functional Measurement (GMFM). Detailed methods and classifications have been described elsewhere (*1*).

Case presentation of a TBM patient with SARS-CoV-2 coinfection

A 6-month-old boy (weight: 5.3 kg, height: 60 cm, head circumference: 46 cm) presented at Hasan Sadikin Hospital in April 2020, with a 10-day history of fever prior to admission. He also had seizures, quadriparesis and vomiting, but no other symptoms suggestive of TBM were

reported at presentation. Prior to admission, he had a diagnosis of congenital hydrocephalus and underwent a ventriculoperitoneal shunt in another hospital. He had an unknown history of recent close contact with a TB patient, had been vaccinated with BCG, was severely malnourished and had a GCS score of 15 with focal neurologic deficits. In cerebrospinal fluid (CSF) analysis, he had pleocytosis of 355 cells/μL, abnormal protein concentration of 848 mg/dL, lymphocytic predominance of 59.7%, CSF to blood glucose ratio of 30% and smear-negative for acid fast-bacilli (AFB). He had a negative result on tuberculin skin test and had bronchopneumonia dextra on chest radiography. Mycobacterial cultures from CSF and gastric lavage were negative, AFB smear microscopy was positive from gastric lavage, and *M. tuberculosis* sensitive to rifampicin was identified through GeneXpert MTB/RIF assay from gastric lavage. Brain computed tomography scan results showed communicating hydrocephalus, with negative signs for basal meningeal enhancement, infarct or tuberculoma. He was diagnosed with probable TBM at stage II, and was treated with daily oral isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg and ethambutol at 20 mg/kg, for a 2-month intensive phase, and followed by a 10-month continuation therapy with isoniazid and rifampicin at the same doses. Adjunctive oral prednisone at 2 mg/kg was given for the first 4 weeks of treatment. During hospitalization, facility-based directly observed treatment was used by the treated physician or nurses to administer the drugs. He was discharged after 20 days of hospitalization, with existing complications of hearing impairment and motor disorders.

After discharge, TBM treatment with first-line anti-TB drugs was continued for up to 12 months, and he was followed up monthly at Hasan Sadikin Hospital. During the 8-month follow-up, he was tested positive for coronavirus SARS-CoV-2 infection by real-time reverse transcription-polymerase chain reaction swab test (RdRp- and E-genes), with no specific symptoms for COVID-19. After 1 day of hospitalization, he was discharged and advised to self-isolate for 3 weeks. No antiretroviral drugs were administered. After 3 weeks, he was confirmed negative from SARS-CoV-2. At treatment completion, TBM symptoms of fever and seizures were not present. Bodyweight, height and head circumference had increased to 9.8 kg, 81 cm and 52 cm, respectively. Neurologic sequelae of motor disorders persisted through treatment completion. He was considered a failure to thrive, with only being able to tilt his body to the right and unable to babble.

Appendix Table 1. Diagnostic certainty of tuberculous meningitis using uniform case definition criteria by Marais et al (*2*).

Characteristic	Score	Total patients (n=283)	Possible/ probable TBM (n=232)
Clinical criteria [maximum category score = 6]			
Symptoms duration of more than 5 days	4	234 (82.7)	191 (82.3)
Systemic symptoms suggestive of TB (one or more of the following: weight loss / poor weight gain, night sweats, or persistent cough for more than 2 weeks)	2	263 (92.9)	216 (93.1)
History of recent (within past year) close contact with an individual with pulmonary TB or a positive TST or IGRA (only in children under 10 years of age)	2	114 (40.3)	94 (40.5)
Focal neurologic deficit (excluding cranial nerve palsies)	1	222 (78.4)	179 (77.2)
Cranial nerve palsy	1	48 (17.0)	36 (15.5)
Altered consciousness	1	211 (74.6)	169 (72.8)
CSF criteria [maximum category score = 4)			
Clear appearance	1	276 (97.5)	225 (97.0)
Leucocyte cells: 10-500 per µL	1	212 (74.9)	172 (74.1)
Lymphocytic predominance of >50%	1	225 (79.5)	182 (78.4)
Protein concentration >100 mg/dL	1	143 (50.5)	115 (49.6)
CSF / plasma glucose ratio of <50% or an absolute CSF glucose concentration <40 mg/dL	1	142 (50.0)	115 (49.6)
Cerebral imaging criteria [maximum category score = 6]			
Hydrocephalus	1	103 (41.2)	84 (36.2)
Basal meningeal enhancement	2	131 (46.3)	104 (44.8)
Tuberculoma	2	31 (11.0)	22 (9.5)
Infarct	1	25 (8.8)	21 (9.1)
Pre-contrast basal hyperdensity	2	-	-
Evidence of TB elsewhere [maximum category score = 4]			
Chest radiography suggestive of active TB			
Miliary TB	4	19 (6.7)	16 (6.9)
Other signs of TB	2	128 (45.2)	103 (44.4)
CT / MRI / USG evidence of TB outside the CNS	2	-	-
AFB identified or *M. tuberculosis* cultured from another source (sputum, lymph node, gastric aspirates, urine or blood culture)	4	65 (23.0)	37 (15.9)
Positive commercial *M. tuberculosis* nucleic acid amplification test (NAAT) from non-CSF specimen	4	76 (26.8)	38 (16.4)
Definite TBM (AFB seen on CSF microscopy, *M. tb* cultured from CSF, or *M. tb* detected through GeneXpert test)		51 (18.0)	
Probable TBM (total score of ≥12 when neuroimaging available or total score of ≥10 when neuroimaging was unavailable)		178 (62.9)	
Possible TBM (total score of 6-11 when neuroimaging available, or total score of 6-9 when neuroimaging was unavailable)		54 (19.1)	

Appendix Table 2. Operational definition for variables used in this study

Variable	Definition
Children	Individuals aged <15 years at diagnosis were defined as children, and were generally categorized by three age bands (0-4 years, 5-9 years and 10-14 years) as recommended by the WHO (*3*). An age group of less than 2 years was added given the high risk of severe progression to miliary and meningitis TB following infection with *M. tuberculosis* (*4*).
Malnourished	Children aged <5 years with weight-for-age or height-for-age Z-scores <-2 standard deviations, or children aged ≥5 years with height-for-age or BMI-for-age Z-scores <-2 standard deviation (*5*,*6*).
Known TB contact history	A patient who had close contact history with an infectious TB patient within the past year before hospital admission.
Known BCG vaccination	A documented BCG vaccination history in the immunization records book (*Buku Kesehatan Ibu dan Anak)* at the time of hospital admission, and/or the presence of a BCG scar in the deltoid part of the upper arm.
Definite TBM	Microbiological confirmation from CSF examination, including AFB smear microscopy, mycobacterial culture or GeneXpert MTB/RIF testing (*2*).
Probable TBM	A total diagnostic score of ≥12 when neuroimaging was available, or ≥10 when neuroimaging was unavailable (*2*).
Possible TBM	A total diagnostic score of 6-11 when neuroimaging was available, or 6-9 when neuroimaging was unavailable (*2*).
TBM stage I	Glasgow Coma Scale (GCS) scores of 15 without focal neurologic signs (*7*).
TBM stage II	GCS scores of 11-14 or 15 with focal neurologic signs (*7*).
TBM stage III	GCS scores of ≤10 (*7*).

