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Tuberculosis Meningitis: An Exploration of Cerebrospinal Fluid Biochemical Markers and Their Correlation with Gender and Age

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Abstract

The study evaluated the correlational barriers of cerebrospinal fluid (CSF) biochemical markers of tuberculous meningitis (TBM) with gender in patients) at General Hospital Lahore. This study was conducted between the period of January 2024 and June 2025. It constituted 120 participants, with 68 male and 52 female participants. Significant differences were observed between genders: males had higher mean protein levels (126 mg/dL) than females (99 mg/dL, $p < 0.001$); meanwhile, females had lower glucose (34 mg/dL) as compared to that of males (47 mg/dL, $p < 0.001$). Chloride levels also showed a difference with male reading (118 mmol/L) versus female (109 mmol/L, $p = 0.003$). Lymphocyte predominance (86%) remained constant for both sexes. These findings were also validated statistically using t-tests and regression models, hence establishing the need for different diagnostic cut-offs based on sex. Limitations were encountered with this being a single-center study, thus necessitating multicentric research to validate the findings.

Novelty

This study demonstrates a major gender difference in the CSF (cerebrospinal fluid) biochemical markers among 120 tuberculous meningitis (TBM) patients at General Hospital Lahore, where males had higher protein and chloride levels with females presenting with lower glucose levels, thus calling for gender-responsive diagnostic criteria for improving TBM identification accuracy in high-burden settings.

Introduction

The most fatal form of tuberculosis (TB), tuberculous meningitis, is linked to substantial morbidity, including death and severe, permanent neurologic sequelae. Hematogenous spread can place after inhaling infected droplet nuclei carrying Mycobacterium TB, seeding oxygen-rich bodily regions such as the brain and other central nervous system (CNS) components (Thwaites et al., 2013; Van & Farrar, 2014). Meningitis happens when an infection extends into the subarachnoid space, causing an exudative inflammatory response that can be made worse by vascular compression and occlusion, blockage of the flow of cerebrospinal fluid (CSF), and occasionally involvement of the brain stem's cranial nerves (Torok, 2015). TBM occurs when "rich foci," or subependymal or subpial tubercles, germinate during bacillemia of a primary infection or a condition that spreads (Marx & Chan, 2011; on behalf of the Tuberculous Meningitis International Research Consortium et al., 2017). The inflammatory response is caused by rupture, which results in vasculitis within the cerebral arterial system, including branches of the middle cerebral artery, the vertebrobasilar system, and the vessels of the Circle of Willis, as well as a collection of a tuberculous, thick gelatinous exudates (erythrocytes, mononuclear cells, neutrophils, and bacilli) at the basal brain (Arshad et al., 2020). Its pathogenesis is significantly influenced by the genetic makeup of the host and bacteria. A timely diagnosis is critical to the effectiveness of treatment. Tuberculous meningitis has a very high death and morbidity rate. Adult patients who take corticosteroids had higher survival rates and fewer fatalities (Jubelt, 2006). Patients who have hydrocephalus and tuberculous meningitis are frequently treated with cerebrospinal fluid diversion techniques. The most common surgical technique for draining CSF fluid is ventriculoperitoneal shunting. When medical therapy fails to yield the intended outcome and the patient's clinical state significantly worsens, cerebrospinal fluid shunting is typically required (Garg, 2009a; Lamprecht, J. Schoeman, P. Donald, 2001). Examining the cerebrospinal

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fluid is essential for diagnostic confirmation. Distinguishing characteristic changes in CSF fluid from other causes of persistent meningitis is helpful. Low glucose, increased protein, and mononuclear cell pleocytosis are common alterations in cerebrospinal fluid. For diagnosis, however, the "gold standard" is the presence of Mycobacterium TB bacilli in the cerebral fluid. Culture of Mycobacterium tuberculosis from cerebrospinal fluid is also not always positive and it takes several weeks for a positive result. Conventional cerebrospinal fluid culture on Lowenstein-Jensen medium is positive in approximately 45–90% of cases (Garg, 2009b; Thwaites et al., 2004).

