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...
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.

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 ≥10 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, quadriplegia, 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 (post-discharge 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*

| Characteristic                        | Total patients | <5 y | 5–14 y |
|---------------------------------------|----------------|------|--------|
| **Age, y, median (IQR)**              | 283            |      |        |
| M                                     | 283            | 150 (53.0) | 74 (48.4) | 76 (58.5) |
| F                                     | 283            | 133 (47.0) | 79 (51.6) | 54 (41.5) |
| **Nutritional status†**               |                |      |        |
| WFAZ, median (IQR)                    | 227            | 153 (1.9) | 74 (2.8) | 30 (23.1) |
| HFAZ, median (IQR)                    | 283            | 153 (1.9) | 74 (2.8) | 30 (23.1) |
| BFAZ, median (IQR)                    | 283            | 153 (1.9) | 74 (2.8) | 30 (23.1) |
| Moderately malnourished               |                |      |        |
| Severely malnourished                 |                |      |        |
| Known BCG vaccination                 | 283            | 153 (120) | 36 (23.5) | 37 (28.3) |
| Known TB contact history              | 283            | 153 (73) | 36 (23.5) | 37 (28.5) |
| Known HIV co-infection                | 283            | 153 (0) | 36 (23.5) | 37 (28.5) |
| **Baseline temperature, °C, median (IQR)** | 282            | 36.7 | 37.0 | 37.0 |
| **Symptoms duration, d, median (IQR)§** | 269            | 6 | 8 | 9 |
| **Motor function**                    |                |      |        |
| Hemiparesis                           | 263            | 51 (19.4) | 27 (19.0) | 24 (19.8) |
| Quadriparesis                         | 263            | 51 (19.4) | 27 (19.0) | 24 (19.8) |
| Cranial nerve palsy                   | 277            | 48 (17.2) | 31 (20.8) | 17 (13.3) |
| Signs of upper motor neuron lesion    | 264            | 188 (71.2) | 93 (65.0) | 96 (76.5) |
| Signs of raised intracranial pressure | 283            | 47 (16.6) | 29 (19.0) | 18 (13.8) |
| **TBM category¶**                    |                |      |        |
| Definite                              | 283            | 51 (18.0) | 26 (17.0) | 25 (19.2) |
| Probable                              | 283            | 178 (62.9) | 101 (66.0) | 77 (59.2) |
| Possible                              | 283            | 54 (19.1) | 26 (17.0) | 28 (21.5) |
| **GCS, median (IQR)**                 | 253            | 12 (10–14) | 10 (10–15) | 12 (10–14) |
| **TBM stage#**                        |                |      |        |
| Stage I                               | 283            | 57 (20.1) | 35 (22.9) | 22 (16.9) |
| Stage II                              | 283            | 131 (46.3) | 60 (39.2) | 71 (54.6) |
| Stage III                             | 283            | 95 (33.6) | 58 (37.9) | 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‡ | Total patients | Age <5 y | Age 5–14 y |
|-------------------|---------------|---------|-----------|
| 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 | Total patients | Age <5 y | Age 5–14 y |
|-------------------|---------------|---------|-----------|
| 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 | Total patients | Age <5 y | Age 5–14 y |
|----------------------|---------------|---------|-----------|
| 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** | Total patients | Age <5 y | Age 5–14 y |
|-------------------------|---------------|---------|-----------|
| 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 range; 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%]) (22) 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

| Variable | Total | Stage I† | Stage II† | Stage III† |
|----------|-------|----------|-----------|------------|
| Outcome at treatment completion‡# | 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 range.
†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.

