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Early Mortality among Immunocompetent Patients of Tuberculous Meningitis: A Prospective Study

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Abstract. Most deaths in tuberculous meningitis occur in the early part of the illness. We assessed the determinants of early deaths, occurring within 2 months of intensive therapy. We prospectively included consecutive newly diagnosed adults with HIV-negative tuberculous meningitis. Patients were given WHO-recommended antituberculosis treatment and were followed up for 9 months. We enrolled 152 patients. A total of 26 deaths were recorded during 2 months. The logistic regression analysis revealed that papilledema ($P = 0.029$, odds ratio (OR) = 4.8 [1.2–19.8]), increasing age ($P = 0.001$, OR = 1.07 [1.03–1.1]), stage-III disease (Glasgow coma scale score ≤ 10; $P = 0.01$, OR = 4.2 [1.4–12.3]), and hydrocephalus ($P = 0.003$, OR = 8.4 [2.1–33.6]) were independently associated with death. In addition, cerebral infarcts ($P = 0.012$, OR = 5.6 [1.5–21.3]), paraparesis ($P = 0.004$, OR = 8.8 [2.02–38.1]), and age ($P = 0.005$, OR = 1.05 [1.02–1.09]) were associated with poor functional outcome. In conclusion, disease severity predicts early deaths in tuberculous meningitis.

Tuberculous meningitis is associated with substantial morbidity and mortality. The mortality in tuberculous meningitis ranges from 20% to 50%.[1,2] In Vietnam, a meta-analysis evaluated 9-month tuberculous meningitis–associated mortality among 1,699 (951 HIV-uninfected and 748 HIV-infected) subjects. During the 9 months, 219 (23%) HIV-uninfected subjects died. In the HIV-infected group, 384 (51.3%) subjects died. Predictors for increased mortality in both the groups were higher disease severity grade and lower cerebrospinal fluid (CSF) lymphocyte cell count.[3]A meta-analysis of pediatric data showed an increased risk of death (19·3%) in children, and the survivors were at increased risk (53·9%) of neurological sequelae. Diagnosis at advanced stages was the most important predictor of adverse outcomes.[4] In HIV-infected patients, tuberculous meningitis is associated with a very high mortality of 50%. In drug-resistant tuberculous meningitis in patients with HIV coinfection, mortality is almost always certain.[5]

Many studies have noted that most tuberculous meningitis–related deaths occur while the patient is in the hospital. In a retrospective study, which included 263 patients (100 HIV-infected), 80 patients died while they were still in the hospital. Forty patients died within the first 14 days of admission. HIV infection, age older than 40 years, positive CSF tuberculosis culture, and Medical Research Council disease severity grade II or III were major determinants of mortality.[6] In an Indian study, the in-hospital mortality was approximately 27% (27/98).[7,8]

In this prospective study, we evaluated the determinants of death, occurring during 2 months, while patients were receiving a 4-drug intensive treatment regimen. The study period ranged from September 2016 to September 2018. Prior ethical approval for the study was taken from the Institutional Ethics Committee. Written informed consent was obtained from the patients or their legal guardian. Consecutive patients who fulfilled the Consensus International Tuberculous Meningitis Case Definition Criteria were included.[9] We did not include HIV-infected patients.

All included patients underwent a detailed neurological evaluation and were subjected to blood hematological and biochemical parameters and HIV ELISA. Patients were also subjected to chest X-ray. Cerebrospinal fluid specimens were evaluated for routine biochemical and microscopic parameters. Ziehl–Neelson staining along with CSF culture was performed. Each CSF specimen was subjected to cartridge-based nucleic acid amplification test. Gram staining and India ink staining were also performed. Magnetic resonance imaging of the brain was performed. Imaging features, especially leptomeningeal enhancement, tuberculomas, basal exudates, hydrocephalus, and cerebral infarcts were recorded. Tuberculous meningitis was categorized into three severity stages. Stage I was defined with a Glasgow Coma Scale (GCS) score of 15 and without any focal neurological deficit. Stage II was characterized with a GCS score of 11–14 or with focal neurological deficit. Stage III was characterized with a GCS score ≤ 10.[10]

All enrolled patients were given WHO-recommended antituberculosis treatment. For the initial 2 months, patients received daily oral isoniazid, rifampicin, and pyrazinamide, along with intramuscular streptomycin in recommended doses. In the continuation phase of at least 7 months, patients received isoniazid and rifampicin.[11] The patients also received intravenous dexamethasone for 4 weeks in tapering doses followed by oral dexamethasone for 4 weeks.[10] Every patient was given 20 mg of oral pyridoxine per day.