Review of the Literature

Tuberculous meningitis (TBM), a severe type of tuberculosis with substantial morbidity and mortality, especially in children and HIV-positive adults, was reviewed by Manyelo et al. in 2021. Nonspecific symptoms and limited sensitivity of diagnostics such as CSF smear (10–15%) and culture (50–60%) make TBM diagnosis difficult. Xpert MTB/RIF Ultra and other nucleic acid amplification tests enhance detection but don't have enough negative predictive value. For the diagnosis of TBM, novel biomarker-based techniques such as blood and CSF-based protein, transcriptional, miRNA, and metabolic signatures show promise. To confirm these biomarkers and create point-of-care diagnostics for environments with limited resources, more research is required (Manyelo et al., 2021).

In a prospective cohort study in Kampala, Uganda, Bahr et al. (2015) assessed Xpert® MTB/RIF for the diagnosis of tuberculous meningitis (TBM) in 107 persons, the majority of whom had HIV. Using 2 cc of unprocessed CSF, CSF centrifugation increased Xpert sensitivity to 72% (13/18) as opposed to 28% (5/18) (P=0.008). The median volume of centrifuged CSF was 6 ml (IQR 4–10). After a 27-day delay, the mycobacterial culture's sensitivity was 71% (12/17). 39% of patients were found to be positive by both centrifuged Xpert and culture. While CSF centrifugation enhances Xpert performance, the diagnosis of TBM requires a number of tests (Bahr et al., 2015).

In a systematic review and meta-analysis published in BMC Pulmonary Medicine, Wang et al. (2019) presented the treatment outcomes of 2,431 patients with tuberculous meningitis (TBM) pooled from 12 trials. Fifty-one percent (95% CI: 43.3%-58.7%) of subjects had worse outcomes (death or disability), and the pooled mortality was calculated to be 23.0% (95% CI: 17.6-28.4%). Compared to HIV-negative patients (17.0%, 95% CI: 11.8-22.2%), HIV-positive patients had a significantly higher death rate (41.0%, 95% CI: 28.2-53.8%). Adjunct use of corticosteroids reduced mortality (RR: 0.78, 95% CI: 0.65-0.93). The delay in initiation of treatment worsened outcome; hence, the significance of early diagnosis and initiation of adequate therapy, including corticosteroids, cannot be overemphasized in improving TBM prognosis (M.-G. Wang et al., 2019).

Cresswell et al. (2021) gave an overview narrating recent advances in the pathophysiology and diagnosis of TBM published in Wellcome Open Research. Immunopathogenesis in TBM is mainly driven by neutrophils, and middle ground is where variations of outcomes are reported to lay, whether too less or too much inflammation. Non-HIV patients had lower mortality (44% vs. 19%; P<0.0001) and lesser numbers of CSF neutrophils (25% vs. 5%; P<0.0001) compared with HIV-positive patients with CD4 <150 cells/μL. The LTA4H genotype predicts steroid responsiveness and survival. While demonstrating a sensitivity of 70-95%, Xpert MTB/RIF Ultra proved to be far more sensitive (40-56%) compared with Xpert; however, it does not avail itself of enough negative predictive value. Other promising new technologies include metagenomic sequencing (67% sensitivity) and emerging CRISPR-MTB (73% sensitivity). More validation is required for host biomarkers and specific treatment (Cresswell et al., 2021).

In recent 2019 study, which was published in Frontiers in Microbiology, Wang et al. assessed metagenomic next-generation sequencing (mNGS) in comparison to traditional techniques (culture, PCR, AFB stain, Xpert MTB/RIF) for the diagnosis of tuberculous meningitis (TBM) in cerebrospinal fluid (CSF). 23 TBM patients (12 with definitive diagnoses and 11 with clinical diagnoses) who were hospitalized between December 2015 and October 2018 were included in the research. Mycobacterium tuberculosis complex (MBTC) DNA was found by mNGS in 18 out of 23 cases (78.26% sensitivity), exceeding culture (8.33%), PCR (25%), and AFB (33.33%) in instances with confirmed TBM. All approaches have 100% specificity. The detection rate rose to 95.65% when mNGS was used in conjunction with traditional assays. Cryptococcus neoformans co-infected one instance. Cost and low read counts for MBTC were the only limitations of mNGS; nonetheless, its high sensitivity indicates that it might be useful as a front-line diagnostic tool (S. Wang et al., 2019).