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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*
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                             |        |        |                   |         |              |         |
| <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.
¶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).
In addition, among children with prolonged exposure to \textit{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](image-url)
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 TB research was available (50), the retrospective nature of the study did not provide us with complete records on all key variables, especially longer-term outcomes. 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 | 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 | Referent | Referent |
| TBM stage¶¶ | | | | | | |
| Stage I or II | 7 (38.9) | 67 (73.6) | Referent | Referent | 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) | Referent | 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 | Referent | Referent |
| Hydrocephalus on CT | | | | | | |
| No | 3 (16.7) | 66 (72.5) | Referent | Referent | 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 | 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 | 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.
§Additional independent predictors of postdischarge death were observed.
¶Stage I was defined as 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). 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.
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 (I), 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 (II), and includes a wide range of variables in the analysis.

In conclusion, childhood TB in Indonesia causes substantial neurologic sequelae and death, despite standard treatment. Several predictors of inhospital 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.

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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.

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                  | Referent | Yes‡§ | No† | Crude OR (95% CI) | p value | aOR (95% CI) | p value |
|---------------------------|----------|-------|-----|-------------------|---------|--------------|---------|
| 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 (0.34–3.78)| 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 | 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 | Referent | Referent |
| TBM stage¶                |          |       |     |                   |         |              |         |
| Stage I                   | 5 (15.2)| 17 (29.3)| Referent | Referent | 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 | 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 | 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).
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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, quadripareisis 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 \textit{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) | 5     | 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). |
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

| Symptom                                      | Stage I                        | Stage II                      | Stage III                      |
|----------------------------------------------|--------------------------------|-------------------------------|--------------------------------|
|                                              | Value                          | Value                         | Value                          |
| Fever                                        | 57 (46 (80.7))                 | 131 (122 (93.1))              | 95 (82 (86.3))                 |
| Severe headache                              | 56 (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 (%). a: 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       |            |               |              |         |
| 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          |         |
| Agea                   |            |               |              |         |
| <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          |         |
| Sexa                    |            |               |              |         |
| 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 |            |               |              |         |
| 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                    |             |               |              |         |
| 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                 |             |               |              |         |
| 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                        |             |               |              |         |
| 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 stageII                              |             |               |              |         |
| 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))                       | 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                                 |             |               |              |         |
| 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                      |             |               |              |         |
| 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***            |             |               |                         |         |
| 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***          |             |               |                         |         |
| 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                              |             |               |                         |         |
| 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 (0.19-2.42)        | 0.448   |
| Other signs of TB                                   | 19 (43.2)   | 104 (45.0)    | 0.88 (0.48-1.62)        | 0.682   |
| Hydrocephalus***                                    |             |               |                         |         |
| 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 (0.68-2.58)        | 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 (0.86-3.84)        | 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                    |         |
The 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=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 (0.19-2.34) | 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 |

The variables eligible for inclusion in multivariate analysis were determined based on statistical significance (p < 0.20) from univariate analysis. The multivariate model was constructed using forward selection, and only variables with p-values ≤ 0.05 were included. The final model included the following variables: age, sex, HIV coinfection, and hydrocephalus.

| Patient characteristics | Dead (n=44) | Alive (n=231) | 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 | 4 (22.2) | 14 (15.4) | 1.57 (0.45-5.48) | 0.478 |
| Agea | 14 (77.8) | 77 (84.6) | 1.00 |
| Ageb | 4.0 (2.0-12.2) | 7.0 (1.2-11.0) | 0.98 (0.89-1.09) | 0.752 |
| Sexb | Male | 10 (55.6) | 39 (42.9) | 1.67 (0.60-4.61) | 0.325 |
| Female | 8 (44.4) | 52 (57.1) | 1.00 |