The primary outcome was deaths occurring within 2 months of intensive therapy. We also the assessed time to death and disability of survivors using modified Barthel Index (MBI). Poor functional outcome was defined as MBI ≤ 12, whereas good functional outcome was defined as MBI > 12.[12]

Statistical analysis was performed using SPSS software (version 24.0; SPSS Inc, Chicago, IL). For univariate analysis, the categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney U test. The multivariate analysis was performed using the binary logistic regression. Univariate time-to-death analysis was performed using the

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TABLE 1
Baseline clinical, laboratory, and neuroimaging characteristics of 152 tuberculous meningitis cases

Serial number	Variables	Values
1.	Age in years	
	Mean ± SD	31.04 ± 14.45
	Median (IQR)	26.50 (20)
2.	Gender *N* (%)	
	Males	72 (47.4)
	Females	80 (52.6)
3.	Fever, *N* (%)	151 (99.3)
4.	Headache, *N* (%)	144 (94.7)
5.	Vomiting, *N* (%)	105 (69.1)
6.	Vision loss, *N* (%)	12 (7.9)
7.	III cranial nerve palsy, *N* (%)	7 (4.6)
8.	VI Cranial nerve palsy, *N* (%)	61 (40.1)
9.	Papilledema, *N* (%)	69 (45.4)
10.	Hemiparesis, *N* (%)	23 (15.1)
11.	Paraparesis, *N* (%)	14 (9.2)
12.	Seizures, *N* (%)	42 (27.6)
13.	Altered sensorium, *N* (%)	96 (63.2)
14.	Duration of illness in days-	
	Mean ± SD	63.9 ± 65.4
	Median (IQR)	45 (70)
15.	Diagnostic category, *N* (%)	
	Probable/possible	128 (84.2)
	Definite	24 (15.8)
16.	Stage, *N* (%)	
	Stage I	38 (25)
	Stage II	76 (50)
	Stage III	38 (25)
17.	Meningeal enhancement, *N* (%)	126 (82.9)
18.	Hydrocephalus, *N* (%)	62 (40.8)
19.	Basal exudates, *N* (%)	35 (23)
20.	Tuberculoma, *N* (%)	54 (35.5)
21.	Infarcts, *N* (%)	20 (13.2)
22.	Vertebral involvement, *N* (%)	8 (5.3)
23.	Arachnoiditis, *N* (%)	6 (3.9)
24.	CSF	
	Cells	
	Mean ± SD	258.9 ± 271.3
	Median (IQR)	187.5 (292.3)
	Protein	
	Mean ± SD	263.5 ± 509.7
	Median (IQR)	148.0 (85.8)
	Sugar	
	Mean ± SD	42.1 ± 28.2
	Median (IQR)	36.5 (35.9)

CSF = cerebrospinal fluid; IQR = interquartile range; SD = standard deviation.

log-rank test and Kaplan–Meier curves, and multivariate survival analysis was performed using the Cox proportional hazards regression model. All *P*-values < 0.05 were taken as significant.

The baseline characteristics of 152 tuberculous meningitis patients are shown in Table 1. We did not identify any resistant strain in our study. A total of 26 (17.1%) patients died during 2 months of intensive phase of antituberculosis treatment. On univariate analysis, increasing age ($P < 0.001$), papilledema ($P < 0.001$, OR = 13.3 [3.8–46.9]), VI nerve palsy ($P = 0.045$, OR = 2.4 [1.01–5.6]), hemiparesis ($P = 0.002$, OR = 4.2 [1.6–11.3]), stage III disease ($P < 0.001$, OR = 5.0 [2.04–12.08]), and hydrocephalus ($P < 0.001$, OR = 8.8 [3.07–24.7]) were the factors significantly associated with death (Table 2). The logistic regression model was statistically significant, χ^2 (4) = 50.3, $P < 0.001$. The model explained 47% (Nagelkerke R^2) variance in the outcome (death) and correctly classified 90.8% cases. The model found that papilledema ($P = 0.029$, OR = 4.8 [1.2–19.8]), increasing age ($P = 0.001$, OR = 1.07 [1.03–1.1]), stage III disease ($P = 0.010$, OR = 4.2 [1.4–12.3]), and hydrocephalus ($P = 0.003$, OR = 8.4 [2.2–33.6]) were independently associated with death.

