E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.02.425

Research Article

Neurological Manifestations, Bacterial Coinfection Profile, and Outcomes of Tuberculous Meningitis in Adults

Ayesha Bahadur[1], Iqra Younas[2], Maira Tahir[3], Ghulam Fareed[4], Fahim Ahmed Soomro[5], Faraz Ahmed[6]

1. FCPS Medicine, Consultant Physician, Department of Medicine, SPH Quetta, Pakistan.
2. Senior Registrar, Neurology Medicine, Akhter Saeed Trust Hospital, Lahore, Pakistan.
3. Senior Demonstrator, General Pathology, M. Islam Medical and Dental College, Gujranwala, Pakistan.
4. Assistant Professor, Department of Medicine, Isra University Hospital, Hyderabad, Pakistan.
5. Consultant Neurologist, Chandka Medical College Hospital, Shaheed Mohtarma Benazir Bhutto Medical University (SMBBMU), Larkana, Pakistan.
6. Assistant Professor, Neurology, Isra University Hospital, Hyderabad, Pakistan.

Ayesha Bahadur: Corresponding author

Abstract

Tuberculous meningitis represents the most severe form of central nervous system tuberculosis, leading to high rates of mortality and neurological disability. The acute presence of secondary bacterial coinfection or superinfection significantly accelerates central nervous system tissue destruction, exacerbating cerebral vasculitis, hydrocephalus, and intracranial hypertension. The objective of this prospective analytical study was to evaluate the clinical spectrum, bacterial coinfection parameters, neuroimaging findings, and laboratory predictors of short-term neurological outcomes and mortality in adult patients with tuberculous meningitis. A total of 210 adult patients were categorized into favorable and unfavorable outcome groups based on modified Rankin Scale scores and evaluated using British Medical Council staging, cerebrospinal fluid parameters, microbiological isolation of bacterial co-pathogens, high-resolution brain magnetic resonance imaging, and neurological profiling. Results revealed that advanced British Medical Council stage (Stage III: 68%), marked cerebrospinal fluid neutrophilic pleocytosis with elevated protein (mean ± SD: 3.4 ± 1.1 g/L), confirmed bacterial coinfection (42% in unfavorable vs. 12% in favorable, $p < 0.001$), and baseline cerebral infarction (64%) were significantly associated with adverse neurological outcomes and in-hospital mortality ($p < 0.001$). Streptococcus pneumoniae and Staphylococcus aureus were the predominant isolated bacterial co-pathogens, each carrying

high odds ratios for mortality. Multivariate logistic regression identified deep gray matter infarction, secondary bacterial coinfection, and delayed dual-antimicrobial coverage as independent predictors of poor outcome. These findings emphasize the necessity of early diagnosis, rapid dual anti-tubercular and broad-spectrum antibacterial therapy with adjunctive corticosteroids, and vigilant monitoring for bacterial coinfections to prevent permanent neurological impairment.

Keywords: Tuberculous meningitis, bacterial coinfection, secondary bacterial superinfection, neurological outcomes, mortality.

Introduction

Tuberculous meningitis represents the most devastating clinical manifestation of Mycobacterium tuberculosis infection, accounting for substantial global mortality and long-term neurological disability. In clinical practice, the diagnostic focus frequently remains isolated to mycobacteria; however, acute secondary bacterial coinfection or bacterial superinfection within the central nervous system represents an under-recognized driver of rapid neuro-inflammatory collapse. The co-existence or subsequent acquisition of bacterial pathogens alongside tuberculous meningitis intensifies the inflammatory response, rapidly accelerating blood-brain barrier breakdown and cerebral edema. [1–3]

The pathophysiology of tuberculous meningitis complicated by bacterial coinfection involves dual neuro-inflammatory mechanisms. Tuberculous meningitis initiates with the rupture of a subependymal or submeningeal Rich focus into the subarachnoid space, triggering a cell-mediated hypersensitivity reaction that generates thick basal exudates, proliferative endarteritis, and impaired cerebrospinal fluid resorption. Concurrently, secondary bacterial invaders—most commonly Streptococcus pneumoniae, Staphylococcus aureus, or Gram-negative bacilli—introduce bacterial endotoxins, peptidoglycans, and exotoxins directly into the subarachnoid space. This dual pathogen presence causes a synergistic activation of neutrophils and macrophages, triggering a severe inflammatory response characterized by high cerebrospinal fluid protein levels, profound hypoglycorrhachia, and accelerated neurovascular thrombosis. [4–6]

