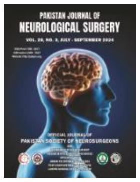

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Original Research

Tuberculous Meningitis: A Retrospective Study on Complications and Imaging Findings and Their Outcomes

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ABSTRACT

Objective: This study aims to emphasize the need for radiologists to remain vigilant about the common imaging findings and complications of CNS-TB (central nervous system tuberculosis), particularly TBM (tuberculous meningitis), to improve diagnosis and patient management.

Materials and methods: The authors conducted a retrospective analysis of radiological findings from 96 TBM patients at a tertiary care hospital, focusing on the frequency of TBM complications identified through MRI and CT, and their correlation with age, gender, and outcomes.

Results: A total of 96 patients having TBM (median age 21.6 years, range 8 months–70 years) were identified. There were 36 (37.5%) males and 60 (62.5%) females. Complications occurred in a significant portion of the cohort: tuberculoma (n = 55, 57.3%), hydrocephalus (n = 45, 46.9%), infarcts (n = 27, 28.1%), and cerebritis (n = 4, 4.2%). 11 patients of the study population died. Deaths were primarily related to tuberculomas (45.45%), hydrocephalus (27.27%), and infarcts (45.45%). Adult females showed a higher prevalence of fatal complications, indicating significant gender differences.

Conclusion: In TBM, the most common complications are tuberculomas and hydrocephalus, followed by infarcts and cerebritis. Notably, adult females show a higher prevalence of fatal complications. These results emphasize the need for early detection and targeted management strategies to improve patient outcomes.

Keywords: Tubercular Meningitis (TBM), Central Nervous System Tuberculosis (CNS-TB), Infarcts, Hydrocephalus, Tuberculomas.

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INTRODUCTION

Tuberculosis is a global pandemic. Approximately 25% of the human population is colonized by Mycobacterium tuberculosis, while about 1% are believed to develop central nervous system tuberculosis (CNS-TB). The most common form of CNS-TB is tuberculous meningitis (TBM). Tuberculosis (TB) ranks as the world's second most deadly infectious disease, following coronavirus disease (COVID-19), and is responsible for nearly double the number of deaths caused by HIV/AIDS. Annually, over 10 million people are diagnosed with TB every year.[1] About 0.6 million people died in South Asia due to tuberculosis in 2020.[2] Tuberculous meningitis (TBM) is the most severe form of extrapulmonary tuberculosis having a mortality rate of 25% while 50% of cases have long-term neurological disability.[3] Since TBM often presents with nonspecific symptoms making it difficult to diagnose, therefore, unique presentations of the disease might be overlooked. Prompt diagnosis followed by effective treatment can help prevent neurological damage or a fatal outcome.[4,5] Consequently, the primary concern for clinicians is the prompt diagnosis and treatment of TBM.

Tuberculosis (TB) is caused by Mycobacterium tuberculosis which is an acid-fast bacillus.[6] While TB primarily infects the lungs, it can disseminate to almost every organ through the hematogenous route.[7] The inhalation of Mycobacterium tuberculosis into the alveolar spaces leads to a primary tuberculous infection.[8] CNS tuberculosis results from the hematogenous spread of bacteria from the lungs to the subpial and subependymal regions, brain parenchyma, and meninges, leading to the formation of mycobacterium-rich foci known as "Rich foci."[9] When these foci rupture, they elicit an intense inflammatory response mediated by cytokines.[10] The inflammatory exudates accumulate in the basal cisterns and meninges, enveloping the structures in and around these areas. This inflammation can cause vasculitis and neuritis in the arteries and nerves of the basal cisterns, potentially leading to infarcts and cranial nerve palsies.[11] Hydrocephalus, often the initial sign of tuberculous meningitis, typically begins as communicating hydrocephalus due to the blockage of cerebrospinal fluid (CSF) resorption in the basal cisterns by the inflammatory exudates.[12] The formation of tuberculomas occurs from unruptured Rich foci.[13] Cerebritis, or inflammation of the brain tissue, can occur in the context of tuberculous meningitis (TBM), though it is less common compared to other complications like hydrocephalus or cranial nerve palsies.[14]