On time-to-death (survival) univariate analysis, stage III disease ($P < 0.001$), cranial nerve VI palsy ($P = 0.044$), papilledema ($P < 0.001$), hemiparesis ($P = 0.003$), and hydrocephalus ($P < 0.001$) were associated with poor survival. Among continuous variables, only increasing age ($P = 0.001$) was associated with a poor survival. On multivariate Cox proportional hazard model, increasing age ($P = 0.001$, hazard ratio (HR) = 1.04 [1.02–1.06]), papilledema ($P = 0.024$, HR = 4.4 [1.2–16.3]), and hydrocephalus ($P = 0.008$, HR = 4.1 [1.4–11.9]) were independently associated with death.

At the end of 2 months, in addition to 26 deaths, 33 patients had a poor functional outcome (MBI ≤ 12). On univariate analysis, age, papilledema, paraparesis, cerebral infarcts, and spinal arachnoiditis at baseline were the factors found to be significantly associated with poor functional outcome (Table 3). For multivariate regression analysis, a prediction model was created. The logistic regression model was statistically significant, χ^2 (4) = 31.6, $P < 0.001$. The model explained 32.4% (Nagelkerke R^2) variance in the outcome (disability) and correctly classified 78.6% cases. The cerebral infarcts ($P = 0.012$, OR = 5.6 [1.5–21.3]), paraparesis ($P = 0.004$, OR = 8.8 [2.02–38.1]), and higher age ($P = 0.005$, OR = 1.05 [1.02–1.09]) were associated with poor functional outcome.

Prognosis of tuberculous meningitis has not changed in the last 50 years. More than half of patients still either die or become disabled.[1,2] Initial 2 months are crucial as most of the deaths occur during this period. So, we assessed the factors responsible for early deaths in tuberculous meningitis. On multivariate analysis, we noted that deaths were more common with advancing age and in patients with more severe disease. Papilledema and hydrocephalus were significant clinical predictors of death. Both papilledema and hydrocephalus have ability to foretell life-threatening increase in intracranial pressure.

There are two important issues, in the management of tuberculous meningitis, which need to be addressed. One is the prompt identification of factors responsible for early deaths. Second is the use of interventions that can prevent early deaths. Many previous studies have addressed these issues. Both host factors and *Mycobacterium tuberculosis*-related factors contribute to early mortality. Innate and adaptive immune responses induce an inflammatory response and initiate a cascade of pathologic mechanisms, leading to brain injury out of proportion to that is required to contain the disease. Exaggerated immune responses exacerbate cerebral edema and brain injury.[13,14]

Can early deaths in tuberculous meningitis be predicted? Findings of our study and another previously published study indicate that a more severe disease at the time of initiation of treatment reliably predicts an early mortality.[15] Advancing age and disseminated tuberculosis are another predictors of death. The risk of death increases in patients with previous tuberculosis and those with focal neurological signs, and almost doubles for patients who did not receive corticosteroids.[3] A more recent report has observed that pretreatment CSF bacterial load directly correlates with inflammatory response and predicts an increased risk of adverse outcome.[16]

What can be done to reduce the risk of early mortality? Treatment is most effective when started in the early stages of

TABLE 2
Univariate analysis showing predictors of mortality among 152 patients of tuberculous meningitis