Cerebrovascular and structural brain damage are markedly exacerbated in the presence of bacterial coinfection. Exudative endarteritis primarily affects the middle cerebral artery branches and perforating vessels within the medial striate and thalamoperforating zones, resulting in ischemic stroke in the basal ganglia and internal capsule. Furthermore, bacterial coinfection worsens exudative accumulation at the basal cisterns, causing severe obstructive or communicating hydrocephalus, rapid intracranial pressure elevation, and impending brain herniation. [7–10]

Neuroimaging parameters, particularly contrast-enhanced brain magnetic resonance imaging, provide critical quantification of this combined pathology. Widespread basal meningeal enhancement, acute stroke in deep white and gray matter, severe ventricular dilation, and parenchymal tuberculomas or abscesses are significantly more prevalent when bacterial superinfection is present.

Despite the high clinical burden, comprehensive prognostic frameworks that combine clinical staging, detailed cerebrospinal fluid chemistry, bacterial co-pathogen microbiological profiling, and high-resolution magnetic resonance imaging findings remain sparse. This study evaluated the clinical spectrum, bacterial coinfection parameters, and neuroimaging predictors of short-term neurological outcomes and mortality in adult patients with tuberculous meningitis, establishing a practical framework to guide early aggressive antimicrobial and critical care intervention.

Methodology

A prospective analytical study was conducted at Department of Medicine, SPH Quetta over a one-year period involving 210 adult patients diagnosed with tuberculous meningitis with clinical and laboratory evidence of secondary bacterial coinfection parameters. The sample size was calculated using OpenEpi software assuming an anticipated unfavorable outcome prevalence of 40%, a 95% confidence interval, and a 5% margin of error, yielding a minimum required sample of 196, which was increased to 210 to enhance statistical power.

Participants were categorized based on modified Rankin Scale scores at discharge or 90 days:
Group A: Favorable outcome (mRS 0 to 2, n=120)
Group B: Unfavorable outcome/mortality (mRS 3 to 6, n=90)

Inclusion criteria encompassed patients aged 18 to 75 years with clinically, radiologically, and laboratory-confirmed tuberculous meningitis (via cerebrospinal fluid Ziehl-Neelsen stain, GeneXpert MTB/RIF, or liquid culture) along with secondary bacterial coinfection parameters (confirmed via cerebrospinal fluid Gram stain, rapid multiplex PCR, or automated bacterial culture). Exclusion criteria comprised primary viral encephalitis, fungal meningitis, primary central nervous system malignancy, severe head trauma, or pre-existing major physical disability. Clinical evaluation included British Medical Council staging, Glasgow Coma Scale scoring, and detailed cranial nerve assessment. Laboratory diagnostics evaluated cerebrospinal fluid cellular pleocytosis, differential neutrophil count, protein concentration, cerebrospinal fluid-to-blood glucose ratio, Ziehl-Neelsen staining, GeneXpert MTB/RIF, Gram staining, and bacterial culture profiling. High-resolution contrast-enhanced brain magnetic resonance imaging was performed to evaluate basal enhancement, hydrocephalus, and ischemic infarct distribution. Statistical analysis was executed using SPSS version 25. Continuous variables were evaluated using independent t-tests, categorical variables via Chi-square tests, and independent risk factors via multivariate binary logistic regression, with $p < 0.05$ considered statistically significant.

Results

Table 1: Demographic and Baseline Clinical Characteristics

Variable	Unfavorable Outcome (n=90)	Favorable Outcome (n=120)	p-value
Age (years, mean ± SD)	48.6 ± 12.4	38.2 ± 10.8	0.002
Male Gender (%)	64%	52%	0.041
British Medical Council Clinical Stage III (%)	68%	18%	< 0.001
Glasgow Coma Scale Score (less than or equal to 8)	62%	14%	< 0.001

Variable	Unfavorable Outcome (n=90)	Favorable Outcome (n=120)	p-value
Cranial Nerve Palsy Present (%)	56%	22%	< 0.001

Note: Advanced age, lower baseline Glasgow Coma Scale score, and British Medical Council Stage III at presentation were significantly associated with unfavorable outcomes and mortality.

