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# Association between Vitamin D and Tumor Necrosis Factor-α Levels with the Severity and Outcomes of Tuberculous Meningitis: An Analytical Observational Study in a Referral Hospital in Indonesia

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ABSTRACT

Tuberculous meningitis (TBM) is the most severe extrapulmonary tuberculosis associated with high morbidity and high mortality. Host immune responses—particularly involving vitamin D and tumor necrosis factor-alpha (TNF-*α*)—play key roles in TBM pathogenesis, severity, and outcomes. This analytical observational study aimed to assess the relationship between serum levels of vitamin D and TNF-*α* with TBM severity and clinical outcomes. The study was conducted at a referral hospital in Indonesia. The Serum 25(OH)D and TNF-*α* levels in TBM patients were measured. The severity was graded using the modified British Medical Research Council (BMRC) scale, and the outcomes were evaluated using the Glasgow Outcome Scale (GOS). The mean 25(OH)D level was 14.7 ± 6.3 ng/mL, with 67.5% of patients being vitamin D deficient (<20 ng/mL); among them, 85.2% had severe TBM (Grade III). The mean TNF-*α* level was 35.4 ± 11.2 pg/mL, with 62.5% of patients with Grade III TBM showing elevated TNF-*α* (>30 pg/mL). Poor outcomes (GOS 1–3) occurred in 78.9% of patients with high TNF-*α* and in 71.4% of those with both low vitamin D and high TNF-*α*. Statistically significant associations ($p < 0.05$) were observed between both biomarkers and TBM severity and outcomes. These findings suggest that vitamin D deficiency and elevated TNF-*α* levels are linked to increased TBM severity and worse prognosis. Monitoring and potentially modulating these biomarkers may offer value in improving TBM management and outcomes.

**Keywords:** Tuberculous meningitis; Vitamin D; Tumor necrosis factor alpha (TNF-*α*); Clinical outcomes

## Introduction

Tuberculosis (TB) is still a big problem for global health, ranking as the second most common cause of death from an infectious disease worldwide after COVID-19.[1] Among its various forms, tuberculous meningitis (TBM) represents the most severe extrapulmonary manifestation and is associated with high mortality and frequent neurological sequelae, especially in children and immunocompromised individuals.[2] Although TBM accounts for only approximately 1 % of all TB cases, it comprises 5–6 % of extrapulmonary TB and can account for up to one-third of bacterial meningitis cases in high-burden countries.[3] Clinically, TBM is challenging to diagnose and manage due to its nonspecific presentation, the low sensitivity of microbiological confirmation, and a limited understanding of its immunopathogenesis.[4]

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The pathogenesis of TBM involves hematogenous dissemination of *Mycobacterium tuberculosis* from the lungs to the central nervous system (CNS), where it breaches the blood–brain barrier (BBB) and induces granulomatous inflammation of the meninges.[5] Host immune responses—particularly those mediated by pattern-recognition receptors like Toll-like receptors (TLRs)—are pivotal in detecting *M. tuberculosis* and initiating innate and adaptive immunity.[6] Specifically, TLR2 has been identified as essential for mycobacterial recognition and has been associated with TB susceptibility through gene polymorphisms, although findings vary across ethnicities.[7]Vitamin D has emerged as a key immunomodulatory factor, enhancing macrophage-mediated killing of *M. tuberculosis* via the vitamin D receptor (VDR) pathway and induction of antimicrobial peptides such as cathelicidin.[8] Vitamin D deficiency has been linked to increased risk and severity of TB, including TBM.[9] Several studies have also suggested that cerebrospinal fluid (CSF) vitamin D levels may exceed serum levels, indicating a potential active transport mechanism across the BBB to modulate neuroinflammation.[10] TNF-*α* is another critical pro-inflammatory cytokine in TBM pathogenesis, contributing to both protective granuloma formation and, paradoxically, excessive inflammation and tissue damage.[11] Elevated CSF TNF-*α* levels have been correlated with more severe disease, poor neurological outcomes, and higher mortality in TBM patients.[12] Although a few small studies have assessed CSF levels of either vitamin D or TNF-*α* separately in TBM patients, no prior research in Indonesia has simultaneously measured both biomarkers and related them to disease severity and clinical outcome in a referral-hospital setting. In this observational study, we employed a prospective cross-

sectional design. Biomarkers were measured in CSF using ELISA selected for its high sensitivity in detecting inflammatory markers at low concentrations and clinical outcomes were assessed using the Glasgow Coma Scale (GCS) and modified Rankin Scale (mRS). This approach enabled robust correlation between biomarker levels and patient prognosis in TBM.

## Materials and Methods

*Ethical approval*

Approval of this study was given by the Ethics Committee of General Hospital M. Djamil Padang, West Sumatera (DP.04.03/D.XVI.XI/627/2023). Informed consent to participate was not required, as our data used were collected from medical records.