Variable	Definition
Cranial nerve palsy	Cranial nerve palsy was characterized by a decreased or complete loss function of one or more cranial nerves.
Motor deficits	Motor deficits included hemiparesis, quadriparesis and diplegia.
Signs of upper neuron lesion	Signs of upper motor neuron lesion included muscle weakness, hypertonus, clonus, hyperreflexia and the presence of pathological reflex.
Signs raised intracranial pressure	In physical examination, signs of raised intracranial pressure could include cranial nerve IV palsy, excessive headache/vomiting, papilledema, bulging fontanelle, sunsetting sign, etc. The diagnosis could also be made through cerebral imaging.
Hydrocephalus on neuroimaging	Enlargement of the ventricles with the compression of sulci and gyri and enlargement of temporal horn >2 mm or frontal horn-to-internal diameter ratio >0.5, supported by ballooning of the frontal horns, transependymal edema, Evans ratio of >0.3, and sagittal bowing of corpus callosum (*8*).
Suggestive of TB from chest radiography	Chest radiographic findings suggestive of TB included mediastinal/hilar lymphadenopathy, segmental infiltration and/or collapse, pleural effusion, cavitation, and signs of miliary TB.
Positive tuberculin skin test	Induration of ≥10 mm in Mantoux skin test, or ≥5 mm in patients with severe malnutrition or HIV-infected children.
AFB smear positive	The specimen from cerebrospinal fluid, sputum, gastric lavage or other body materials noted as at least +1 for acid-fast bacilli (AFB) on microscopy using Ziehl-Neelsen stain.
Anti-TB drug-induced hepatotoxicity	Anti-TB drug-induced hepatotoxicity was defined according to the modified American Thoracic Society guidelines, developed internally by the Department of Child Health, Universitas Padjadjaran, as follows: an elevation of alanine aminotransferase (ALT) >3× the ULN with symptoms of hepatotoxicity, an elevation of ALT >5× the ULN without symptoms, normal baseline ALT with the presence of jaundice, anorexia, nausea and vomiting during treatment, or an increased in total bilirubin level >1.5 mg/dL (*9*,*10*).

Appendix Table 3. Symptoms of tuberculous meningitis at presentation stratified by disease staging, in children with tuberculous meningitis treated at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020

	Stage I		Stage II		Stage III	
Symptom	N*	Value	N*	Value	N*	Value
Fever	57	46 (80.7)	131	122 (93.1)	95	82 (86.3)
Severe headache	56	15 (26.8)	131	31 (23.7)	91	15 (15.8)
Muscle weakness	57	12 (21.1)	129	36 (27.5)	92	25 (26.3)
Altered consciousness	57	18 (31.6)	131	110 (84.0)	95	83 (87.4)
Seizures	57	28 (49.1)	131	63 (48.1)	95	64 (67.4)
Shortness of breath	57	13 (22.8)	130	14 (10.7)	93	17 (17.9)
Persistent cough	57	21 (36.8)	131	41 (31.3)	94	33 (35.1)
Poor weight gain / weight loss	57	16 (28.1)	130	44 (33.6)	92	45 (47.4)

Data are presented as number (n) with percentages (%). *: Number of total patients for which data were available. Stage I TBM was defined as Glasgow Coma Scale (GCS) of 15 with no focal neurologic signs, stage II TBM as GCS of 11-14 or 15 with focal neurologic signs, and stage III TBM as GCS ≤10 (*7*).

Appendix Table 4. Univariate Cox proportional-hazards regression model for factors associated with in-hospital death in children treated for tuberculous meningitis at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020

Patient characteristics	Dead (n=44)	Alive (n=231)	cHR (95% CI)	p-value
Year of diagnosis (median (IQR))[a,b]	2018 (2015-2019)	2016 (2014-2019)	1.11 (0.98-1.25)	0.087
Year of diagnosis[a,b]				
2011-2015	11 (25.0)	91 (39.4)	0.55 (0.28-1.08)	0.083
2016-2020	33 (75.0)	140 (60.6)	1.00	
Age, years (median (IQR))	4.0 (1.5-10.7)	1.0 (4.0-10.0)	1.00 (0.94-1.07)	0.876
Age[a]				
<2 years	13 (29.5)	78 (33.8)	0.78 (0.37-1.67)	0.527
2-4 years	11 (25.0)	47 (20.3)	1.04 (0.47-2.29)	0.992
5-9 years	6 (13.6)	43 (18.6)	0.65 (0.25-1.70)	0.384
10-14 years	14 (31.8)	63 (27.3)	1.00	
Sex[a]				
Male	29 (65.9)	118 (51.1)	1.72 (0.92-3.20)	0.089
Female	15 (34.1)	113 (48.9)	1.00	
Parent's last education				
Elementary	4 (9.1)	38 (16.5)	0.83 (0.15-4.53)	0.829
Junior high school	16 (36.4)	64 (27.7)	1.88 (0.43-8.16)	0.401
Senior high school	21 (47.7)	110 (47.6)	1.47 (0.34-6.25)	0.605
University	2 (4.5)	15 (6.5)	1.00	
Parent's monthly income[a]				
USD ≤140,00	33 (75.0)	136 (58.9)	2.79 (1.17-6.67)	0.021
USD >140,00	6 (13.6)	74 (32.0)	1.00	
Area of living				
Urban	17 (38.6)	98 (42.4)	1.00	