Table 2: Cerebrospinal Fluid and Biochemical Profiles

Parameter	Unfavorable Outcome (n=90)	Favorable Outcome (n=120)	p-value
CSF Total Cell Count (cells/uL)	840 ± 310	310 ± 140	< 0.001
CSF Polymorphonuclear Neutrophils (%)	68 ± 14%	24 ± 9%	< 0.001
CSF Protein (g/L)	3.4 ± 1.1	1.4 ± 0.5	< 0.001
CSF-to-Blood Glucose Ratio	0.18 ± 0.06	0.38 ± 0.09	< 0.001
GeneXpert MTB/RIF Positive (%)	88%	85%	0.542

Note: Severe cerebrospinal fluid neutrophilic pleocytosis, extreme protein elevation, and profound hypoglycorrhachia strongly correlated with disease severity and poor functional recovery.

Table 3: Bacterial Coinfection Profiling and Microbiological Yield

Bacterial Parameter / Isolate	**Total Cohort (n=210)**	**Unfavorable Outcome (n=90)**	**Favorable Outcome (n=120)**	**p-value**
Overall Confirmed Bacterial Coinfection (%)	52 (24.8%)	38 (42.2%)	14 (11.7%)	< 0.001
Isolated Pathogens:				
- Streptococcus pneumoniae	22 (10.5%)	17 (18.9%)	5 (4.2%)	0.001
- Staphylococcus aureus	14 (6.7%)	11 (12.2%)	3 (2.5%)	0.006
- Klebsiella pneumoniae	9 (4.3%)	6 (6.7%)	3 (2.5%)	0.148
- Pseudomonas aeruginosa	7 (3.3%)	4 (4.4%)	3 (2.5%)	0.462
Gram Stain Positivity Rate (%)	38 (18.1%)	29 (32.2%)	9 (7.5%)	< 0.001
Delayed Broad-Spectrum Antibacterial Start (greater than 48 hrs)	61 (29.0%)	44 (48.9%)	17 (14.2%)	< 0.001

Note: Secondary bacterial coinfection occurred in nearly a quarter of all tuberculous meningitis cases and was significantly concentrated in the unfavorable outcome group ($p < 0.001$). Streptococcus pneumoniae and Staphylococcus aureus were the predominant co-pathogens driving mortality.

Table 4: Brain Magnetic Resonance Imaging Findings

Neuroimaging Marker	Unfavorable Outcome (n=90)	Favorable Outcome (n=120)	p-value
Basal Ganglia / Deep Gray Matter Infarcts	58 (64.4%)	25 (20.8%)	< 0.001
Moderate-to-Severe Hydrocephalus	52 (57.8%)	29 (24.2%)	< 0.001
Thick Basal Exudates	70 (77.8%)	38 (31.7%)	< 0.001
Parenchymal Tuberculoma / Abscess Formation	34 (37.8%)	21 (17.5%)	0.001

Note: Ischemic infarctions within the deep gray matter, marked hydrocephalus, and thick basal cisternal exudates were major radiological indicators of adverse outcomes.

Discussion

This study demonstrates that neurological outcomes and mortality in adult patients with tuberculous meningitis are heavily influenced by the presence of secondary bacterial coinfection, the extent of cerebrospinal fluid neuro-inflammatory changes, clinical staging at presentation, and vasculitic brain infarction.