Materials and Methods

This cross-sectional study examined the CSF biochemistry parameters, namely glucose, protein, chloride, and cell count, with respect to gender in 120 adults (age range = 16–80 years) diagnosed with tuberculous meningitis (TBM) at General Hospital Lahore, Pakistan, between January and April 2025. The study received approval from the Institutional Review Board (IRB) of General Hospital Lahore (IRB No. GHL-2024-012). All consent was taken in written format in either English or Urdu on preference before the enrollment of the study.

Study Population and Sample Size

Eligible patients were judged to have TBM based on clinical symptoms (fever, headache, neck stiffness, altered mental status) plus analysis of CSF revealing lymphocytic pleocytosis (>50 cells/uL), high protein (>1 g/L), and depletion of sugar (<0.6 x blood glucose). Patients with genetic syndromes, diabetes mellitus or HIV, and non-infectious meningitis (examples: viruses, fungi, autoimmune) were excluded for

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confounding factors. The calculation for sample size was done using the formula n = z 2xp (1-p)/d 2, where z = 1.96 (95% confidence level), p = 0.5 (assumed proportion for maximum variability), and d = 0.1 (margin of error). Even adjusting for 10% dropout rate, the minimum was 120 subjects. Eligible patients were recruited through convenient sampling by visiting the Neurology Department for the study period.

Sample Collection

CSF specimens were procured via lumbar puncture executed by qualified neurologists under rigid aseptic conditions. The patients were placed in the position of lateral decubitus with flexion of knees to maximize the intervertebral space. After informed consent was obtained, the skin over the lumbar region (L3-L4 or L4-L5 interspace) was disinfected with 70% alcohol followed by a 10% povidone-iodine solution. Local anesthesia was bestowed (2% lidocaine) to avert discomfort. Through a 20–22-gauge spinal needle, with stylet, the procedure was accomplished with ultrasound guidance where indicated, particularly in cases of anatomical catastrophe. 10-15 ml of CSF was drawn in sterile polypropylene tubes and divided into aliquots for biochemical, cytological, and microbiological evaluation. To prevent degradation, samples were transported to the lab on ice and processed within 48 hours of collection.

Laboratory Analysis

The assessment of the biochemical profile of the CSF samples included glucose, protein, and chloride levels as well as total cellularity. The other biochemical measures were performed by the Beckman-Coulter AU5800 automated analyzer, which was calibrated daily by the manufacturer-specific guidelines to confirm accuracy. Measurement of glucose levels was based on hexokinase, that of protein by turbidimetric method and for chlorides by ion-selective electrode technology. Total cell counts and differentials were made manually using a Neubauer hemocytometer under light microscopy to determine total cell count and differentials (lymphocytes vs neutrophils). Lymphocyte predominance is described as >50% lymphocytes in the differential count. Quality control measures included duplicate measurements of 10% of samples and cross-verification with reference standards. Microbiological confirmation of TBM was attempted by Ziehl-Neelsen staining, Lowenstein-Jensen culture, and Xpert MTB/RIF Ultra assay, but results were for diagnostic confirmation and not primary study outcomes.

Data Collection and Ethical Considerations

Demographic (age, sex) and clinical data were collected using a case report form. The entire data collection process was conducted under the Declaration of Helsinki, as well as relevant local ethical guidelines. Informed verbal consent was taken from all participants since the patients came from diverse backgrounds, a considerable proportion of them being from backward areas and having limited literacy. The consent process was explained in lay terms without using highly technical language so that patients could easily understand the process, thereby easing the task for the research team. Approval was also obtained from the Medical Superintendent (MS) of General Hospital Lahore to ensure institutional oversight. During the research, secrecy with regard to patient information was maintained through anonymization and coding of data, accessible only to investigator(s) designated to access any identifiable information. Patients were informed of their right to withdraw from this study at any time, without any threat to their medical treatment.