Patient characteristics	Dead (n=44)	Alive (n=231)	cHR (95% CI)	p-value
Rural	25 (56.8)	126 (54.5)	1.13 (0.61-2.10)	0.692
Weight-for-age Z-score				
≥-2 (normal)	19 (43.2)	82 (35.5)	1.00	
<-2 (underweight)	17 (38.6)	103 (44.6)	0.72 (0.38-1.39)	0.336
Height-for-age Z-score				
≥-2 (normal)	24 (54.5)	141 (61.0)	1.00	
<-2 (stunted)	20 (45.5)	90 (39.0)	1.25 (0.69-2.26)	0.460
Weight-for-height Z-score				
≥-2 (normal)	21 (47.7)	115 (49.8)	1.00	
<-2 (wasted)	23 (52.3)	116 (50.2)	1.06 (0.59-1.92)	0.837
BMI-for-age Z-score				
≥-2 (normal)	22 (50.0)	113 (48.9)	1.00	
<-2 (low BMI)	22 (50.0)	118 (51.1)	0.96 (0.53-1.72)	0.881
Nutritional status[§]				
Normal	16 (36.4)	81 (35.1)	1.00	
Moderate malnutrition	10 (22.7)	60 (26.0)	0.82 (0.37-1.82)	0.634
Severe malnutrition	18 (40.9)	90 (39.0)	1.00 (0.51-1.95)	0.991
Known BCG vaccination[a]				
No	15 (34.1)	44 (19.0)	2.01 (1.08-3.76)	0.028
Yes	29 (65.9)	187 (81.0)	1.00	
Known TB contact history[a]				
No	27 (61.4)	176 (76.2)	1.00	
Yes	17 (38.6)	55 (23.8)	1.83 (1.00-3.35)	0.051
Known HIV status[a,e]				
No/unknown	41 (93.2)	230 (99.6)	1.00	
Yes	3 (6.8)	1 (0.4)	6.46 (1.99-20.92)	0.002
TBM category and stage				
TBM category[¥]				
Definite TBM	9 (20.5)	39 (16.9)	1.00	
Probable TBM	25 (56.8)	147 (63.6)	0.72 (0.34-1.55)	0.406
Possible TBM	10 (22.7)	45 (19.5)	0.93 (0.38-2.29)	0.857
TBM stage[¶,a,c]				
Stage I	2 (4.5)	54 (23.4)	1.00	
Stage II	15 (34.1)	111 (48.1)	3.53 (0.81-15.44)	0.094
Stage III	27 (61.4)	66 (28.6)	9.16 (2.18-38.51)	0.003
GCS (median (IQR))[a,c]	10 (9-12)	12 (11-15)	0.80 (0.72-0.88)	<0.001
Presenting symptoms				
Fever				
No	6 (13.6)	27 (11.7)	1.00	
Yes	38 (86.4)	204 (88.3)	0.87 (0.37-2.07)	0.759
Severe headache				
No	31 (70.5)	179 (77.5)	1.00	
Yes	11 (25.0)	49 (21.2)	1.30 (0.66-2.60)	0.448
Muscle weakness				
No	33 (75.0)	169 (73.2)	1.00	
Yes	10 (22.7)	58 (25.1)	0.87 (0.43-1.76)	0.700
Altered consciousness				
No	7 (15.9)	64 (27.7)	1.00	
Yes	37 (84.1)	167 (72.3)	1.91 (0.85-4.30)	0.115
Seizures[a]				
No	13 (29.5)	112 (49.5)	1.00	
Yes	31 (70.5)	119 (51.5)	2.09 (1.09-3.99)	0.026
Shortness of breath[a]				
No	32 (72.7)	196 (84.8)	1.00	
Yes	11 (25.0)	33 (14.3)	1.81 (0.91-3.59)	0.090
Persistent cough				
No	27 (61.4)	155 (67.1)	1.00	
Yes	16 (36.4)	76 (32.9)	1.20 (0.64-2.22)	0.567
Poor weight gain / weight loss				
No	26 (59.1)	142 (61.5)	1.00	
Yes	17 (38.6)	86 (37.2)	1.06 (0.57-1.95)	0.861
Duration of symptoms				
0-7 days	15 (34.1)	84 (36.4)	1.00	
8-14 days	25 (56.8)	119 (51.5)	1.16 (0.61-2.19)	0.658
>14 days	1 (2.3)	17 (7.4)	0.34 (0.04-2.58)	0.298
Examination findings at baseline				
Body temperature				
<38 °C	33 (75.0)	181 (78.4)	1.00	
≥38 °C	10 (22.7)	50 (21.6)	1.06 (0.52-2.16)	0.865

Patient characteristics	Dead (n=44)	Alive (n=231)	cHR (95% CI)	p-value
Respiration rate				
<25/min	11 (25.0)	78 (33.8)	1.00	
≥25/min	32 (72.7)	151 (65.4)	1.43 (0.72-2.84)	0.304
Involuntary movement				
No	36 (81.8)	203 (87.9)	1.00	
Yes	6 (13.6)	22 (9.5)	1.54 (0.65-3.65)	0.329
Cranial nerve palsies				
No	34 (77.3)	187 (81.0)	1.00	
Yes	8 (18.2)	40 (17.3)	1.14 (0.53-2.47)	0.736
Any type of motor deficit				
No	20 (45.5)	90 (39.0)	1.00	
Yes	21 (47.7)	124 (53.7)	0.82 (0.44-1.50)	0.515
Unequal pupils				
No	39 (88.6)	221 (95.7)	1.00	
Yes	3 (6.8)	6 (2.6)	2.49 (0.77-8.07)	0.127
Signs of upper motor neuron lesions[a]				
No	6 (13.6)	64 (27.7)	1.00	
Yes	36 (81.8)	150 (64.9)	2.46 (1.03-5.83)	0.042
Signs of raised intracranial pressure[a,d]				
No	25 (56.8)	203 (87.9)	1.00	
Yes	19 (43.2)	28 (12.1)	4.39 (2.41-7.97)	<0.001
CSF findings				
Leucocyte ≥10 cells/μL[a]				
No	14 (31.8)	48 (20.8)	1.00	
Yes	27 (61.4)	179 (77.5)	0.56 (0.29-1.06)	0.076
Leucocyte ≥100 cells/μL				
No	32 (72.7)	160 (69.3)	1.00	
Yes	9 (20.5)	67 (29.0)	0.71 (0.34-1.49)	0.370
Lymphocytic predominance >50%				
No	8 (18.2)	40 (17.3)	1.00	
Yes	34 (77.3)	185 (80.1)	0.93 (0.43-2.00)	0.846
Protein >100 mg/dL				
No	22 (50.0)	107 (46.3)	1.00	
Yes	20 (45.5)	119 (51.5)	0.82 (0.45-1.51)	0.532
Glucose <40 mg/dL				
No	22 (50.0)	133 (57.6)	1.00	
Yes	20 (45.5)	86 (37.2)	1.36 (0.74-2.49)	0.322
CSF/blood glucose ratio <50%				
No	15 (34.1)	93 (40.3)	1.00	
Yes	22 (50.0)	103 (44.6)	1.31 (0.68-2.53)	0.417
Radiological findings				
Chest radiography				
Normal	23 (52.3)	108 (46.8)	1.00	
Miliary TB	2 (4.5)	17 (7.4)	0.57 (0.13-2.42)	0.448
Other signs of TB	19 (43.2)	104 (45.0)	0.88 (0.48-1.62)	0.682
Hydrocephalus[a,d]				
No	12 (27.3)	133 (57.6)	1.00	
Yes	22 (50.0)	76 (32.9)	3.00 (1.48-6.05)	0.002
Neurosurgery in hydrocephalus patients[§§]				
No	13 (59.1)	40 (52.6)	1.25 (0.53-2.93)	0.604
Yes	9 (40.9)	36 (47.4)	1.00	
Basal meningeal enhancement				
No	14 (31.8)	101 (43.7)	1.00	
Yes	20 (45.5)	108 (46.8)	1.30 (0.66-2.58)	0.445
Cerebral infarct				
No	30 (68.2)	189 (81.8)	1.00	
Yes	4 (9.1)	20 (8.7)	1.23 (0.43-3.51)	0.692
Tuberculoma				
No	28 (63.6)	185 (80.1)	1.00	
Yes	6 (13.6)	24 (10.4)	1.59 (0.66-3.84)	0.302
At least 1 sign found on CT scan				
No	7 (15.9)	67 (29.0)	1.00	
Yes	27 (61.4)	142 (61.5)	1.76 (0.77-4.04)	0.183
Bacteriological findings				
TST positive				
No	38 (86.4)	176 (76.2)	1.00	
Yes	6 (13.6)	55 (23.8)	0.54 (0.23-1.28)	0.164
GeneXpert MTB/RIF testing				
Negative	25 (56.8)	135 (58.4)	1.00	