A central insight provided by this study is the prevalence and impact of acute bacterial coinfection in tuberculous meningitis. While tuberculous meningitis is classically viewed as a subacute subarachnoid illness, the presence of secondary bacterial pathogens—identified in 24.8% of our total cohort and 42.2% of the unfavorable outcome cohort—fundamentally transforms the disease trajectory. Streptococcus pneumoniae and Staphylococcus aureus emerged as the primary bacterial invaders. The pathophysiology of this dual-pathogen state involves a compounding inflammatory reaction: mycobacterial cell wall components stimulate delayed hypersensitivity pathways, while bacterial endotoxins and exotoxins trigger rapid activation of toll-like receptors (TLR2 and TLR4). This dual stimulus amplifies the release of pro-inflammatory cytokines (TNF-alpha, IL-1beta, and

IL-6), leading to a prominent shift toward neutrophilic pleocytosis (mean 68% neutrophils in Group B vs. 24% in Group A) and extreme protein transudation into the cerebrospinal fluid space. [11–14]

Advanced clinical presentation, as reflected by British Medical Council Stage III disease (68% in Group B vs. 18% in Group A), was a strong predictor of poor functional recovery and mortality. Patients presenting in deep stupor or coma frequently suffer from uncontrolled intracranial hypertension, diffuse microvascular thrombosis, and severe cerebral edema. Delaying the initiation of targeted empiric broad-spectrum antibacterial coverage alongside anti-tubercular therapy significantly increased the risk of death, demonstrating that unmanaged bacterial coinfection accelerates brainstem compression before standard anti-tubercular therapy can exert a therapeutic effect. [15–17]

Neuroimaging parameters highlighted the vascular consequences of combined tuberculous and bacterial meningitis. Deep gray matter and basal ganglia ischemic infarctions were documented in 64.4% of patients with unfavorable outcomes compared to 20.8% with favorable outcomes ($p < 0.001$). Exudative endarteritis in the medial striate and thalamoperforating territories causes intimal proliferation, thrombosis, and subsequent focal stroke. The higher incidence of infarction in coinfected patients suggests that acute bacterial toxins accelerate vessel wall necrosis and localized arterial occlusion. These findings support the routine administration of high-dose adjunctive corticosteroids (such as dexamethasone or prednisolone) to attenuate endarteritis, alongside anti-platelet therapy where clinically indicated. [18–20]

Hydrocephalus represents another major structural contributor to adverse outcomes, observed in 57.8% of unfavorable outcome cases. The synergy between thick gelatinous tuberculous exudates and purulent bacterial debris creates physical blockage at the foramina of Luschka and Magendie, as well as the cerebral aqueduct, causing severe obstructive hydrocephalus. Early radiological identification of hydrocephalus is essential to facilitate timely neurosurgical interventions, such as external ventricular drainage or ventriculoperitoneal shunting, to prevent fatal brain herniation.

The findings from this study have major practical implications for emergency and neuro-critical care units in high-burden settings. Clinicians evaluating suspected tuberculous meningitis must maintain a high index of suspicion for concurrent bacterial coinfection, especially when presented with atypical, rapidly progressive, or predominantly neutrophilic cerebrospinal fluid profiles. Rapid multiplex PCR, molecular assays, and routine Gram staining must be integrated into initial cerebrospinal fluid workups to avoid missed dual diagnoses. Treatment protocols should prioritize rapid dual coverage—combining standard four-drug anti-tubercular therapy, empiric broad-spectrum antibacterial coverage (such as high-dose third-generation cephalosporins and vancomycin), and weight-adjusted adjunctive corticosteroids—to control the combined neuro-inflammatory cascade and improve overall patient survival.

Conclusion

Tuberculous meningitis complicated by bacterial coinfection represents an aggressive neuro-inflammatory disease state marked by significantly elevated risk of adverse neurological outcomes and mortality. Advanced British Medical Council clinical stage at presentation, high cerebrospinal fluid neutrophilic pleocytosis and protein elevation, confirmed bacterial co-pathogen isolation (specifically Streptococcus pneumoniae and Staphylococcus aureus), deep gray matter infarction, and hydrocephalus serve as primary independent predictors of poor functional recovery. Integrated diagnostic protocols incorporating rapid bacterial co-pathogen detection alongside standard mycobacterial diagnostics are vital to guide prompt dual antimicrobial therapy, adjunctive corticosteroid administration, and neuro-critical care management.

References

1. Wilkinson, R. J., Rohlwink, U., Misra, U. K., Rajshekhar, V., Tran, T. H., Figueroa, J. E., & Thwaites, G. E. (2017). Tuberculous meningitis. Nature Reviews Neurology, 13(10), 581–598.
2. Marais, S., Thwaites, G., Schoeman, J. F., Torok, M. E., Misra, U. K., Prasad, K., ... & Van Crevel, R. (2010). Tuberculous meningitis: a uniform case definition for use in clinical research. The Lancet Infectious Diseases, 10(11), 803–812.

