



DIAGNOSTIC AND PROGNOSTIC SIGNIFICANCE OF CSF IL-6, TNF- α , AND LRG-1 IN TUBERCULAR MENINGITIS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objectives: This study evaluated cerebrospinal fluid (CSF) biomarkers—leucine-rich alpha-2 glycoprotein (LRG), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α)—for diagnostic and prognostic value in tubercular meningitis (TBM). **Materials And Methods:** CSF from 24 TBM patients was analyzed (ELISA). Clinical severity was assessed using Glasgow Coma Scale (GCS), British Medical Research Council (BMRC) grades, and Modified Vellore grading; outcomes at 1 month via Glasgow Outcome Scale (GOS). **Results:** Elevated IL-6 and LRG correlated with lower GCS and higher severity ($p < 0.05$), TNF- α weaker. High IL-6 and LRG linked to poor outcomes (GOS 1–3). **Conclusions:** CSF IL-6 and LRG are strong prognostic indicators; TNF- α is weaker. Further standardization is needed.

KEYWORDS : Tubercular meningitis, CSF biomarkers, Prognosis, LRG, Glasgow Coma Scale, Glasgow Outcome Scale

INTRODUCTION

Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis, causing high mortality and long-term neurological disability, especially in young adults and children. Despite anti-tubercular therapy, outcomes remain poor due to diagnostic and risk assessment challenges.

The insidious onset and overlapping symptoms with other meningitis forms hinder early prognostication [1].

CSF biomarkers like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α) provide insights into TBM's immunopathology. IL-6, secreted by monocytes, glial and endothelial cells, drives the acute-phase response and is elevated in TBM [2].

TNF- α increases blood-brain barrier (BBB) permeability, leukocyte recruitment, and granuloma formation, contributing to infarcts and severe outcomes [3].

A 2022 meta-analysis confirmed both cytokines are consistently elevated in TBM [2], and a 2024 study linked elevated CSF levels to higher clinical stages and severe radiological findings [4]. LRG1, involved in angiogenesis and inflammation, is elevated in bacterial meningitis and correlates with IL-6, suggesting synergistic inflammatory roles [5]. Radiological features (infarcts, hydrocephalus, exudates) correlate with IL-6 and TNF- α levels [3].

However, integrated studies combining CSF profiles, clinical grades, imaging, and outcomes are lacking.

This study assessed CSF IL-6, TNF- α , and LRG1 in TBM, correlating them with clinical presentation, imaging, severity (GCS), and outcome (GOS).

Methodology

Study Design And Setting

A prospective observational study at a North India tertiary care center (Jan 2024–Mar 2025), ethics-approved (No. Dean/2024/EC/7172), with consent obtained (Figure 1).

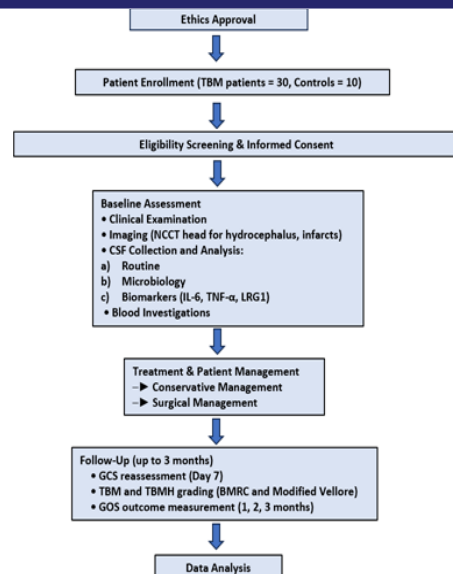


Figure 1. Study Flow

Participant Selection

Included: patients with clinical/radiological TBM signs. **Excluded:** no consent, intrathecal antibiotics, alternative diagnoses. Of 30 enrolled, 6 died within 10 days; 24 analyzed. Ten controls had suspected viral/atypical meningitis.

Data Collection

All patients underwent NCCT head, CSF analysis, blood work, clinical exam. CSF was collected sterilely, analyzed for microscopy, AFB smear, CBNAAT, culture, IL-6, TNF- α , and LRG1 (stored at 2–8°C for LRG1). GCS, BMRC TBM grade, Vellore TBMH grade, cranial nerve, fundoscopic exams were performed. GOS tracked at 3 months.