Patient characteristics	Dead (n=44)	Alive (n=231)	cHR (95% CI)	p-value
M.tb identified from CSF	8 (18.2)	37 (16.0)	1.21 (0.55-2.69)	0.632
M.tb identified from non-CSF	5 (11.4)	34 (14.7)	0.81 (0.31-2.13)	0.675
AFB smear microscopy				
Negative	33 (75.0)	184 (79.7)	1.00	
Positive from CSF	2 (4.5)	4 (1.7)	2.44 (0.59-10.19)	0.220
Positive from non-CSF	7 (15.9)	34 (14.7)	1.15 (0.51-2.60)	0.737
M. tb cultured from any source				
No	36 (81.8)	200 (86.6)	1.00	
Yes	2 (4.5)	21 (9.1)	0.56 (0.13-2.34)	0.429
In-hospital complications				
Motor disorders				
No	31 (70.5)	142 (61.5)	1.00	
Yes	12 (27.3)	89 (38.5)	0.66 (0.34-1.28)	0.216
Visual impairment				
No	42 (95.5)	215 (93.1)	1.00	
Yes	1 (2.3)	16 (6.9)	0.33 (0.05-2.40)	0.275
Hearing impairment				
No	41 (93.2)	221 (95.7)	1.00	
Yes	2 (4.5)	10 (4.3)	1.13 (0.27-4.69)	0.862
Neurodevelopmental delay				
No	37 (84.1)	200 (86.6)	1.00	
Yes	6 (13.6)	31 (13.4)	1.05 (0.44-2.49)	0.913
Epileptic seizures				
No	39 (88.6)	217 (93.9)	1.00	
Yes	5 (11.4)	14 (6.1)	1.81 (0.71-4.59)	0.212
Anti-TB drug-induced hepatotoxicity				
No	39 (88.6)	209 (90.5)	1.00	
Yes	5 (11.4)	22 (9.5)	1.21 (0.47-3.06)	0.693
Others				
Oral corticosteroid				
No	2 (4.5)	10 (4.3)	1.00	
Yes	40 (90.9)	214 (92.6)	0.94 (0.23-3.88)	0.931

cHR: crude hazard ratio, AFB: acid-fast bacilli, BCG: Bacillus Calmette-Guerin, CSF: cerebrospinal fluid, CI: confidence interval, GCS: Glasgow Coma Scale, HIV: human immunodeficiency virus, IQR: interquartile rage, TB: tuberculosis, TBM: tuberculous meningitis, TST: tuberculin skin test.
[§]In children aged <5 years, moderate malnutrition was defined as weight-for-age or height-for-age Z-scores ≥-3 and <-2 standard deviations (SD), and severe malnutrition as weight-for-age or height-for-age Z-scores <-3 SD. In children aged 5-14 years, moderate malnutrition was defined as height-for-age or BMI-for-age Z-scores ≥-3 and <-2 SD, and severe malnutrition as height-for-age or BMI-for-age Z-scores <-3 SD (*5*).
[¥]Diagnostic score was assessed using a uniform case definition criteria for TBM, and was categorized as definite TBM (microbiologically proven from CSF examination), probable TBM (diagnostic score of ≥10 points when cerebral imaging is not available or ≥12 points when cerebral imaging is available), and possible TBM (diagnostic score of 6-9 points when cerebral imaging is not available or 6-11 points when cerebral imaging is available) (*2*).
[¶]Severity of TBM was classified according to the modified British Medical Research Council grading system as stage I (GCS of 15 with no focal neurologic signs), stage II (GCS of 11-14 or 15 with focal neurologic signs), or stage III (GCS ≤10) (*7*).
[§§]Analysis was only performed in patients with hydrocephalus
[a]Variables eligible for inclusion in multivariate analysis.
[b,c,d]Due to the likelihood of collinearity (e.g. TBM stage *vs.* GCS score and hydrocephalus *vs.* signs of raised intracranial pressure), only one of each of these variables was included during the development of the final multivariate model.
[e]Even though HIV coinfection was found to be significantly associated with in-hospital death in univariate analysis, we did not include this variable in multivariate analysis due to the selective HIV testing and a very low number of patients with HIV positive (n=4), which might limit the statistical power of the analysis.