Variables	Dead (*n* = 26)	Survived (*n* = 126)	*P*-value	Odds ratio (95% confidence interval)
Age in years				
Mean ± SD	39.5 ± 13.8	29.3 ± 14.0	< 0.001	N.A.
Median (IQR)	35.5 (22.0)	25.0 (15.0)	–	–
Gender				
Male, *N* (%)	11 (42.3)	61 (48.4)	0.570	0.8 (0.3–1.8)
Fever, *N* (%)	26 (100)	125 (99.2)	1.000	N.A.
Headache, *N* (%)	24 (92.3)	120 (95.3)	0.625	0.6 (0.1–3.2)
Vomiting, *N* (%)	20 (76.9)	85 (67.5)	0.342	1.6 (0.6–4.3)
Vision loss, *N* (%)	4 (15.4)	8 (6.3)	0.126	2.7 (0.7–9.7)
III Cranial nerve palsy, *N* (%)	2 (7.7)	5 (4)	0.343	2.02 (0.4–11.01)
VI cranial nerve palsy *N* (%)	15 (57.7)	46 (36.5)	0.045	2.4 (1.01–5.6)
Papilledema, *N* (%)	23 (88.5)	46 (36.5)	< 0.001	13.3 (3.8–46.9)
Hemiparesis, *N* (%)	9 (34.6)	14 (11.1)	0.002	4.2 (1.6–11.3)
Paraparesis, *N* (%)	2 (7.7)	12 (9.5)	1.000	0.8 (0.2–3.8)
Seizures, *N* (%)	8 (30.8)	34 (27.0)	0.694	1.2 (0.5–3.02)
Altered sensorium, *N* (%)	20 (76.9)	76 (60.3)	0.110	2.2 (0.8–5.8)
Duration of illness in days				
Mean ± SD	73.5 ± 69.08	61.9 ± 64.8	0.555	N.A.
Median (IQR)	32.5 (101.3)	45.0 (70.0)	–	–
Diagnostic category, *N* (%)				
Probable/possible	23 (88.5)	105 (83.3)	0.768	0.7 (0.2–2.4)
Definite	3 (11.5)	21 (16.7)	–	–
Stage III, *N* (%)	14 (53.8)	24 (19.0)	< 0.001	5.0 (2.04–12.08)
Meningeal enhancement, *N* (%)	24 (92.3)	100 (79.4)	0.167	3.1 (0.7–14.06)
Hydrocephalus, *N* (%)	21 (80.8)	41 (32.5)	< 0.001	8.7 (3.07–24.7)
Basal exudates, *N* (%)	8 (30.8)	27 (21.4)	0.303	1.6 (0.6–4.2)
Tuberculoma, *N* (%)	5 (19.2)	49 (38.9)	0.072	0.4 (0.1–1.06)
Infarcts, *N* (%)	6 (23.1)	14 (11.1)	0.100	2.4 (0.8-7.0)
Vertebral involvement, *N* (%)	1 (3.8)	7 (5.6)	1.000	0.7 (0.08–5.8)
Arachnoiditis, *N* (%)	0 (0)	6 (4.8)	0.590	N.A.
CSF				
Cells				
Mean ± SD	223.5 ± 223.4	266.2 ± 280.4	0.448	N.A.
Median (IQR)	137.5 (272)	200.0 (300)	–	–
Protein				
Mean ± SD	240.4 ± 172.1	268.3 ± 554.8	0.062	N.A.
Median (IQR)	172.7 (239.8)	143.0 (87.8)	–	–
Sugar				
Mean ± SD	43.6 ± 28.8	41.8 ± 28.2	0.936	N.A.
Median (IQR)	31.3 (37.5)	38.1 (35.5)	–	–

CSF = cerebrospinal fluid; IQR = interquartile range; SD = standard deviation.

disease and should be initiated promptly on the basis of strong clinical suspicion without waiting for laboratory confirmation. Adjunctive corticosteroid therapy has been shown to reduce morbidity and mortality in all but late stages.[10] Pharmacokinetic studies suggested that in tuberculous meningitis, higher rifampicin doses may be required to achieve sufficient CSF drug penetration enabling effective mycobacterial killing in the central nervous system.[17] Unfortunately, intensified antituberculosis treatment, which included a higher dose rifampicin (15 mg/kg/day) and levofloxacin (20 mg/kg/day), was not associated with a better survival than standard treatment.[18] Many small trials have suggested a beneficial role of aspirin in tuberculous meningitis. Aspirin improves tuberculous meningitis–associated outcome by reducing the incidence of cerebral infarctions.[19]

Our findings suggest that hydrocephalus resulting from an elevated intracranial pressure was associated with mortality. Cerebrospinal fluid diversion procedures, ventriculoperitoneal shunting, or endoscopic third ventriculostomy is considered lifesaving in many patients with advanced tuberculous meningitis.[20] Precise role of CSF diversion still needs to be determined. An elective CSF diversion, in deteriorating patients, should be evaluated in a randomized-controlled fashion.