Biomarker Analysis

IL-6, TNF- α : standard biochemical assays. LRG1: ELISA using specific antibodies, optical density quantification.

Statistical Analysis

Normality: Kolmogorov-Smirnov test. Non-parametric tests: Kruskal-Wallis, Wilcoxon. Fisher's exact for qualitative variables. SPSS v25; significance $p < 0.05$.

RESULTS

The study included 30 TBM patients (mean age 27.2 years, 50% male/female). Nearly half (46.7%) presented with loss of consciousness, and 73.3% had significant neurological impairment. CSF protein was >100 mg/dL in 63.3%, indicating blood-brain barrier disruption (Table 1).

Table 1: Baseline Clinical, Radiological, and Biomarker Characteristics of TBM Patients (N=30)

Characteristic	Category / Statistic	Value
Demographics		
Age (years)	Mean ± SD	27.2 ± [SD not provided].
	Median (Range)	26 (8 - 50)
Gender	Male, n (%)	15 (50.0%)
	Female, n (%)	15 (50.0%)
Clinical Presentation		
Headache / Vomiting only	n (%)	8 (26.7%)
Altered Sensorium/Seizure/Deficit	n (%)	8 (26.7%)
Loss of Consciousness	n (%)	14 (46.7%)
Baseline CSF Findings		
CSF Protein (mg/dL)	40-100, n (%)	9 (30.0%)
	100-500, n (%)	15 (50.0%)
	>500, n (%)	4 (13.3%)
Baseline CSF Biomarkers		
IL-6 (pg/mL)	Mean ± SD	70.27 ± 70.54
	Median (Range)	63 (26 - 324)
TNF-α (pg/mL)	Mean ± SD	119.17 ± 50.12
	Median (Range)	129 (45 - 221)
LRG-1 (µg/mL)	Mean ± SD	59.73 ± 17.71
	Median (Range)	57.5 (34 - 98)

CSF IL-6, TNF-α, and LRG1 levels were elevated, with highest levels in patients with infarcts (IL-6 175.20 pg/mL, TNF-α 183.40 pg/mL, LRG1 80.60 µg/mL; Table 2). Biomarker levels rose progressively with worsening BMRC TBM (IL-6 p=0.0072; TNF-α p=0.0468; LRG1 p=0.0034) and TBMH grades (Table 2).

Table 2: Association of CSF Biomarkers with Clinical and Radiological Severity

Variable	IL-6 (pg/mL)	TNF-α (pg/mL)	LRG-1 (µg/mL)
	Mean ± SD	Mean ± SD	Mean ± SD
BMRC TBM Grade			
Grade 1 (n=7)	37.14 ± 14.10	99.57 ± 53.27	48.00 ± 11.36
Grade 2 (n=12)	70.83 ± 36.94	110.48 ± 37.37	54.67 ± 13.84
Grade 3 (n=11)	129.82 ± 85.70	153.45 ± 44.21	75.55 ± 15.41
p-value	0.0072	0.0468	0.0034
Modified Vellore TBMH Grade			
No HCP (n=3)	32.33 ± 9.29	168.33 ± 0.58	48.33 ± 6.66
Grade 1 (n=5)	47.20 ± 11.58	85.40 ± 18.98	50.60 ± 10.62
Grade 2 (n=1)	105.00	69.00	57.00
Grade 3 (n=9)	67.33 ± 18.31	110.11 ± 33.33	53.78 ± 11.13
Grade 4 (n=12)	130.75 ± 84.43	157.33 ± 39.95	74.92 ± 14.40
p-value	0.0142	0.0278	0.0085
Radiological Findings			

Basilar Exudates only (n=3)	32.00 ± 9.85	168.33 ± 0.58	48.33 ± 6.66
Moderate to Gross HCP (n=19)	76.79 ± 52.05	111.58 ± 43.74	60.00 ± 16.61
Infarcts on MRI (n=5)	175.20 ± 87.68	183.40 ± 33.98	80.60 ± 5.73
p-value	0.0026	0.0375	0.0175

A strong inverse correlation existed between biomarkers and GCS: IL-6 ρ=-0.704 (p<0.0001), TNF-α ρ=-0.409 (p=0.0246), LRG1 ρ=-0.589 (p=0.0006) (Table 3). IL-6 and LRG1 significantly predicted GCS in regression (IL-6 p=0.002; LRG1 p=0.003; Table 4).