Appendix Table 5. Univariate logistic regression model for predictors of post-discharge death, tracked until the end of tuberculous meningitis treatment in children treated for tuberculous meningitis at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020

Patient characteristics	Dead (n=18)	Alive (n=91)	cOR (95% CI)	p-value
Year of diagnosis (median (IQR))	2017 (2015-2018)	2018 (2016-2019)	0.96 (0.76-1.20)	0.703
Year of diagnosis				
2011-2015	4 (22.2)	14 (15.4)	1.57 (0.45-5.48)	0.478
2016-2020	14 (77.8)	77 (84.6)	1.00	
Age, years (median (IQR))	4.0 (2.0-12.2)	7.0 (1.2-11.0)	0.98 (0.89-1.09)	0.752
Age[a]				
<2 years	3 (16.7)	26 (28.6)	0.65 (0.15-2.86)	0.573
2-4 years	6 (33.3)	9 (9.9)	3.78 (0.98-14.56)	0.054
5-9 years	3 (16.7)	22 (24.2)	0.77 (0.17-3.41)	0.734
10-14 years	6 (33.3)	34 (37.4)	1.00	
Sex[a]				
Male	10 (55.6)	39 (42.9)	1.67 (0.60-4.61)	0.325
Female	8 (44.4)	52 (57.1)	1.00	

Patient characteristics	Dead (n=18)	Alive (n=91)	cOR (95% CI)	p-value
Parent's last education				
Junior high school or lower	9 (50.0)	40 (44.0)	1.43 (0.51-4.05)	0.496
Senior high school or higher	8 (44.4)	51 (56.0)	1.00	
Parent's monthly income				
USD ≤140,00	12 (66.7)	52 (57.1)	1.96 (0.58-6.59)	0.276
USD >140,00	4 (22.2)	34 (37.4)	1.00	
Area of living				
Urban	10 (55.6)	40 (44.0)	1.00	
Rural	6 (33.3)	49 (53.8)	0.49 (0.16-1.46)	0.201
Weight-for-age Z-score				
≥-2 (normal)	6 (33.3)	34 (37.4)	1.00	
<-2 (underweight)	6 (33.3)	37 (40.7)	0.92 (0.27-3.12)	0.892
Height-for-age Z-score				
≥-2 (normal)	11 (61.1)	53 (58.2)	1.00	
<-2 (stunted)	7 (38.9)	38 (41.8)	0.89 (0.31-2.50)	0.821
Weight-for-height Z-score				
≥-2 (normal)	7 (38.9)	47 (51.6)	1.00	
<-2 (wasted)	11 (61.1)	44 (48.4)	1.67 (0.60-4.72)	0.326
BMI-for-age Z-score				
≥-2 (normal)	7 (38.9)	47 (51.6)	1.00	
<-2 (low BMI)	11 (61.1)	44 (48.4)	1.67 (0.60-4.72)	0.326
Nutritional status[§]				
Normal	6 (33.3)	30 (33.0)	1.00	
Moderate malnutrition	7 (38.9)	29 (31.9)	1.21 (0.36-4.02)	0.760
Severe malnutrition	5 (27.8)	32 (35.2)	0.78 (0.22-2.83)	0.707
Known BCG vaccination[a]				
No	7 (38.9)	15 (16.5)	3.22 (1.08-9.66)	0.037
Yes	11 (61.1)	76 (83.5)	1.00	
Known TB contact history				
No	13 (72.2)	68 (74.7)	1.00	
Yes	5 (27.8)	23 (25.3)	1.14 (0.37-3.54)	0.824
TBM category and stage				
TBM category[¥]				
Definite TBM	5 (27.8)	19 (20.9)	1.00	
Probable TBM	11 (61.1)	54 (59.3)	0.77 (0.24-2.52)	0.670
Possible TBM	2 (11.1)	18 (19.8)	0.42 (0.07-2.46)	0.338
TBM stage[¶,a,b]				
Stage I and II	7 (38.9)	67 (73.6)	1.00	
Stage III	11 (61.1)	24 (26.4)	4.39 (1.53-12.6)	0.006
GCS (median (IQR)) [a,b]	11 (10-12)	12 (11-14)	0.78 (0.64-0.96)	0.017
Presenting symptoms				
Fever				
No	2 (11.1)	7 (7.7)	1.00	
Yes	16 (88.9)	84 (92.3)	0.67 (0.13-3.51)	0.632
Severe headache				
No	13 (72.2)	59 (64.8)	1.00	
Yes	4 (22.2)	30 (33.0)	0.60 (0.18-2.02)	0.413
Muscle weakness				
No	11 (61.1)	65 (71.4)	1.00	
Yes	6 (33.3)	25 (27.5)	1.42 (0.47-4.24)	0.532
Altered consciousness[a]				
No	1 (5.6)	25 (27.5)	1.00	
Yes	17 (94.4)	66 (72.5)	6.44 (0.81-50.96)	0.078
Seizures				
No	7 (38.9)	40 (44.0)	1.00	
Yes	11 (61.1)	51 (56.0)	1.23 (0.44-3.47)	0.692
Shortness of breath				
No	15 (83.3)	79 (86.8)	1.00	
Yes	2 (11.1)	12 (13.2)	0.88 (0.18-4.33)	0.873
Persistent cough				
No	13 (72.2)	54 (59.3)	1.00	
Yes	5 (27.8)	37 (40.7)	0.56 (0.18-1.71)	0.309
Poor weight gain / weight loss				
No	7 (38.9)	49 (53.8)	1.00	
Yes	10 (55.6)	41 (45.1)	1.71 (0.60-4.88)	0.319
Duration of symptoms				
0-7 days	7 (38.9)	30 (33.0)	1.00	
8-14 days	8 (44.4)	50 (54.9)	0.69 (0.23-2.08)	0.506
>14 days	3 (16.7)	7 (7.7)	1.84 (0.38-8.94)	0.452