MRI is the preferred for suspected CNS tuberculosis, because of its detection in changes across all forms of CNS TB in its early stages.[15] This technique is highly effective in identifying complications such as infarcts, hydrocephalus, and vasculitis with great precision. Compared to CT, MRI offers superior specificity for detecting intracranial tuberculous pathologies.[16] While MRI is the preferred imaging modality, however, contrast-enhanced computed tomography (CT) also plays a critical role, particularly for imaging patients with a low Glasgow Coma Scale (GCS) score and in unstable patients. In such cases, CT allows for rapid image acquisition.[17] Moreover motion artifacts diminish the quality of MRI images in irritated patients. CT helps to eliminate these motion artifacts with its quick imaging capabilities.[18]

In this report, we reviewed the radiologic and clinical findings of 96 patients with TBM encountered during 9 years. Previous studies have explored various aspects of TBM, including its epidemiology, clinical features, and treatment outcomes. However, there is a paucity of comparative data on the complications of TBM in adults versus pediatric patients and males versus female and their outcomes. Therefore, the rationale of this study is to address the gap in this retrospective cohort study by observing the frequency and types of complications (e.g., hydrocephalus, infarct, tuberculomas, and cerebritis) in adult and pediatric patients as well as between male and female groups and to find the correlation of complications with gender, age group, and outcomes.

MATERIAL AND METHOD

Study Design & Setting

We retrospectively reviewed the electronic records of TBM patients from Lady Reading Hospital (LRH), Peshawar, between 2015 and 2024 (9 years). Ethical Review Committee of LRH Peshawar granted ethical approval for this study (Ref: No. 286/LRH/MTI). Informed consent was obtained from all individual participants included in the study. Participants were informed about the purpose, procedures, potential risks, and benefits of the study. They were assured of the confidentiality of their responses and their right to withdraw from the study at any time without any consequences.

Inclusion Criteria

Inclusion criteria for this study included patients with a confirmed diagnosis of tuberculous meningitis (TBM) who have undergone both brain MRI and CT scans. Eligible participants were having complete medical records, and no contraindications to MRI or CT imaging, such as pacemakers, metallic implants, or contrast allergies.

Exclusion Criteria

TBM (tuberculous meningitis) patients who underwent brain MRI and CT and those without a confirmed TBM diagnosis, incomplete medical records, contraindications to MRI or CT (such as pacemakers, metallic implants, or certain contrast allergies), co-infections with other CNS infections, and pre-existing neurodegenerative diseases, were excluded. Additionally, patients undergoing immunosuppressive therapy, those with a history of CNS trauma or surgery, pregnant women, and those who did consent to participate were also excluded.

Data Collection

We evaluated the biochemical, clinical, and histopathological data to find out if it meets the diagnostic criteria for TBM from the database of LRH. The images were jointly reviewed, and any discrepancies were resolved through consensus. All of the patients who were diagnosed with TBM according to the definition by Marais and colleagues were included in the study.[19]

Imaging Equipment

CT examinations were performed using a Toshiba/Canon 160-slice CT scanner, providing high-resolution imaging with advanced multi-slice capabilities while MRI was performed using a Toshiba/Canon 1.5 Tesla MRI scanner. Imaging findings were evaluated for the presence and number of tuberculomas, hydrocephalus, infarcts, and cerebritis.

Criteria for Characterizing Infarcts

Cerebral infarcts were assessed using the methods described by Hsieh and colleagues and Tai et al.