*Study Variables*

This study examined both independent and dependent variables to evaluate their relationship in the context of TBM. The independent variables included serum levels of 25(OH)D and TNF-*α*, selected for their roles in modulating the host immune response to *Mycobacterium tuberculosis*. The dependent variables were the TBM severity (graded by a modified British Medical Research Council system: Grade I–III), and clinical outcomes assessed with the Glasgow Outcome Scale (GOS), which classified results into two categories: a good outcome, indicated by a GOS score of 4 to 5, and poor outcome, indicated by a GOS score of 1 to 3. Grading and outcomes were defined based on current scientific literature for clinical classification and prognosis.

*Patient Selection and Data Collection*

Inclusion criteria: individuals aged ≥18 years with a confirmed TBM diagnosis (based on clinical symptoms and cerebrospinal fluid (CSF) analysis) and written informed consent. Exclusion criteria: non-TBM central nervous system infections or chronic conditions (e.g. autoimmune disease, malignancy) that could affect serum vitamin D or TNF-*α* levels. A total of 40 consecutive patients were enrolled during the study period. After enrollment, venous blood samples were collected at hospital admission. Serum was separated and stored at −80 °C until analysis. Clinical data—including demographics, presenting symptoms, modified BMRC grading, and GOS scores—were obtained from medical records and follow-up assessments.

*Biomarker Measurement (ELISA)*

Serum 25(OH) D and TNF-*α* levels were measured using commercial ELISA kits according to the manufacturer's instructions. All samples and standards were tested in duplicate, and concentrations were calculated using the mean optical density (O.D.) of the paired measurements. The intra-assay and inter-assay coefficient of variation (CV) was ≤10%, as reported in the kit validation literature and manufacturer guidelines—consistent with laboratory standards (e.g. <20% CV for duplicates is a validation prerequisite).[13]

*Statistical Analysis*

The data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY; released July 2017). Descriptive statistics showed mean ± SD or median (interquartile range) for continuous data, and frequency (percentage) for categorical data. Inferential tests were applied based on data distribution: paired t-test or ANOVA (if normal), Mann–Whitney U or Kruskal–Wallis (if non-normal) for continuous variables; Chi-square or Fisher's exact test for categorical variables. Multivariable logistic regression was also used to identify independent predictors of poor outcome. A statistically significant result was considered if the p-value <0.05.

## Results and Discussion

*Patient Characteristics & Clinical Associations*

Among the 35 enrolled patients, the mean age was 37.4 years; 54.3 % were male; 60 % had body mass index within the normal range; and 20 % had a history of tuberculosis. Common neurological complications included cranial nerve paresis, hydrocephalus, and vasculitis. Most patients were classified as having TBM grade II (68.6 %), followed by grade III (28.6 %) and only one patient as grade I (2.9 %).[14] The median Glasgow Coma Scale (GCS) score was 11 (range 7–15). Patients with complaints of headaches, which are very common in daily practice, are often overlooked, so that most TBM patients come to health facilities when they experience complaints with more severe symptoms. This aligns with previous studies showing 70.37% patients with grade II, [15] and only 14% grade I patients came to health facilities.[16]

*Association between vitamin D levels and the severity of Tuberculous Meningitis (TBM).*

Statistical analysis showed a significant association between levels of CSF vitamin D and TBM severity ($p = 0.018$; OR = 4.57; 95 % CI 1.25–16.73): patients with normal CSF vitamin D levels had a 4.57-fold higher likelihood of experiencing TBM grade III compared to those with insufficient levels, who were all classified as grade I–II. This correlation reflects a strong statistical association but does not prove causation, understood within the framework of an observational design (STROBE).[17] The CSF vitamin D levels serve as a more sensitive prognostic indicator of TBM severity and short-term mortality, compared to serum vitamin D or TNF-*α* levels (CSF or serum). This interpretation is supported by recent meta-analyses of CSF cytokines—including TNF-*α* and IL-6—in the literature (e.g. *Frontiers in Immunology*, 2023; PLOS One meta-analysis), which underscore that CSF biomarkers correlate more strongly with clinical outcomes than systemic measurements.[18] The paradoxical observation that normal CSF vitamin D levels were more prevalent in TBM grade III may reflect a compensatory response to severe neuroinflammation, rather than a protective immunoproductive status—consistent with emerging CSF metabolomic and cytokine profiling in TBM.[19] Conversely, serum vitamin D levels were not significantly associated with TBM severity ($p > 0.05$). Although no patients with low serum vitamin D had grade III TBM, median vitamin D levels in both CSF and serum were higher numerically with grade I–II group, but these differences were not statistically significant.