Table 3: Association of CSF Biomarkers with Neurological Status (GCS) and 1-Month Outcome (GOS)

Variable	IL-6 (pg/mL)	TNF-α (pg/mL)	LRG-1 (µg/mL)
	Mean ± SD	Mean ± SD	Mean ± SD
Glasgow Coma Scale (GCS) Group			
Severe (3-8) (n=8)	145.25 ± 92.87	149.63 ± 46.63	74.88 ± 14.76
Moderate (9-12) (n=6)	65.83 ± 12.52	134.83 ± 33.11	55.17 ± 4.83
Mild (13-15) (n=16)	64.75 ± 47.68	95.50 ± 46.12	53.25 ± 16.48
p-value	0.0207	0.0333	0.0054
Glasgow Outcome Scale (GOS) at 1-Month			
Died (GOS 1) (n=6)	131.17 ± 100.94	151.00 ± 40.05	76.67 ± 15.46
GOS 2 (n=1)	145.00	198.00	87.00
GOS 3 (n=4)	121.50 ± 37.48	154.50 ± 60.62	76.25 ± 4.99
GOS 4 (n=1)	105.00	69.00	57.00
Good Recovery (GOS 5) (n=18)	56.61 ± 21.29	97.06 ± 41.38	50.83 ± 10.51
p-value	0.0063	0.0279	0.0035
Spearman's Correlation (ρ)			
Correlation with GCS Score	-0.704 (p<0.0001)	-0.409 (p=0.0246)	-0.589 (p=0.0006)
Correlation with GOS Score	-0.645 (p<0.0001)	-0.489 (p=0.0061)	-0.656 (p<0.0001)

Table 4: Linear Regression Analysis of CSF Biomarkers as Predictors of Admission GCS Score

Predictor Variable	Unstandardize d Coefficient (B)	Standar d Error	p-value	Mode l R ²
Model 1: IL-6	-10.51	3.02	0.002	0.302
Model 2: TNF-α	-3.94	2.17	0.081	0.105
Model 3: LRG-1	-2.44	0.77	0.003	0.264

Poorer GOS outcomes corresponded to higher biomarker levels, with significant correlations for IL-6 (ρ=-0.645), TNF-α (ρ=-0.489), and LRG1 (ρ=-0.656) (Table 3).

DISCUSSION

Our study highlights IL-6 as a central inflammatory mediator in TBM, showing strong correlations with radiological severity, clinical grade, GCS, and GOS, supporting its role in inflammation-driven damage, consistent with Sharma et al. (2017), Kalita et al. (2022), and Kruthika (2022) [6-8]. TNF-α levels were moderately elevated, peaking in infarct cases and showing weaker GCS/GOS associations, aligning with Bhasin et al. (2021) and Shukla et al. (2022) on its role in vascular injury rather than overall disease activity [3,9]. LRG1 emerged as a stable biomarker, progressively rising with severity and correlating with GCS and GOS, building on Chong et al. (2018) and Ma et al. (2024) [5,10]. Biomarker levels, especially IL-6 and LRG1, were highest in infarct cases, supporting Sharma et al. (2017) and Bhasin et al. (2021) findings [3,6]. Their significant inverse correlation with GCS and GOS underscores their prognostic value, aligning with Kalita et al. (2022) and Sinha et al. (2015) [7,11]. A panel of IL-

6, LRG1, and TNF- α could complement clinical and radiological assessment, particularly in low-resource settings, as supported by multiplex biomarker studies [12].

CONCLUSION

CSF IL-6 and LRG1 are strong prognostic markers in TBM, linked to severe grades, low GCS, poor GOS. IL-6 correlates with inflammation/infarcts; LRG1 reflects disease burden. TNF- α indicates infarct risk. Combined biomarkers with clinical/imaging data enhance risk stratification and guide care in imaging-limited settings.

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