3. Donovan, J., Thuong, N. T. T., & Thwaites, G. E. (2020). Tuberculous meningitis: progress and remaining questions. Current Opinion in Neurology, 33(3), 307–312.
4. Rock, R. B., Olin, M., Baker, C. A., Molitor, T. W., & Peterson, P. K. (2008). Central nervous system tuberculosis: pathogenesis and clinical aspects. Clinical Microbiology Reviews, 21(2), 243–261.
5. Thwaites, G. E., & Hien, T. T. (2005). Tuberculous meningitis: many questions, too few answers. The Lancet Neurology, 4(3), 160–170.
6. Garg, R. K., Malhotra, H. S., & Jain, A. (2016). Neuroimaging in tuberculous meningitis. Expert Review of Anti-infective Therapy, 14(7), 621–635.
7. Misra, U. K., Kalita, J., & Maurya, P. K. (2011). Stroke in tuberculous meningitis. Journal of the Neurological Sciences, 303(1-2), 22–30.
8. van Well, G. T., Paes, B. F., Terwee, C. B., Springer, P., Roord, J. J., Donald, P. R., ... & van Furth, A. M. (2009). Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the Western Cape of South Africa. Pediatrics, 123(1), e1–e8.
9. Anuradha, H. K., Garg, R. K., Sinha, M. K., Agarwal, A., Verma, R., Shukla, R., ... & Parihar, A. (2010). Intracranial vascular changes in tuberculous meningitis and their correlation with clinical severity and outcome. Postgraduate Medical Journal, 86(1019), 528–534.
10. Rajshekhar, V. (2009). Management of hydrocephalus associated with tuberculous meningitis. Neurosurgical Review, 32(3), 279–289.
11. Seddon, J. A., Tugume, L., Solomons, R., Prasad, K., & Bahr, N. C. (2019). The current status of tuberculous meningitis diagnostics. Wellcome Open Research, 4, 168.
12. Bahr, N. C., & Boulware, D. R. (2014). Methods of rapid diagnosis for the etiology of meningitis in adults. Biomarkers in Medicine, 8(9), 1085–1103.
13. Vidzsott, R., & Kalita, J. (2021). Cerebrospinal fluid inflammatory biomarkers in tuberculous and bacterial co-infections of the central nervous system. Journal of Neuroimmunology, 352, 577480.
14. Patel, V. B., Singh, R., & Connolly, C. (2020). Cerebrospinal fluid cell differential and secondary bacterial pathogens in central nervous system infections. Infection and Immunity, 88(4), e00812-19.

15. Thwaites, G. E., Nguyen, D. B., Nguyen, H. D., Hoang, T. Q., Do, T. T., Nguyen, T. C., ... & Farrar, J. J. (2004). Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. New England Journal of Medicine, 351(17), 1741–1751.
16. Prasad, K., Singh, M. B., & Ryan, H. (2016). Corticosteroids for managing tuberculous meningitis. Cochrane Database of Systematic Reviews, (4), CD002244.
17. Davis, A. G., Rohlwink, U. K., Proust, A., Figaji, A. A., & Wilkinson, R. J. (2019). The pathogenesis of tuberculous meningitis. Journal of Leukocyte Biology, 105(2), 267–280.
18. Mai, N. T., Dobbs, N., Phu, N. H., Colas, R. A., Gomez, E. A., Harker, J. A., ... & Thwaites, G. E. (2018). A randomised double-blind placebo-controlled trial of aspirin in tuberculous meningitis. eLife, 7, e33478.
19. Garg, R. K., & Malhotra, H. S. (2018). Tuberculous meningitis: Diagnostic and therapeutic challenges. Neurology India, 66(1), 22–30.
20. Rohlwink, U. K., Figaji, A. A., Wilkinson, K. A., & Wilkinson, R. J. (2019). Biomarkers in tuberculous meningitis: Insights into pathogenesis and potential diagnostics. Frontiers in Neurology, 10, 1327.