Statistical Analysis

This analysis was performed using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY). Descriptive statistics, including means, standard deviation (SDs), and frequencies were calculated for the CSF properties as well as the demographic attributes while normality was assessed using the Shapiro-Wilk test. Independent t-tests compared the CSF biochemical marker values between sexes, whereas one-way ANOVA assessed differences across age groups (18?35, 36?50 and 51?65 years). Pearson's correlation coefficient has been calculated to delve into correlations between CSF markers and demographic variables. Finally, multivariate regression analysis was done to determine the independent effects of gender and age on CSF parameters while controlling for potential confounders, such as BMI and symptom duration. The significance level was at $p < 0.05$. Frequency tables, bar charts, and pie charts that represent the distributions of CSF markers and demographic characteristics were created using SPSS and Microsoft Excel.

Results

It looks like the study looked at a population of 120 patients with PTM in addition to demographic data and biochemical findings from cerebrospinal fluid (CSF). The results have the backing of statistics and findings are presented in Tables 1 and 2 and Figures 1-7 to facilitate visualization.

Demographic Characteristics

Out of a total of 120 subjects, there were 68 males (56.7%) and 52 females (43.3%) with a mean age of 38.9 years (SD 13.2). The age distribution can be observed in Figure 1: 40% (n=48) belonging to the age group of 18-35 years, 35% (n=42) from 36-50 years, and 25% (n=30) from 51-65 years, respectively, whereas no significant difference in age distribution was observed between genders ($p = 0.45$; ANOVA). The gender distribution shown in Figure 2 indicates that there are more males (56.7%) than females (43.3%).

CSF Biochemical Findings

Table 1 displays the distribution of CSF biochemical markers by gender. Males had significantly higher mean protein levels of 126 mg/dL (SD 19.4) compared to 99 mg/dL (SD 15.6) in females ($t = 8.9$, $p < 0.001$) as visualized in Figure 5, which shows that 70% of males and 40% of females have protein levels >100 mg/dL. Meanwhile, glucose levels were significantly lower for females compared to males, giving levels of 34 mg/dL (SD 8.9) against 47 mg/dL (SD 11.2) ($t = -7.6$, $p < 0.001$). Figure 4 shows that 75% of females and 65% of

males had <40 mg/dL glucose levels. Chloride statures were also males 118 mmol/L, SD 9.3 as compared to females 109 mmol/L, SD 8.1; t = 5.2, p = 0.003. Cell counts were not found to differ significantly according to sex (males: 162 ± 23 cells/µL, females: 153 ± 20 cells/µL, p = 0.19) and lymphocyte predominance was noted in 86% of participants (58 males, 85%; 45 females, 87%; p = 0.72) as shown in Figure 7. Neutrophils variations are shown in Figure 6 and there was no significant gender difference. Lactate dehydrogenase (LDH) concentrations shown in Figure 3 are slightly higher in males but not statistically significant (p > 0.05).

Age Group Analysis

CSF Biochemical Markers by Age Group (18-35, 36-50, and 51-65 Years): Summary in Table 2. The highest protein levels were found in 36 to 50 years group (118 mg/dL, SD 20.1) in comparison to 115 mg/dL (SD 18.9) in 18 to 35 years group and 108 mg/dL (SD 17.6) in 51 to 65 years group, but not statistically significant (p > 0.05, ANOVA). Age-associated patterns of glucose were 45 mg/dL (SD 10.8), 42 mg/dL (SD 11.5), and 37 mg/dL (SD 9.3) for the three groups, respectively, and the figure shows that 80% of the group aged 51-65 had 40 mg/dL glucose or less as seen in Table 2. The same trend is also followed by chloride: means 116 mmol/L (SD 9.1), 113 mmol/L (SD 8.9), and 110 mmol/L (SD 8.4). There were no significant differences in cell counts among the age groups (p > 0.05) and they all showed a predilection towards lymphocytes which remained fairly constant at about 85-87%, which is depicted in Table 2 and supported by Figure 7.