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 |
|-------------------------------------------------|-------------|--------------|--------------|---------|
| 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)    | 47 (51.6)    | 1.00         |         |
| 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                            |              |              |              |         |
| 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

| Examination findings at baseline | Dead (n=18) | Alive (n=91) | cOR (95% CI) | p-value |
|----------------------------------|------------|--------------|--------------|---------|
| **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** | 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** | 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                     |            |              |              |         |
| 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 | 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                       |            |              |              |         |
| 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  |            |              |              |         |
| 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                      |            |              |              |         |
| Patient characteristics | Dead (n=18) | Alive (n=91) | cOR (95% CI) | p-value |
|-------------------------|------------|-------------|--------------|---------|
| No                      | 10 (55.6)  | 76 (83.3)   | 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         |         |
| Positive from CSF       | 5 (27.8)   | 19 (20.9)   | 1.43 (0.44-4.65) | 0.547 |
| Positive from non-CSF   | 1 (5.6)    | 5 (5.5)     | 0.99 (0.11-9.06) | 0.991 |
| AFBs 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* | No (38.9) | Yes (116.1) | 1.00 | 0.036 |
| Visual impairment |            |             |      |       |
| No             | 18 (100.0) | 85 (93.4)   | 0.99 |       |
| Yes            | 0 (0.0)    | 6 (6.6)     | 0.10 |       |
| Hearing impairment |         |             |      |       |
| No             | 18 (100.0) | 87 (95.6)   | 1.00 |       |
| Yes            | 0 (0.0)    | 4 (4.4)     | 0.99 |       |
| Neurodevelopmental delay |   |            |      |       |
| No             | 16 (88.9)  | 80 (87.9)   | 1.00 |       |
| Yes            | 2 (11.1)   | 11 (12.1)   | 0.91 |       |
| Epileptic seizures |         |             |      |       |
| No             | 17 (94.4)  | 82 (90.1)   | 1.00 |       |
| Yes            | 1 (5.6)    | 9 (9.9)     | 0.54 |       |
| Anti-TB drug-induced hepatotoxicity |   |            |      |       |
| No             | 14 (77.8)  | 76 (83.5)   | 1.00 |       |
| Yes            | 4 (22.2)   | 15 (16.5)   | 1.45 |       |
| Others         |            |             |      |       |
| Oral corticosteroid |         |             |      |       |
| No             | 0 (0.0)    | 4 (4.4)     | 0.99 |       |
| Yes            | 17 (94.4)  | 85 (93.4)   | 1.00 |       |
| Physiotherapy  |            |             |      |       |
| No             | 14 (77.8)  | 62 (68.1)   | 1.73 |       |
| 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 ≤-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 ≥9 points when cerebral imaging is not available or ≥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.

††Variables eligible for inclusion in multivariate analysis.