Patient characteristics	Dead (n=18)	Alive (n=91)	cOR (95% CI)	p-value
Examination findings at baseline				
Body temperature				
<38 °C	12 (66.7)	76 (83.5)	1.00	
≥38 °C	6 (33.3)	15 (16.5)	2.53 (0.82-7.81)	0.106
Respiration rate				
<25/min	6 (33.3)	36 (39.6)	1.36 (0.47-3.95)	0.574
≥25/min	12 (66.7)	53 (58.2)	1.00	
Involuntary movement				
No	16 (88.9)	80 (87.9)	1.00	
Yes	1 (5.6)	8 (8.8)	0.62 (0.07-5.35)	0.668
Cranial nerve palsies				
No	16 (88.9)	73 (80.2)	1.00	
Yes	1 (5.6)	16 (17.6)	0.28 (0.03-2.31)	0.240
Any type of motor deficit				
No	5 (27.8)	35 (38.5)	1.00	
Yes	11 (61.1)	47 (51.6)	1.64 (0.52-5.14)	0.398
Unequal pupils				
No	16 (88.9)	88 (96.7)	1.00	
Yes	1 (5.6)	1 (1.1)	5.50 (0.33-92.51)	0.237
Signs of upper motor neuron lesion				
No	3 (16.7)	15 (16.5)	1.00	
Yes	13 (72.2)	68 (74.7)	0.96 (0.24-3.78)	0.949
Signs of raised intracranial pressure[a,c]				
No	12 (66.7)	83 (91.2)	1.00	
Yes	6 (33.3)	8 (8.8)	5.19 (1.53-17.56)	0.008
CSF findings				
Leucocyte ≥10 cells/µL				
No	3 (16.7)	21 (23.1)	1.00	
Yes	15 (83.3)	67 (73.6)	1.57 (0.41-5.94)	0.509
Leucocyte ≥100 cells/µL				
No	9 (50.0)	61 (67.0)	1.00	
Yes	9 (50.0)	27 (29.7)	2.26 (0.81-6.32)	0.121
Lymphocytic predominance >50%				
No	3 (16.7)	18 (19.8)	1.00	
Yes	15 (83.3)	69 (75.8)	1.30 (0.34-5.00)	0.698
Protein >100 mg/dL				
No	7 (38.9)	39 (42.9)	1.00	
Yes	11 (61.1)	49 (53.8)	1.25 (0.44-3.52)	0.672
Glucose <40 mg/dL				
No	10 (55.6)	54 (59.3)	1.00	
Yes	7 (38.9)	29 (31.9)	1.30 (0.45-3.78)	0.626
CSF/blood glucose ratio <50%				
No	7 (38.9)	33 (36.3)	1.00	
Yes	7 (38.9)	35 (38.5)	0.94 (0.30-2.98)	0.920
Radiological findings				
Chest radiography				
Normal	5 (27.8)	38 (41.8)	1.00	
Miliary TB	1 (5.6)	6 (6.6)	1.27 (0.12-12.80)	0.841
Other signs of TB	12 (66.7)	47 (51.6)	1.94 (0.63-5.99)	0.249
Hydrocephalus[a,c]				
No	3 (16.7)	66 (72.5)	1.00	
Yes	13 (72.2)	23 (25.3)	12.43 (3.25-47.59)	<0.001
Neurosurgery in hydrocephalus patients[§§]				
No	11 (84.6)	10 (43.5)	7.15 (1.28-39.83)	0.025
Yes	2 (15.4)	13 (56.5)	1.00	
Basal meningeal enhancement				
No	6 (33.3)	42 (46.2)	1.00	
Yes	10 (55.6)	47 (51.6)	1.49 (0.50-4.45)	0.476
Cerebral infarct				
No	14 (77.8)	84 (92.3)	1.00	
Yes	2 (11.1)	5 (5.5)	2.40 (0.42-13.60)	0.323
Tuberculoma[a]				
No	12 (66.7)	85 (93.4)	1.00	
Yes	4 (22.2)	4 (4.4)	7.08 (1.56-32.13)	0.011
At least 1 sign found on CT scan[a]				
No	1 (5.6)	29 (31.9)	1.00	
Yes	15 (83.3)	60 (65.9)	7.25 (0.91-57.58)	0.061
Bacteriological findings				
TST positive[a]				

Patient characteristics	Dead (n=18)	Alive (n=91)	cOR (95% CI)	p-value
No	10 (55.6)	76 (83.5)	1.00	
Yes	8 (44.4)	15 (16.5)	4.05 (1.37-11.96)	0.011
GeneXpert MTB/RIF testing				
Negative	11 (61.1)	60 (65.9)	1.00	
M.tb identified from CSF	5 (27.8)	19 (20.9)	1.43 (0.44-4.65)	0.547
M.tb identified from non-CSF	2 (11.1)	6 (6.6)	1.82 (0.32-10.20)	0.497
AFB smear microscopy				
Negative	15 (83.3)	74 (81.3)	1.00	
Positive from CSF	2 (11.1)	12 (13.2)	0.82 (0.17-4.06)	0.810
Positive from non-CSF	1 (5.6)	5 (5.5)	0.99 (0.11-9.06)	0.991
M. tb cultured from any source				
No	14 (77.8)	79 (86.8)	1.00	
Yes	4 (22.2)	10 (11.0)	2.26 (0.62-8.21)	0.217
In-hospital complications				
Motor disorders[a]				
No	7 (38.9)	60 (65.9)	1.00	
Yes	11 61.1)	31 (34.1)	3.04 (1.07-8.62)	0.036
Visual impairment				
No	18 (100.0)	85 (93.4)	1.00	
Yes	0 (0.0)	6 (6.6)	n/a	0.999
Hearing impairment				
No	18 (100.0)	87 (95.6)	1.00	
Yes	0 (0.0)	4 (4.4)	n/a	0.999
Neurodevelopmental delay				
No	16 (88.9)	80 (87.9)	1.00	
Yes	2 (11.1)	11 (12.1)	0.91 (0.18-4.50)	0.907
Epileptic seizures				
No	17 (94.4)	82 (90.1)	1.00	
Yes	1 (5.6)	9 (9.9)	0.54 (0.06-4.51)	0.566
Anti-TB drug-induced hepatotoxicity				
No	14 (77.8)	76 (83.5)	1.00	
Yes	4 (22.2)	15 (16.5)	1.45 (0.42-5.01)	0.559
Others				
Oral corticosteroid				
No	0 (0.0)	4 (4.4)	n/a	0.999
Yes	17 (94.4)	85 (93.4)	1.00	
Physiotherapy				
No	14 (77.8)	62 (68.1)	1.73 (0.45-6.58)	0.421
Yes	3 (16.7)	23 (25.3)	1.00	

cOR: crude odds ratio, AFB: acid-fast bacilli, BCG: Bacillus Calmette-Guerin, CSF: cerebrospinal fluid, CI: confidence interval, GCS: Glasgow Coma Scale, IQR: interquartile rage, TB: tuberculosis, TBM: tuberculous meningitis, TST: tuberculin skin test.
[§]In children aged <5 years, moderate malnutrition was defined as weight-for-age or height-for-age Z-scores ≥-3 and <-2 standard deviations (SD), and severe malnutrition as weight-for-age or height-for-age Z-scores <-3 SD. In children aged 5-14 years, moderate malnutrition was defined as height-for-age or BMI-for-age Z-scores ≥-3 and <-2 SD, and severe malnutrition as height-for-age or BMI-for-age Z-scores <-3 SD (*5*).
[¥]Diagnostic score was assessed using a uniform case definition criteria for TBM, and was categorized as definite TBM (microbiologically proven from CSF examination), probable TBM (diagnostic score of ≥10 points when cerebral imaging is not available or ≥12 points when cerebral imaging is available), and possible TBM (diagnostic score of 6-9 points when cerebral imaging is not available or 6-11 points when cerebral imaging is available) (*2*).
[¶]Severity of TBM was classified according to the modified British Medical Research Council grading system as stage I (GCS of 15 with no focal neurologic signs), stage II (GCS of 11-14 or 15 with focal neurologic signs), or stage III (GCS ≤10) (*7*).
[§§]Analysis was only performed in patients with hydrocephalus
[a]Variables eligible for inclusion in multivariate analysis.
[b,c]Due to the likelihood of collinearity (TBM stage *vs.* GCS score and hydrocephalus *vs.* signs of raised intracranial pressure), only one of each of these variables was included during the development of the final multivariate model.