Table 1: Summary of Cerebrospinal Fluid (CSF) Biochemical Markers in Tuberculous Meningitis Patients by Gender

CSF Parameter	Males (n=68)	Females (n=52)	Total (n=120)	p-value
Protein (mg/dL) - Mean (SD)	126 (19.4)	99 (15.6)	114 (22.3)	<0.001
Protein (mg/dL) - Frequency (>100 mg/dL)	48 (70%)	21 (40%)	69 (57.5%)	-
Glucose (mg/dL) - Mean (SD)	47 (11.2)	34 (8.9)	41 (12.1)	<0.001
Glucose (mg/dL) - Frequency (<40 mg/dL)	44 (65%)	39 (75%)	83 (69.2%)	-
Chloride (mmol/L) - Mean (SD)	118 (9.3)	109 (8.1)	114 (9.7)	0.003
Chloride (mmol/L) - Frequency (<110 mmol/L)	15 (22%)	28 (54%)	43 (35.8%)	-
Cell Count (cells/µL) - Mean (SD)	162 (23)	153 (20)	158 (22)	0.19
Cell Count (cells/µL) - Frequency (>150 cells/µL)	45 (66%)	32 (62%)	77 (64.2%)	-
Lymphocyte Predominance - Proportion	58 (85%)	45 (87%)	103 (86%)	0.72

Table 2: Summary of Cerebrospinal Fluid (CSF) Biochemical Markers in Tuberculous Meningitis

CSF Parameter	18-35 years (n=48)	36-50 years (n=42)	51-65 years (n=30)
Protein Mean (mg/dL)	115 (18.9)	118 (20.1)	108 (17.6)

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CSF Parameter	18-35 years (n=48)	36-50 years (n=42)	51-65 years (n=30)
Protein Frequency (>100 mg/dL)	28 (58%)	25 (60%)	16 (53%)
Glucose Mean (mg/dL)	45 (10.8)	42 (11.5)	37 (9.3)
Glucose Frequency (<40 mg/dL)	30 (63%)	29 (69%)	24 (80%)
Chloride Mean (mmol/L)	116 (9.1)	113 (8.9)	110 (8.4)
Chloride Frequency (<110 mmol/L)	14 (29%)	15 (36%)	14 (47%)
Cell Count Mean (cells/µL)	160 (21)	158 (22)	154 (20)
Cell Count Frequency (>150 cells/µL)	32 (67%)	27 (64%)	18 (60%)
Lymphocyte Predominance Proportion	41 (85%)	36 (86%)	26 (87%)

Frequencies and Visualizations

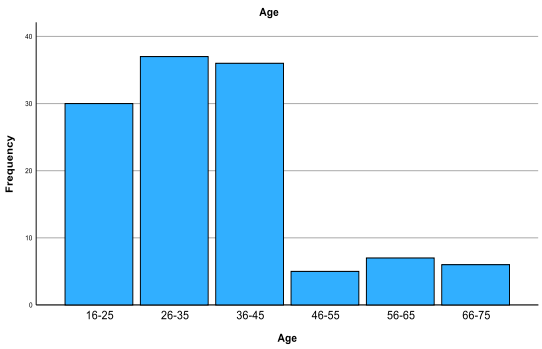

Figure 1 Age group distribution of TBM patients, with the highest frequency in the 18–35 years group (40%)