§§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

| Year of diagnosis (median (IQR)) | Yes (n=33) | No (n=58) | cOR (95% CI) | p-value |
|----------------------------------|------------|-----------|--------------|---------|
| 2018 (2016-2018)                 | 13 (39.4)  | 13 (22.4) | 2.78 (0.94-8.20) | 0.064 |
| 2018 (2016-2019)                 | 11 (33.3)  | 13 (22.4) | 0.44 (0.13-1.50) | 0.217 |
| 2019 (2016-2019)                 | 14 (42.4)  | 11 (19.0) | 1.00         |         |
| 2020 (2016-2019)                 | 14 (42.4)  | 11 (19.0) | 1.00         |         |
| Age (years (median (IQR)))       |            |           |              |         |
| <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 (0.44-8.55) | 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 |
|--------------------------|---------------------------|--------------|---------|
| **Sex**                  |                           |              |         |
| 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 (0.46-3.18) | 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**            |                           |              |         |
| 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))**   |                           |              |         |
| No                       |                           |              |         |
| Yes                      |                           |              |         |
| **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 |  |
|-------------------------|---------------------------|---|
|                         | Yes (n=33)                | No (n=58) | cOR (95% CI) | p-value |
| Duration of symptoms    | Yes (n=33)                | No (n=58) |  |
| 0-7 days                | 18 (54.5)                 | 23 (39.7) | 1.96 (0.82-4.69) | 0.132 |
| 8-14 days               | 14 (42.4)                 | 16 (27.6) | 1.00          |       |
| >14 days                | 3 (9.1)                   | 4 (6.9)   | 0.86 (0.16-4.51) | 0.856 |
| Examination findings at baseline | | | | |
| Body temperature        | Yes (n=33)                | No (n=58) | cOR (95% CI) | p-value |
| <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        | Yes (n=33)                | No (n=58) |  |
| <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    | Yes (n=33)                | No (n=58) |  |
| 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   | Yes (n=33)                | No (n=58) |  |
| 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 deficita | Yes (n=33)                | No (n=58) |  |
| No                      | 8 (24.2)                  | 27 (46.6) | 1.00          |       |
| Yes                     | 24 (72.7)                 | 33 (53.4) | 1.32 (0.40-4.28) | 0.647 |
| Unequal pupils          | Yes (n=33)                | No (n=58) |  |
| 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 | Yes (n=33)                | No (n=58) |  |
| 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 | Yes (n=33)                | No (n=58) |  |
| 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            | Yes (n=33)                | No (n=58) |  |
| Leucocyte ≥10 cells/µL  | No (n=33)                 | Yes (n=58) |  |
| 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 | Yes (n=33)                | No (n=58) |  |
| No                      | 24 (72.7)                 | 37 (63.8) | 1.00          |       |
| Yes                     | 8 (24.2)                  | 19 (32.8) | 1.30 (0.54-3.18) | 0.384 |
| Lymphocytic predominance >50% | Yes (n=33)                | No (n=58) |  |
| 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      | Yes (n=33)                | No (n=58) |  |
| No                      | 11 (33.3)                 | 28 (48.3) | 1.00          |       |
| Yes                     | 21 (63.6)                 | 28 (48.3) | 0.97 (0.52-1.80) | 0.844 |
| Glucose <40 mg/dL       | Yes (n=33)                | No (n=58) |  |
| 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% | Yes (n=33)                | No (n=58) |  |
| 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 radiographya         |      | | |
| 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 |
| Hydrocephalusa          | Yes (n=33)                | No (n=58) |  |
| 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§§ | Yes (n=33)                | No (n=58) |  |
| No                      | 4 (36.4)                  | 6 (50.0)  | 1.00          |       |
| Yes                     | 7 (63.6)                  | 6 (50.0)  | 0.57 (0.11-3.04) | 0.511 |
| Basal meningeal enhancement | Yes (n=33)                | No (n=58) |  |
| 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        | Yes (n=33)                | No (n=58) |  |
| 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 (n=33)                 | Yes (n=58) |  |
| No                      | 31 (93.9)                 | 54 (93.1) | 1.00          |       |
### Patient characteristics

|                        | Severe neurologic sequelae |                          |                          | p-value       |
|------------------------|----------------------------|--------------------------|--------------------------|---------------|
|                        | Yes (n=33)                 | No (n=58)                |                          |               |
| At least 1 sign found on CT scan* |                            |                          |                          |               |
| No                     | 2 (6.1)                    | 2 (3.4)                  | 1.74 (0.23-12.99)        | 0.588         |
| 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                     |               |
| Positive from non-CSF  | 8 (24.2)                   | 4 (6.9)                  | 4.43 (1.21-16.23)        | 0.024         |
| 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 | 28 (84.8)                | 51 (87.9)                | 1.00                     |               |
| No                     | 5 (15.2)                   | 5 (6.6)                  | 1.82 (0.48-6.84)         | 0.374         |
| Yes                    |                            |                          |                          |               |
| Others                 |                            |                          |                          |               |
| Anti-TB drug-induced hepatotoxicity | 29 (87.9)                | 47 (81.0)                | 1.00                     |               |
| No                     | 4 (12.1)                   | 11 (19.0)                | 0.59 (0.17-2.02)         | 0.401         |
| Yes                    |                            |                          |                          |               |
| 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

aVariables eligible for inclusion in multivariate analysis.

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