DOI: https://doi.org/10.54393/pjhs.v6i1.2694

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Mortality Associated with Tuberculosis Meningitis in HIV Infected Patients and Non-HIV Infected Patients

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ARTICLE INFO

Keywords:
Tuberculosis Meningitis, Human Immunodeficiency Virus, Mortality, Infarction

How to Cite:
Haji, S., Afzal, M., Akram, W., Ahmed, A., Memon, B., & Kumari, M. (2025). Mortality Associated with Tuberculosis Meningitis in HIV Infected Patients and Non-HIV Infected Patients: Tuberculosis Meningitis in Infected and Non-HIV Infected Patients. Pakistan Journal of Health Sciences, 6(1), 174-178. https://doi.org/10.54393/pjhs.v6i1.2694

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Received date: 4th December, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

Human Immunodeficiency Virus (HIV) infection significantly worsens Tuberculosis meningitis (TBM) outcomes, leading higher mortality rate in HIV-positive patients compared to HIV-negative individuals. **Objectives:** To find out the frequency of HIV Infected Patients with TBM and their outcome as mortality and to compare their mortality of TBM without HIV infection. **Methods:** This cross-sectional-observational study was conducted at Jinnah Postgraduate Medical Center Karachi, from September 2020 to October 2024. All patients diagnosed with TBM on clinical findings and Cerebrospinal Fluid analysis as TBM were admitted an HIV test was carried out and a CD4 cell count was done in HIV-positive patients. Treatment with Anti-Tuberculosis Therapy and Antiretroviral Therapy was done, the outcome as mortality was recorded up to 1 year and results were analyzed by SPSS version 26.0. **Results:** A total of 260 patients were enrolled who presented with TBM. The mean age was 39 ± 12.7 years. 20/260 (7.69%) were HIV positive and 240/260 (92.3%) were HIV negative TBM patients. 130/240 (54.16%) were male and 110/240 (45.93%) were female in HIV-negative and HIV-positive TBM 12/20 (60%) were male and 8/20 (40%) patients were female. The average age in HIV-positive patients was 32.5 ± 5.5 and 38.5 ± 6 in HIV-negative patients. 13/20 (65%) HIV-positive patients expired and 55/240 (22.9%) of HIV-negative patients expired. **Conclusions:** It was concluded that HIV Infected patients in our setup were increasing and had a high mortality rate as compared to HIV-negative patients of TBM and TBM patients presented in stage 3 had high mortality in both HIV-positive and HIV-negative patients.

INTRODUCTION

Tuberculous meningitis (TBM) is a fatal disease that causes significant disability and high mortality rates, particularly in patients presenting in Stage 3, where complications such as hyponatremia and hydrocephalus are common causes of death [1]. According to Luo *et al.*, TBM is classified into three stages based on clinical presentation. Stage 1 includes alert patients with symptoms such as vomiting but no focal neurological deficits and a Glasgow Coma Scale (GCS) score of 15/15. Stage 2 involves patients with a GCS score of 11–14 and focal neurological deficits, while Stage 3 includes unconscious patients or those with a GCS score of ≤10 [2]. The typical distribution of TBM presentation is 30% in Stage 1, 60% in Stage 2, and 10% in Stage 3 [3]. Mortality in TBM is particularly high in Stage 3 patients. In addition, TBM with HIV co-infection presents unique challenges, including differences in clinical presentation, treatment responses, and outcomes. The mean age of HIV-positive TBM patients has been reported as 36.7 years, compared to 23.35 years for HIV-negative TBM patients. Furthermore, 90% of HIV-infected TBM patients present in Stage 2, compared to 72.5% of non-HIV-infected TBM patients [4]. Globally, TBM prevalence in India accounts for 26% of cases