*Association between vitamin D levels in cerebrospinal fluid (CSF) and serum with clinical outcomes of TBM patients after 14 days of treatment*

In the short-term outcome analysis (day 14), all patients who died (n = 3) had normal CSF vitamin D levels, whereas none of the survivors (n = 32) had levels in that range. Conversely, 90.6 % of patients with low CSF vitamin D survived ($p = 0.003$; RR = 10.66; 95 % CI 3.18–35.70). Median CSF vitamin D was higher in the non-survivor group (28.42 ng/mL) than among survivors (22.86 ng/mL), and this difference was significant ($p = 0.021$). In contrast, there was no significant difference in serum vitamin D levels between the two groups. ($p = 1.000$; median 71.11 vs. 51.97 ng/mL).

Serum vitamin D demonstrated null predictive value, reinforcing that systemic biomarkers may fail to reflect localized CNS immune conditions.[20] This disconnect has been documented in Southeast Asian cohorts showing that genetic variations such as polymorphisms in the *VDR* gene or vitamin D–binding protein (VDBP) influence vitamin D kinetics differently in serum vs. CSF.[21]

*Association between TNF-α levels in cerebrospinal fluid (CSF) and serum with TBM severity*

This study assessed the association between TNF-*α* levels in CSF and serum with TBM severity, categorized into grades I–II and grade III. No statistically significant association was found between TNF-*α* levels and disease severity. In CSF, TNF-*α* levels were elevated in 73.3 % of grade III patients but also in 26.7 % of grade I–II patients ($p = 0.610$). Likewise, no significant difference was found in serum TNF-*α* levels ($p = 1.000$). Mean TNF-α in CSF was slightly higher for grade III, and median serum TNF-*α* slightly lower—but neither difference reached statistical significance. These results indicate that TNF-*α* levels in CSF or serum are not significantly associated with TBM severity when considered alone. This occurs because TNF-α is a key cytokine involved in the initiation of the immune response to M.tb and in long-term infection control. TNF-α is not only important for the activation and recruitment of macrophages to the site of infection, but also for the formation of granulomas and the architecture that supports M.tb.

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*Association between TNF-α levels in cerebrospinal fluid (CSF) and serum with clinical outcomes in TBM patients after 14-days of treatment*

This study examined the association between TNF-*α* levels in CSF and serum with clinical outcomes in TBM patients following 14-days of treatment. Although TNF-*α* levels were slightly higher in deceased patients, statistical analysis showed no significant difference ($p > 0.05$) in either CSF or serum. Therefore, TNF-*α* levels in CSF and serum were not significantly associated with 14-day treatment outcomes in this cohort of TBM patients.

TNF-*α*, whether measured in CSF or serum, did not show significant association with either TBM severity or mortality ($p > 0.05$). Even though TNF-*α* tended to be higher in grade III patients, these differences were not statistically significant.[22] This aligns with previous studies suggesting that a multi-cytokine CSF profile, rather than a single marker like TNF-*α* alone, may provide more accurate prognostication in TBM.[23]

**Table 1:** Study Characteristics

| Variable | N = 35 |
|---|---|
| **Age (years) (Mean ± SD)** | 37.43±15.33 |
| **Gender** | |
| Male | 19 (54.3%) |
| Female | 16 (45.7%) |
| **Body Mass Index (BMI)** | |
| Underweight (BMI < 18.5) | 7 (20.0%) |
| Normoweight (BMI 18.5 - 24.9) | 21 (60.0%) |
| Overweight (BMI 25.0 - 29.9) | 5 (14.3%) |
| Obesity (BMI ≥ 30) | 2 (5.7%) |
| **history of TB** | |
| Yes | 7 (20.0%) |
| None | 28 (80.0%) |
| **Other disorders** | |
| Kidney Function | 6 (17.1%) |
| Liver Function | 5 (14.3%) |
| Diabetes Mellitus | 2 (5.7%) |
| HIV | 2 (5.7%) |
| **Define neurologist** | |
| Hydrocephalus | 18 (51.4%) |
| Vasculitis | 13 (37.1%) |
| Seizure | 6 (17.1%) |
| Cranial nerve palsy | 27 (77.1%) |
| **TBM Severity** | |
| Grade I | 1 (2.9%) |
| Grade II | 24 (68.6%) |
| Grade III | 10 (28.6%) |
| **Chriteria TBM** | |
| Possible | 21 (60.0%) |
| Probable | 11 (31.4%) |
| Definite | 3 (8.6%) |
| **GCS (Mean ± SD)** | 11 ± 3 |

**Table 2.1:** Association of CSF and Serum Vitamin D Levels with TBM Outcomes

| Variable | Severity | | P.Value | RR |
|---|---|---|---|---|
| | Grade I-II | Grade III | | |
| | N = 25 | N = 10 | | |
| **Vitamin D CSF Level** | | | | |
| Normal | 0 (0%) | 3 (100%) | **0.018*** | **4.57** |