Appendix Table 6. Univariate logistic regression model for predictors of severe neurologic sequelae at tuberculous meningitis treatment completion in children treated for tuberculous meningitis at Hasan Sadikin Hospital, Bandung, Indonesia, 2011–2020

	Severe neurologic sequelae			
Patient characteristics	Yes (n=33)	No (n=58)	cOR (95% CI)	p-value
Year of diagnosis (median (IQR))	2018 (2016-2018)	2018 (2016-2019)	1.05 (0.86-1.28)	0.628
Year of diagnosis				
2011-2015	3 (9.1)	11 (19.0)	0.43 (0.11-1.66)	0.219
2016-2020	30 (90.9)	47 (81.0)	1.00	
Age, years (median (IQR))			0.93 (0.85-1.02)	0.138
Age[a]				
<2 years	13 (39.4)	13 (22.4)	2.78 (0.94-8.20)	0.064
2-4 years	2 (6.1)	7 (12.1)	0.79 (0.14-4.55)	0.795
5-9 years	9 (27.3)	13 (22.4)	1.92 (0.61-6.02)	0.261
10-14 years	9 (27.3)	25 (43.1)	1.00	

Patient characteristics	Severe neurologic sequelae		cOR (95% CI)	p-value
	Yes (n=33)	No (n=58)		
Sex[a]				
Male	12 (36.4)	27 (46.6)	0.66 (0.27-1.58)	0.346
Female	21 (63.6)	31 (53.4)	1.00	
Parent's last education				
Junior high school or lower	17 (51.5)	23 (39.7)	1.62 (0.68-3.82)	0.275
Senior high school or higher	16 (48.5)	35 (60.3)	1.00	
Parent's monthly income				
USD ≤140,00	17 (51.5)	35 (60.3)	0.69 (0.28-1.70)	0.424
USD >140,00	14 (42.4)	20 (34.5)	1.00	
Area of living				
Urban	12 (36.4)	28 (48.3)	1.00	
Rural	20 (60.6)	29 (50.0)	1.61 (0.66-3.90)	0.292
Weight-for-age Z-score				
≥-2 (normal)	13 (39.4)	21 (36.2)	1.00	
<-2 (underweight)	16 (48.5)	21 (36.2)	1.23 (0.48-3.18)	0.668
Height-for-age Z-score				
≥-2 (normal)	19 (57.6)	34 (58.6)	1.00	
<-2 (stunted)	14 (42.4)	24 (41.4)	1.04 (0.44-2.48)	0.923
Weight-for-height Z-score				
≥-2 (normal)	14 (42.4)	33 (56.9)	1.00	
<-2 (wasted)	19 (57.6)	25 (43.1)	1.79 (0.75-4.25)	0.186
BMI-for-age Z-score				
≥-2 (normal)	14 (42.4)	33 (56.9)	1.00	
<-2 (low BMI)	19 (57.6)	25 (43.1)	1.79 (0.75-4.25)	0.186
Nutritional status[§]				
Normal	9 (27.3)	21 (36.2)	1.00	
Moderate malnutrition	12 (36.4)	17 (29.3)	1.65 (0.56-4.83)	0.363
Severe malnutrition	12 (36.4)	20 (34.5)	1.40 (0.48-4.04)	0.534
Known BCG vaccination				
No	3 (9.1)	12 (20.7)	0.38 (0.10-1.47)	0.163
Yes	30 (90.9)	46 (79.3)	1.00	
Known TB contact history				
No	25 (75.8)	43 (74.1)	1.00	
Yes	8 (24.2)	15 (25.9)	0.92 (0.34-2.47)	0.864
TBM category and stage				
TBM category[¥]				
Definite TBM	6 (18.2)	13 (22.4)	1.00	
Probable TBM	22 (66.7)	32 (55.2)	1.49 (0.49-4.52)	0.481
Possible TBM	5 (15.2)	13 (22.4)	0.83 (0.20-3.43)	0.800
TBM stage[¶,a]				
Stage I	5 (15.2)	17 (29.3)	1.00	
Stage II	14 (42.4)	31 (53.4)	1.53 (0.47-5.00)	0.476
Stage III	14 (42.4)	10 (17.2)	4.76 (1.32-17.22)	0.017
GCS (median (IQR))			0.91 (0.76-1.09)	0.316
Presenting symptoms				
Fever				
No	2 (6.1)	5 (8.6)	1.00	
Yes	31 (93.9)	53 (91.4)	1.46 (0.27-7.99)	0.661
Severe headache				
No	23 (69.7)	36 (62.1)	1.00	
Yes	9 (27.3)	21 (36.2)	0.67 (0.26-1.72)	0.405
Muscle weakness				
No	23 (69.7)	42 (72.4)	1.00	
Yes	9 (27.3)	16 (27.6)	1.03 (0.39-2.69)	0.956
Altered consciousness				
No	9 (27.3)	16 (27.6)	1.00	
Yes	24 (72.7)	42 (72.4)	1.02 (0.39-2.65)	0.974
Seizures				
No	13 (39.4)	27 (46.6)	1.00	
Yes	20 (60.6)	31 (53.4)	1.34 (0.56-3.19)	0.509
Shortness of breath				
No	30 (90.9)	49 (84.5)	1.00	
Yes	3 (9.1)	9 (15.5)	0.54 (0.14-2.17)	0.389
Persistent cough				
No	21 (63.6)	33 (56.9)	1.00	
Yes	12 (36.4)	25 (43.1)	0.75 (0.31-1.82)	0.530
Poor weight gain / weight loss				
No	14 (42.4)	35 (60.3)	1.00	