Criteria for Characterizing Cerebritis

The classification based on MRI findings includes T1-weighted images typically showing hypointense lesions, T2-weighted images revealing hyperintense areas indicating edema and inflammation, gadolinium-enhanced MRI showing ring enhancement, particularly in later stages, and diffusion-weighted imaging (DWI) helping to differentiate cerebritis from abscesses by showing less prominent restricted diffusion.[20] The classification based on CT findings includes non-contrast CT showing low-density areas indicative of edema and contrast-enhanced CT demonstrating regions of enhancement, although it is less sensitive than MRI.[21]

Criteria for Characterizing Hydrocephalus

On MRI, key indicators include ventricular enlargement, particularly of the ventricles (third, lateral, and/or fourth ventricles), the hyperintense periventricular signal on T2-weighted images indicating transependymal CSF flow, and possible identification of structural abnormalities such as masses or congenital malformations causing an obstruction. MRI CSF flow studies are also useful for assessing CSF dynamics and obstruction. On CT, hydrocephalus is identified by the dilatation of the ventricular system, with non-contrast scans revealing ventricular enlargement and periventricular lucency indicating CSF leakage into brain tissue. CT can also show brain parenchyma for signs of atrophy or lesions and detect aqueductal stenosis.[12]

Criteria for Characterizing Tuberculoma

On MRI, T1-weighted images typically show hypointense or isointense lesions, while T2-weighted images reveal a mixed signal intensity with a hypointense core and hyperintense rim due to surrounding edema. Contrast-enhanced MRI often displays ring or nodular enhancement, with central non-enhancing areas indicating necrosis. Magnetic resonance spectroscopy (MRS) may show elevated lipid and lactate peaks. On CT, non-contrast scans usually present tuberculomas as hyperdense or isodense lesions, sometimes with calcification. Contrast-enhanced CT similarly shows ring enhancement with a central low-attenuation area corresponding to necrosis and surrounding edema. These imaging characteristics, along with clinical and laboratory findings, are essential for the diagnosis and characterization of tuberculomas.[22]

Data Analysis

Descriptive statistics were compiled, with continuous variables expressed as means and categorical variables expressed as frequencies and percentages. The statistical analyses focused on evaluating the prevalence and distribution of complications such as cerebral infarcts, hydrocephalus, tuberculomas, and cerebritis with respect to age groups and gender. In this study, a Chi-Square Test for Independence was used to assess the association between gender and the occurrence of specific complications (Hydrocephalus, Tuberculoma, Infarct, and Cerebritis) in patients with Tuberculous Meningitis (TBM). A contingency table for each complication, categorizing the observed frequencies by gender (male and female), was created and is embedded in Table 7. The expected frequencies for each cell were calculated under the null hypothesis of no association between gender and complication occurrence, using the formula: Expected Frequency = (Row Total × Column Total) / Grand Total. The chi-square contributions were computed for each cell using the formula: $\chi^2 = \Sigma((O_i - E_i)^2 / E_i)$, where O_i represents the observed frequency and E_i represents the expected frequency. These contributions were then summed to obtain the overall chi-square value for each complication. The chi-square values were compared against critical values from the chi-square distribution table, and p-values were calculated to determine statistical significance, with p-values less than 0.05 indicating a significant association. All analyses were conducted using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Demographics and Study Cohort

In our retrospective study of 96 patients with tuberculous meningitis (TBM), we analyzed the complications observed and their correlation with age and gender. We also calculated the outcome by complications leading to death. The study was conducted at Lady Reading Hospital, Peshawar, covering 9 years. The demographic analysis revealed that the patient cohort comprised 36 males and 60 females, with a mean age of 21.6 years (range 8 months to 70 years) (Table 1).

Table 1: Demographic variables in TBM patients.

Variables	Quantity
Age range; mean	8 months – 70 years; 21.6 years
Total Cases	96
Adults	61
Children	35
Males	36
Females	60

Complications In TBM Patients

Complications occurred in a significant portion of the cohort, with the most common being tuberculoma (57.3%), followed by hydrocephalus (46.9%), infarct (28.1%), and cerebritis (4.2%) (Table 2). Table 3 reflects the gender-wise frequency and percentage of complications while the bar graph highlights the percentage of patients affected by different complications, allowing a comparison between genders (Figure 1).