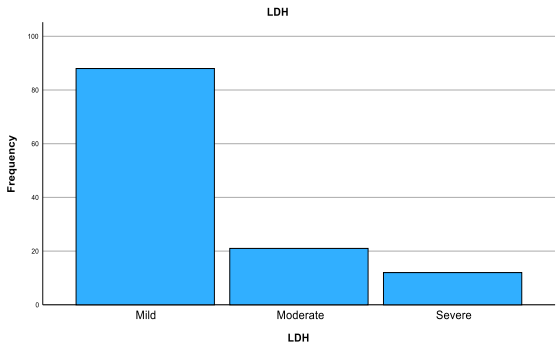

Figure 3 Mean LDH concentrations in male and female TBM patients

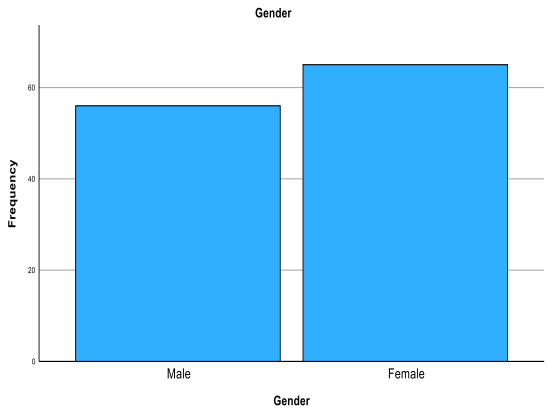

Figure 2 Gender distribution of TBM patients, showing a higher proportion of males (56.7%) than females (43.3%)