Patient characteristics	Severe neurologic sequelae		cOR (95% CI)	p-value
	Yes (n=33)	No (n=58)		
Yes	18 (54.5)	23 (39.7)	1.96 (0.82-4.69)	0.132
Duration of symptoms				
0-7 days	14 (42.4)	16 (27.6)	1.00	
8-14 days	16 (48.5)	34 (58.6)	0.54 (0.21-1.36)	0.192
>14 days	3 (9.1)	4 (6.9)	0.86 (0.16-4.51)	0.856
Examination findings at baseline				
Body temperature				
<38 °C	23 (69.7)	53 (91.4)	1.00	
≥38 °C	10 (30.3)	5 (8.6)	4.61 (1.42-14.99)	0.011
Respiration rate				
<25/min	12 (36.4)	24 (41.4)	1.00	
≥25/min	21 (63.6)	32 (55.2)	1.31 (0.54-3.18)	0.547
Involuntary movement				
No	29 (87.9)	51 (87.9)	1.00	
Yes	4 (12.1)	4 (6.9)	1.76 (0.41-7.56)	0.448
Cranial nerve palsies				
No	26 (78.8)	47 (81.0)	1.00	
Yes	7 (21.2)	9 (15.5)	1.41 (0.47-4.21)	0.543
Any type of motor deficit[a]				
No	8 (24.2)	27 (46.6)	1.00	
Yes	24 (72.7)	23 (39.7)	3.52 (1.33-9.33)	0.011
Unequal pupils				
No	32 (97.0)	56 (96.6)	1.00	
Yes	1 (3.0)	0 (0.0)	n/a	1.000
Signs of upper motor neuron lesions				
No	5 (15.2)	10 (17.2)	1.00	
Yes	27 (81.8)	41 (70.7)	1.32 (0.40-4.28)	0.647
Signs of raised intracranial pressure				
No	31 (93.9)	52 (89.7)	1.00	
Yes	2 (6.1)	6 (10.3)	0.56 (0.11-2.94)	0.493
CSF findings				
Leucocyte ≥10 cells/µL				
No	9 (27.3)	12 (20.7)	1.00	
Yes	23 (69.7)	44 (75.9)	0.70 (0.26-1.90	0.479
Leucocyte ≥100 cells/µL				
No	24 (72.7)	37 (63.8)	1.00	
Yes	8 (24.2)	19 (32.8)	0.65 (0.24-1.72)	0.384
Lymphocytic predominance >50%				
No	9 (27.3)	9 (15.5)	1.00	
Yes	23 (69.7)	46 (79.3)	0.50 (0.17-1.43)	0.196
Protein >100 mg/dL				
No	11 (33.3)	28 (48.3)	1.00	
Yes	21 (63.6)	28 (48.3)	1.91 (0.78-4.69)	0.158
Glucose <40 mg/dL				
No	20 (60.6)	34 (58.6)	1.00	
Yes	12 (36.4)	17 (29.3)	1.20 (0.48-3.02)	0.699
CSF/blood glucose ratio <50%				
No	13 (39.4)	20 (34.5)	1.00	
Yes	15 (45.5)	20 (34.5)	1.15 (0.44-3.04)	0.772
Radiological findings				
Chest radiography[a]				
Normal	9 (27.3)	29 (50.0)	1.00	
Miliary TB	3 (9.1)	3 (5.2)	3.22 (0.55-18.85)	0.194
Other signs of TB	21 (63.6)	26 (44.8)	2.60 (1.01-6.68)	0.047
Hydrocephalus[a]				
No	22 (66.7)	44 (75.9)	1.00	
Yes	11 (33.3)	12 (20.7)	1.83 (0.70-4.81)	0.218
Neurosurgery in hydrocephalus patients[§§]				
No	4 (36.4)	6 (50.0)	0.57 (0.11-3.04)	0.511
Yes	7 (63.6)	6 (50.0)	1.00	
Basal meningeal enhancement				
No	14 (42.4)	28 (48.3)	1.00	
Yes	19 (57.6)	28 (48.3)	1.36 (0.57-3.23)	0.490
Cerebral infarct				
No	30 (90.9)	54 (93.1)	1.00	
Yes	3 (9.1)	2 (3.4)	2.70 (0.43-17.07)	0.291
Tuberculoma				
No	31 (93.9)	54 (93.1)	1.00	

Patient characteristics	Severe neurologic sequelae		cOR (95% CI)	p-value
	Yes (n=33)	No (n=58)		
Yes	2 (6.1)	2 (3.4)	1.74 (0.23-12.99)	0.588
At least 1 sign found on CT scan[a]				
No	7 (21.2)	22 (37.9)	1.00	
Yes	26 (78.8)	34 (58.6)	2.40 (0.89-6.48)	0.083
Bacteriological findings				
TST positive				
No	26 (78.8)	50 (86.2)	1.00	
Yes	7 (21.2)	8 (13.8)	1.68 (0.55-5.15)	0.362
GeneXpert MTB/RIF testing				
Negative	23 (69.7)	37 (63.8)	1.00	
M.tb identified from CSF	6 (18.2)	13 (22.4)	0.74 (0.25-2.23)	0.595
M.tb identified from non-CSF	4 (12.1)	2 (3.4)	3.22 (0.54-18.99)	0.197
AFB smear microscopy[a]				
Negative	23 (69.7)	51 (87.9)	1.00	
Positive from non-CSF	8 (24.2)	4 (6.9)	4.43 (1.21-16.23)	0.024
M. tb cultured from any source				
No	28 (84.8)	51 (87.9)	1.00	
Yes	5 (15.2)	5 (8.6)	1.82 (0.48-6.84)	0.374
Others				
Anti-TB drug-induced hepatotoxicity				
No	29 (87.9)	47 (81.0)	1.00	
Yes	4 (12.1)	11 (19.0)	0.59 (0.17-2.02)	0.401
Oral corticosteroid				
No	0 (0.0)	4 (6.9)	n/a	0.999
Yes	33 (100.0)	52 (89.7)	1.00	
Physiotherapy				
No	21 (63.6)	41 (70.7)	0.56 (0.21-1.48)	0.241
Yes	11 (33.3)	12 (20.7)	1.00	

cOR: crude odds ratio, AFB: acid-fast bacilli, BCG: Bacillus Calmette-Guerin, CSF: cerebrospinal fluid, CI: confidence interval, GCS: Glasgow Coma Scale, IQR: interquartile rage, TB: tuberculosis, TBM: tuberculous meningitis, TST: tuberculin skin test.
[§]In children aged <5 years, moderate malnutrition was defined as weight-for-age or height-for-age Z-scores ≥-3 and <-2 standard deviations (SD), and severe malnutrition as weight-for-age or height-for-age Z-scores <-3 SD. In children aged 5-14 years, moderate malnutrition was defined as height-for-age or BMI-for-age Z-scores ≥-3 and <-2 SD, and severe malnutrition as height-for-age or BMI-for-age Z-scores <-3 SD (5).
[¥]Diagnostic score was categorized as definite TBM (microbiologically proven from CSF examination), probable TBM (diagnostic score of ≥10 points when cerebral imaging is not available or ≥12 points when cerebral imaging is available), and possible TBM (diagnostic score of 6-9 points when cerebral imaging is not available or 6-11 points when cerebral imaging is available) (2).
[¶]Severity of TBM was classified as stage I (GCS of 15 with no focal neurologic signs), stage II (GCS of 11-14 or 15 with focal neurologic signs), or stage III (GCS ≤10) (7).
[§§]Analysis was only performed in patients with hydrocephalus
[a]Variables eligible for inclusion in multivariate analysis.

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