Table 2: Frequency and percentage of complications.

Variable	Quantity, % (n=96)
Hydrocephalus	45, 46.9
Tuberculoma	55, 57.3
Infarct	27, 28.1
Cerebritis	4, 4.2
No Complication	8, 8.3

Table 3: Gender-wise frequency and percentage of complications.

Variable	Quantity,% in Males (n=36)	Quantity, % in Females (n=60)
Hydrocephalus	20, 55.56%	23, 38.3%
Tuberculoma	19, 52.78%	34, 56.7%
Infarct	10, 27.78%	17, 28.3%
Cerebritis	3, 8.33%	1, 1.7%
No Complication	1, 2.8%	7, 11.7%

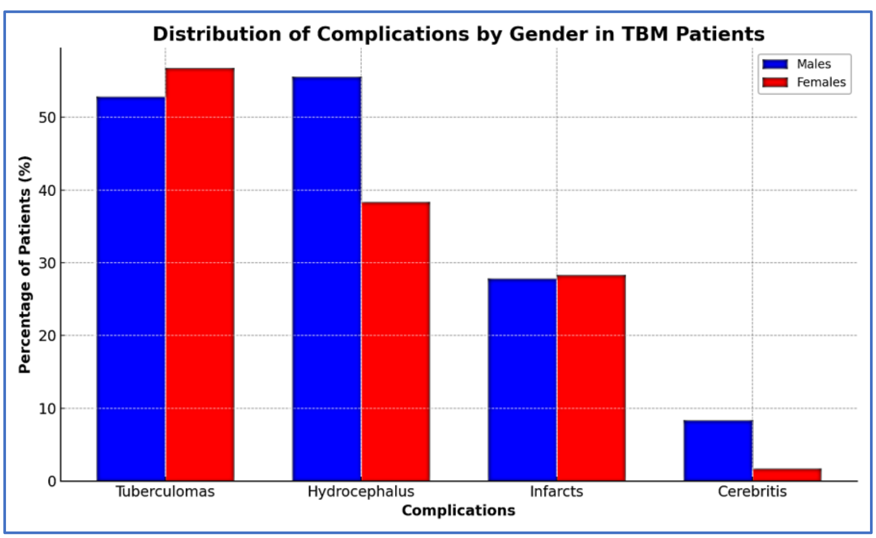

Figure 1: Distribution of Complications by Gender in TBM Patients.

Distribution of Complications Leading to Deaths

The distribution of complications leading to deaths showed that 11 out of 96 patients succumbed to the disease (Table 4). Among the fatalities, tuberculoma and combinations of tuberculoma with other conditions were the leading causes, contributing to 45.45% of the deaths. Hydrocephalus and combinations of hydrocephalus with infarct contributed to 27.27% of the deaths.

Infarct alone and in combination with other conditions accounted for 45.45% of the deaths. Detailed percentages for each complication category were calculated based on the total number of deaths (Table 5) and total cases studied (Table 6).

Table 4: Distribution of Complications Leading to Deaths by Age and Gender.

Complication	Adults (Male)	Adult (Female)	Children (Male)	Children (Female)	Total Deaths
Hydrocephalus		1	1		2
Tuberculoma		2		1	3
Infarct		1			1
Cerebritis					
Tuberculoma and Cerebritis	1				1
Tuberculoma and Infract		2			2
Infarct and Cerebritis		1			1
Hydrocephalus and Infarct		1			1
Total by Age/Gender	1	8	1	1	11

Table 5: Percentages of complications leading to death are calculated based on the total deaths.

Complications	Adults (Male)	Adult (Female)	Children (Male)	Children (Female)	Percentage (of 11)
Hydrocephalus		9.09%	9.09%		18.18%
Tuberculoma		18.18%		9.09%	27.27%
Infarct		9.09%			9.09%
Cerebritis					0%
Tuberculoma & Cerebritis	9.09%				9.09%
Tuberculoma and Infarct		18.18%			18.18%
Infarct and Cerebritis		9.09%			9.09%
Hydrocephalus & Infarct		9.09%			9.09%
Total by Age/Gender	9.09%	72.72%	9.09%	9.09%	100%

Table 6: Percentages of complications leading to death were calculated based on the total cases studied.