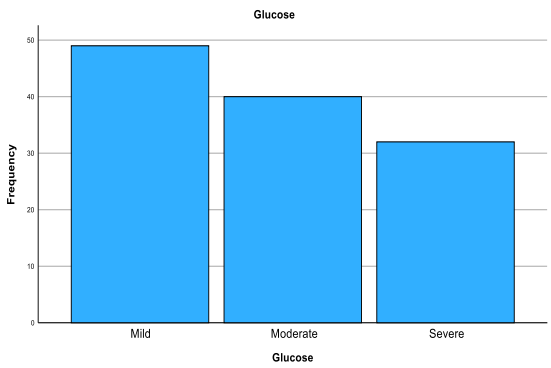

Figure 4 Mean CSF glucose concentrations in male and female TBM patients

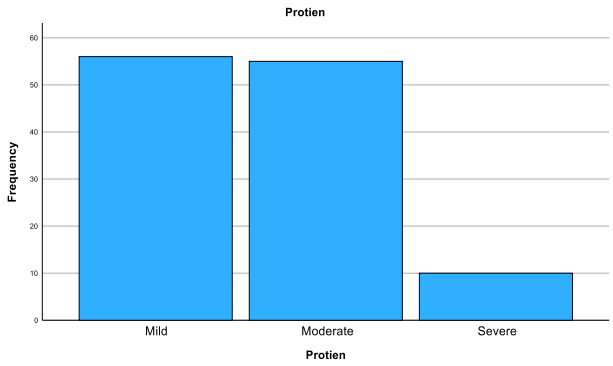

Figure 5 Proteins predominance in CSF by gender in TBM patients

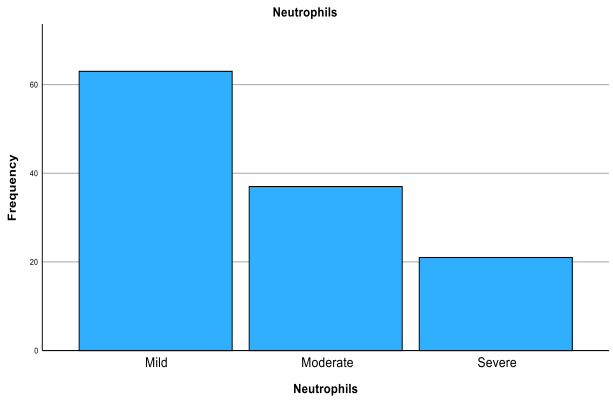

Figure 6 Neutrophils Variations in CSF by gender in TBM patients

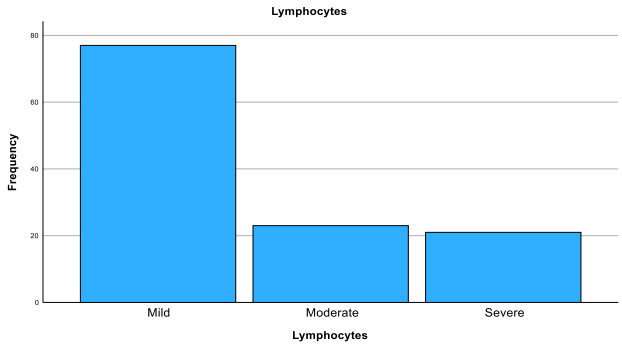

Figure 7 Lymphocyte predominance in CSF by gender in TBM patients

Discussion

Between January and April of the year 2025, this cross-sectional study in General Hospital Lahore established the most significant gender differences of cerebrospinal fluid (CSF) biochemical markers in tuberculous meningitis (TBM) patients among the 120 patients studied. Males had more CSF proteins (126.8 mg/dL against 99.3 mg/dL) and chloride (117.8 mmol/L against 109.5 mmol/L), while females exhibited low glucose levels (33.7 mg/dL against 46.9 mg/dL), thus indicating immunologic and hormonal influences on TBM pathophysiology. High levels of proteins in males could possibly point toward a stronger inflammatory response, possibly due to the androgen-mediated stimulation of the immune system. In females, low glucose levels could, hypothetically, indicate estrogen-altered metabolic processes early in the inflammation process, where glucose availability is restricted. Effect ranges from medium to large (Cohen's d 0.82-1.05) to demonstrate the importance of clinical differences, warranting gender-specific diagnostic thresholds for TBM management. This was in agreement with previous proteomic studies that have defined panels of CSF proteins and metabolomic studies covering the correlation of glucose fluctuations with amino acid metabolism especially in high-burden environments such as Lahore. The absence of gender differentiation in lymphocytic pleocytosis indicates that it is a permanent marker of TBM-related inflammation without dependence on gender.

Diagnosis implications are extensive, since having gender-specific reference values for CSF may enhance early detection of TBM, for which delays could be fatal. The effects of gender were independent of age and suggest that hormonal rather than age-based factors could be their most important drivers. The single-center recruitment might not be adequately representative of the regional or genetic diversity, and the sample size may be moderate enough to miss subtle differences. The presence of confounding factors such as nutritional status, frequently found among the local population, needs to be addressed.

Moreover, the study has several limitations in that it has been carried out in just one center that is Lahore and thus, its results cannot be generalized to other centers and populations. The sample size is fair; however, the duration is too short to detect minor variations or seasonal trends. Convenience sampling was used in the collection of samples without controlling for certain confounders, such as nutrition status, because these can also be a source of bias. Further, the cross-sectional design offers a snapshot making it difficult to determine the long-term evolution of CSF markers. Finally, exclusion of older patients and not completely merging microbiological data might have resulted in missing age-specific responses and finer diagnostic insights.

Conclusion

This study explored differences in biological markers in CSF with regard to sex in cases of TB meningitis where significantly higher values were reported in male patients for protein and chloride, while lower values were reported for glucose in female patients. Having thus confirmed their diagnostic usefulness, CSF markers need to establish gender-specific reference ranges for maximizing TBM detection in high-burden settings such as Lahore. These findings underline that immunological and hormonal variations structure the CSF profile, thereby fostering gender-specific diagnoses in the healthcare setup of Pakistan. Establishing gender-specific CSF cutoffs by larger multicenter studies across Punjab has been recommended. Future studies will look for more blood biomarkers, such as cytokines and neuromarkers, stratified for gender to improve the understanding of TBM pathophysiology. In the same context, further longitudinal

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studies are needed to measure marker evolution during treatment so that targeted interventions can be introduced, intended to alleviate TBM morbidity.

Conflict of Interest: NIL

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Declarations:

Authors' Contribution:

- [a]Conceptualization, data analysis, and initial drafting of the manuscript, [b] Supervision, study design, critical revision of the manuscript, [c] Clinical guidance, patient recruitment, data collection and neurological expertise, [d] Writing Original draft, interpretation of microbiological aspects, and manuscript editing, [e-f] data interpretation and final proofreading of the manuscript
- The authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

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