Our study had few limitations. First, our study had a relatively small cohort from a single center, and the follow-up period of 2 months was short. Another shortcoming was that the proportion of definite cases was small.

In conclusion, severe disease, at diagnosis, reliably predicts early deaths. Better treatment with more effective antituberculosis drugs and measures to curb inflammatory damage with immunomodulatory drugs may help reduce early deaths.

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TABLE 3
Univariate analysis showing predictors of functional disability among 126 patients of tuberculous meningitis

Variables	Final MBI ≤ 12 (*n* = 33)	Final MBI > 12 (*n* = 93)	*P*-value	Odds ratio (95% confidence interval)
Age in years				
Mean ± SD	34.8 ± 15.8	27.3 ± 12.9	0.011	N.A.
Median (IQR)	27.0 (21.5)	24.0 (14.0)	–	–
Gender				
Male, *N* (%)	18 (54.5)	43 (46.2)	0.412	1.4 (0.6–3.1)
Fever, *N* (%)	33 (100)	92 (98.9)	1.000	N.A.
Headache, *N* (%)	32 (97)	88 (94.6)	1.000	1.8 (0.2–16.2)
Vomiting, *N* (%)	22 (66.7)	63 (67.7)	0.910	1.0 (0.4–2.2)
Vision loss, *N* (%)	2 (6.1)	6 (6.5)	1.000	0.9 (0.2–4.9)
III Cranial nerve palsy, *N* (%)	3 (9.1)	2 (2.2)	0.112	4.6 (0.7–28.5)
VI cranial nerve palsy, *N* (%)	16 (48.5)	30 (32.3)	0.096	2.0 (0.8–4.4)
Papilledema, *N* (%)	19 (57.6)	27 (29)	0.003	3.3 (1.5–7.6)
Hemiparesis, *N* (%)	6 (18.2)	8 (8.6)	0.132	2.4 (0.8–7.4)
Paraparesis, *N* (%)	6 (18.2)	6 (6.5)	0.049	3.2 (1.0–10.8)
Seizures, *N* (%)	9 (27.3)	25 (26.9)	0.965	1.02 (0.4–2.5)
Altered sensorium, *N* (%)	24 (72.7)	52 (55.9)	0.090	2.1 (0.8–5.01)
Duration of illness in days				
Mean ± SD	58.8 ± 44.9	63.1 ± 70.7	0.293	N.A.
Median (IQR)	45.0 (60)	33.0 (70)	–	–
Diagnostic category, *N* (%)				
Probable/possible	26 (78.8)	79 (84.9)	0.415	1.5 (0.5–4.2)
Definite	7 (21.2)	14 (15.1)	–	–
Stage III, *N* (%)	9 (27.3)	15 (16.1)	0.161	2.0 (0.8–5.02)
Meningeal enhancement, *N* (%)	30 (90.9)	70 (75.3)	0.079	3.3 (0.9–11.8)
Hydrocephalus, *N* (%)	13 (39.4)	28 (30.1)	0.328	1.5 (0.7–3.5)
Basal exudates, *N* (%)	9 (27.3)	18 (19.4)	0.341	1.6 (0.6–3.9)
Tuberculoma, *N* (%)	14 (42.4)	35 (37.6)	0.628	1.2 (0.5–2.7)
Infarcts, *N* (%)	7 (21.2)	7 (7.5)	0.032	3.3 (1.06–10.3)
Vertebral involvement, *N* (%)	3 (9.1)	4 (4.3)	0.377	2.2 (0.5–10.5)
Arachnoiditis, *N* (%)	4 (12.1)	2 (2.2)	0.040	6.3 (1.09–36.05)
CSF				
Cells				
Mean ± SD	215.8 ± 268.98	284.1 ± 283.6	0.054	N.A.
Median (IQR)	130 (277)	225 (275)	–	–
Protein				
Mean ± SD	341.0 ± 700.74	242.5 ± 494.8	0.277	N.A.
Median (IQR)	162 (84)	138 (85.2)	–	–
Sugar				
Mean ± SD	49.5 ± 43.8	39.07 ± 19.6	0.247	N.A.
Median (IQR)	46 (34.7)	36 (34.6)	–	–

CSF = cerebrospinal fluid; IQR = interquartile range; MBI = modified Barthel's Index; N.A. = not applicable; SD = standard deviation.

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