Complications	Adults (Male)	Adult (Female)	Children (Male)	Children (Female)	Percentage (of 96)
Hydrocephalus		1.04%	1.04%		2.08%
Tuberculoma		2.08%		1.04%	3.13%
Infarct		1.04%			1.04%
Cerebritis					0%
Tuberculoma and Cerebritis	1.04%				1.04%
Tuberculoma and Infarct		2.08%			2.08%
Infarct and Cerebritis		1.04%			1.04%
Hydrocephalus and Infarct		1.04%			1.04%
Total by Age/Gender	1.04%	8.33%	1.04%	1.04%	11.46%

Statistical Analysis of Complications by Gender

The Chi-Square Test for Independence was conducted to examine the association between gender and the occurrence of specific complications in patients with TBM. For each complication (Hydrocephalus, Tuberculoma, Infarct, and Cerebritis), the observed frequencies for males and females (as shown in Table 7) were compared to the expected frequencies calculated under the null hypothesis (no association between gender and complications). The individual Chi-Square contributions and corresponding p-values are provided for each complication (Table 8). The results suggest that none of the complications showed a statistically significant association with gender, as all p-values are above the standard significance threshold (e.g., 0.05).

Additionally, the percentage distribution of complications leading to deaths indicated that tuberculoma and hydrocephalus were the primary contributors, with notable differences in gender distribution, although these differences were not statistically significant based on the Chi-Square test results.

Table 7: Contingency Table for TBM Complications by Gender.

Complication	Male	Female	Total
Hydrocephalus	20	23	43
Tuberculoma	19	34	53
Infarct	10	17	27
Cerebritis	3	1	4
No Complication	1	7	8
Total	53	82	135

Table 8: Chi-square test for independence between gender and complications in TBM patients.

Complication	Observed Frequency (Male, Female)	Expected Frequency (Male, Female)	Chi-Square Contribution	p-value
Hydrocephalus	20, 23	17.61, 25.39	0.551	0.458
Tuberculoma	19, 34	21.7, 31.3	0.569	0.451
Infarct	10, 17	11.06, 15.94	0.171	0.679
Cerebritis	3, 1	1.64, 2.36	1.919	0.166

DISCUSSION

Our retrospective study of 96 patients with tuberculous meningitis (TBM) aimed to determine the frequency and types of complications, including hydrocephalus, infarcts, tuberculomas, and cerebritis, in adult and pediatric patients and between male and female groups. We utilized MRI and CT imaging techniques to find complications. The correlation between complications, demographic variables, and outcomes was elucidated. The findings underscore the severe impact of TBM complications and highlight significant age and gender differences as well as their outcomes.

The demographic analysis revealed that females had a higher percentage (62.5%), with a mean age of 21.6 years (range 8 months to 70 years). However, 57.9% were males in a meta-analysis on TBM patients comprising 6 prospective cohort studies and 26 retrospective cohort studies.[23] This discrepancy may be attributed to the tendency of females to neglect their health. According to study women in Pakistan often face socio-cultural barriers that limit their access to healthcare. These barriers include limited mobility, economic dependency, and a lack of awareness about health issues, leading to underreporting and underdiagnosis of TBM among women.[24] Similar trends were observed in countries with comparable socio-economic conditions.[25] This disparity in health-seeking behavior can result in a higher proportion of females being diagnosed with advanced stages of illnesses when they eventually seek medical care. It is essential to consider these socio-cultural factors when interpreting the demographic characteristics of our cohort and designing public health interventions aimed at improving health outcomes.