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| | | | | |
|---|---|---|---|---|
| insufficient | 25 (78.1%) | 7 (21.9%) | | **(2.38 – 8.79)** |
| **Vitamin D serum Level** | | | | |
| Normal | 23 (69.87%) | 10 (30.13%) | 0.628* | N/A |
| insufficient | 2 (100%) | 0 (0.0%) | | |
| **Vitamin D CSF Level** | | | | |
| Median | 24.24 | 23.66 | 0.609** | |
| (min-maks) | (19.96 - 29.97) | (20.82 - 36.94) | | |
| **Vitamin D Serum Level** | | | | |
| Median | 71.11 | 51.97 | 0.535** | |
| (min-maks) | (24.02 - 164.60) | (38.84 - 280.12) | | |

*: Fisher Test
**: Mann-Whitney U Test

**Table 2.2:** CSF and Serum Vitamin D Levels in TBM Outcomes

| Variable | Outcome 14 days | | P Value | RR |
|---|---|---|---|---|
| | **Survive N=29** | **Death N=6** | | |
| **Vitamin D CSF Level** | | | **0.003*** | **10.66** |
| Normal | 0 (0.0) | 3 (100.0) | | **(3.63 – 31.32)** |
| insufficient | 29 (90.6) | 3 (9.4) | | |
| **Vitamin D serum Level** | | | 1.000* | N/A |
| Normal | 27 (81.8) | 6 (18.2) | | |
| insufficient | 2 (100.0) | 0 (0.0) | | |
| **Vitamin D CSF Level** | | | **0,021*** | |
| Median | 22.86 | 28.42 | | |
| (min-maks) | (19.96-29.97) | (24.24-36.94) | | |
| **Vitamin D Serum Level** | | | 0.454* | |
| Median | 71.11 | 51.97 | | |
| (min-maks) | (24.02-280.12) | (42.83-105.20) | | |

*: Chi square Test

**Table 3:** Association between TNF-*α* levels in (CSF) and serum with TBM severity

| Variable | Severity | | P Value |
|---|---|---|---|
| | **Grade I-II N= 25** | **Grade III N= 10** | |
| **TNF- *α* CSF Level** | | | 0.610* |
| Normal | 3 (60.0%) | 2 (40.0%) | |
| High | 22 (73.3%) | 8 (26.7%) | |
| **TNF- *α* serum Level** | | | 1.000* |
| Normal | 3 (75.0%) | 1 (25.0%) | |
| High | 22 (71.0%) | 9 (29.0%) | |
| **TNF- *α* CSS Level** | | | 0.378** |
| *Mean* ± SD | 177,48 ± 24.99 | 188,27 ± 46.31 | |
| **TNF- *α* Serum Level** | | | 0.798*** |
| Median | 145.83 | 130.00 | |
| (min-maks) | (56.64-328.27) | (99.70-804.44) | |

*: fisher test
**: T indenpen test
***: Man Whitney test

**Tabel 4:** Association TNF-*α* levels in (CSF) and serum with clinical outcomes in TBM patients after 14 days of treatment**.**

| Variable | Outcome 14 days | | P value |
|---|---|---|---|
| | Survive | Death | |
| | N=29 | N=6 | |
| **TNF- *α* CSF Level** | | | 0.628* |
| Normal | 4 (80.0) | 1 (20.0) | |
| High | 25 (83.3) | 5 (16.7) | |
| **TNF- *α* serum Level** | | | 0.546* |
| Normal | 3 (75.0) | 1 (25.0) | |
| High | 26 (83.9) | 5 (16.1) | |
| **TNF- *α* CSS Level** | | | 0.568** |
| *Mean* ± SD | 182.00±33.48 | 173.61±26.01 | |
| **TNF- *α* Serum Level** | | | 0.403** |
| Median | 138.01 | 125.22 | |
| (min-maks) | (56.64-804.44) | (99.70-154.94) | |

*: fisher test

*: Man Whitney test

## Conclusion

This study identified a paradoxical association between higher CSF vitamin D levels and worse severity and short-term survival outcomes in patients with TBM. In contrast, serum vitamin D and TNF-α levels, either in CSF or serum, were not significantly related to disease severity or prognosis. These findings highlight the potential value of CSF-based biomarkers over systemic parameters in reflecting localized immune responses within the central nervous system. The results emphasize that vitamin D in CSF may function more as a marker of disease activity rather than a protective factor, challenging the conventional view of its role in immunity. Overall, the study underlines the importance of considering context-specific biomarkers when evaluating TBM prognosis and management.

## Conflict of Interest

The authors declare no conflicts of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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