Complications were prevalent, with the most common being tuberculoma (57.3%), followed by hydrocephalus (46.9%), infarct (28.1%), and cerebritis (4.2%) (Table 2). The high incidence of tuberculomas aligns with other studies, reinforcing the need for vigilance in monitoring these conditions in TBM patients.[26] Similar trends of complications are found in another study having tuberculoma and hydrocephalus in the first and second numbers.[27]

Hydrocephalus was observed in 46.9% of the TBM patients in our study. Notably, a higher percentage of males (55.56%) were affected by hydrocephalus compared to females (38.3%). This trend is consistent with findings from other studies, which have also reported a higher prevalence of hydrocephalus among male TBM patients.[28]

Tuberculomas had a slightly higher prevalence in females (56.7%) compared to males (52.78%). The slight gender difference might be attributed to females being more likely to present with advanced disease due to delays in seeking medical care, which can result in a higher burden of complications like tuberculomas.

Cerebral infarcts were identified in 28.1% of the patients, with a similar prevalence in both males (27.78%) and females (28.3%). This consistency suggests that the risk of developing infarcts in TBM patients does not significantly differ between genders. Similar results are observed in previous studies.[27] While cerebritis was the least common complication, occurring in 4.2% of the cohort. Interestingly, it was more prevalent in males (8.33%) compared to females (1.7%).

The mortality rate in this cohort was 11.5%, with 11 out of 96 patients succumbing to the disease (Table 4). Notably, tuberculomas, including combinations with other conditions, were the leading cause of death, contributing to 45.45% of the fatalities. Hydrocephalus, including combinations with infarcts, accounted for 27.27% of the deaths. Infarct alone and in combination with other conditions was also significant, contributing to 45.45% of the deaths. These findings suggest that multiple overlapping complications often result in fatal outcomes. Other studies revealed similar or higher mortality rates one study from Texas found that TBM had mortality at diagnosis (8.9%), during treatment (14.1%), and overall (22.9%). Another study shows that the pooled estimate of case fatality rate among confirmed TBM cases was 20.42%.[29] One systemic review reported a 25% mortality rate.[30] A study of TBM on a cohort from the UK revealed a 16% mortality rate. However, the higher mortality rate was due to additional HIV co-infection. On the other hand, in Pakistan, this co-infection is minimal.

In summary, our study highlights the severe impact of TBM complications, particularly tuberculomas, hydrocephalus, and infarcts, on patient outcomes. The significant gender differences observed in mortality rates emphasize the need for targeted interventions. Early detection and comprehensive management of complications are crucial for improving the prognosis of TBM patients. These findings provide valuable insights into the frequency and types of complications in TBM, emphasizing the need for tailored treatment strategies based on age and gender-specific patterns.

CONCLUSIONS

This study underscores the severe impact of TBM complications, particularly tuberculomas, hydrocephalus, and infarcts, on patient outcomes. The significant gender differences observed in mortality rates highlight the need for targeted interventions. Early detection and comprehensive management of complications are crucial in improving the prognosis for TBM patients. These findings provide valuable insights into the frequency and types of complications in TBM, emphasizing the need for tailored treatment strategies based on age and gender-specific patterns.

LIMITATIONS

This study has some limitations, including its retrospective design, potential observation or selection bias due to data collection from a tertiary care hospital, the lack of a control group, and the use of descriptive statistics. The number of confirmed TBM cases was lower compared to some previous studies. Clinical and laboratory details were not included for the patients, which may limit the generalizability of our findings to other populations. Additionally, follow-up prognosis data were not available for the patients. Future prospective studies could be conducted in all TBM patients to gain insights into prognosis and complications, which would be extremely valuable in understanding the pathophysiology and outcomes of TBM.

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Additional Information

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Compliance with ethical standards
The procedures were performed in compliance with the ethical standards.
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AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Nadeemullah	1. Study design and methodology.
2.	Shamsullah Burki	2. Paper writing.
3.	Mohsin Khan	3. Data collection and calculations.
4.	Muhammad Sajid	4. Analysis of data and interpretation of results.
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