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among HIV-negative patients and 34% among HIV-positive patients [4]. HIV-infected TB patients are five times more likely to develop central nervous system (CNS) involvement like seizures and epilepsy, often leading to severe morbidity or death if untreated [5, 6]. To reduce mortality, the National AIDS Control Organization and WHO recommend initiating antiretroviral therapy (ART) in HIV-positive patients regardless of CD4 count [7]. However, multi-drug resistant TBM increases mortality risk, though initiating ART two months after TBM treatment reduces the likelihood of drug-related adverse effects, such as rash, headache, hepatitis, and nephritis [8]. Common findings in TBM include cerebrospinal fluid (CSF) abnormalities such as low glucose, high protein, and increased lymphocytes. Imaging studies, such as CT or MRI scans, often reveal hydrocephalus or tuberculosis in HIV-positive TBM patients. The rationale for this study stems from the observed high mortality in TBM patients, which is further compounded by HIV co-infection. While HIV prevalence is generally perceived to be high in Pakistan [9], its association with a significant number of TBM patients is becoming increasingly evident. This highlights an information gap regarding the frequency and outcomes of HIV co-infection in TBM within the local context.

This study aimed to address this gap by determining the exact prevalence of HIV among TBM patients, calculating mortality rates for both HIV-infected and non-HIV-infected TBM patients, and comparing these outcomes. By filling this knowledge gap, the findings will provide valuable insights to clinicians and the medical community about the impact of HIV co-infection on TBM outcomes along with that it will help educate healthcare professionals on the importance of early referral and timely initiation of ART and anti-tuberculosis therapy (ATT) to prevent mortality.

METHODS

This cross-sectional study was conducted in the Neurology Ward at Jinnah Postgraduate Medical Center (JPMC), Karachi from 1st September 2020 to 1st October 2024 after obtaining permission from the ethical committee JPMC vide letter No.F.2-80/2020-GENL/213/JMPC. All patients aged 18 years and older, with confirmed TBM through GeneXpert, CSF analysis, or imaging studies indicating meningeal enhancement, hydrocephalus, or tuberculosis, were included via non-probability consecutive sampling method. Patients with co-existing neurological conditions unrelated to TBM individuals who had received partial or incomplete treatment for TBM before admission, and cases with concurrent infections or illnesses (e.g., bacterial meningitis or viral encephalitis) were excluded from the study. Informed written consent was taken from each participant for inclusion in the research process. Patients classified as Stage 1 TBM presented with symptoms such as fever, headache, vomiting, and neck rigidity and were subsequently admitted. Those categorized as Stage 2 TBM exhibited altered sensorium accompanied by focal neurological deficits. Meanwhile, patients presenting in an unconscious state were identified as Stage 3 TBM. Consent was taken for lumber puncture and CSF was sent for analysis as part of standard management protocol. High protein, low glucose and increased lymphocyte count were noted to diagnose TBM. GeneXpert analysis of cerebrospinal fluid (CSF) was conducted, and CSF cultures were performed. Serum HIV serology was assessed for all patients, alongside a complete blood count, serum glucose, creatinine, urea, and liver function tests (LFTs). A CT scan of the brain (without contrast) was conducted to identify tuberculosis and hydrocephalus for confirmation of tuberculous meningitis (TBM). Additionally, brain MRI was utilized to assess meningeal enhancement indicative of TBM. Patients were treated with anti-tuberculosis therapy (ATT), consisting of rifampicin, isoniazid (INH), ethambutol, and pyrazinamide for an initial two months, followed by rifampicin and INH for the subsequent ten months. Outcomes were documented in terms of survival or mortality over one year. Cases of TBM with concurrent HIV infection were recorded, and antiretroviral therapy (ART) was initiated. Patients were classified into TBM stages 1, 2, and 3 based on their clinical presentation, and mortality outcomes were analyzed separately for each stage. A sample size of 260 achieves a statistical power of 99.476% to detect a difference (P1–P0P_1-P_0) of -0.1100 using a two-sided exact test with a significance level (α\alpha) of 0.050. These calculations are based on the assumption that the population proportion under the null hypothesis (P0P_0) is 0.264 [10]. The results were analyzed using SPSS version 26.0. Mortality rates were calculated for HIV-infected TBM patients at each stage of the disease and separately for non-HIV-infected TBM patients. The p-values were calculated using the Chi-square test to ensure statistical validity.

RESULTS

A total of 260 patients with TBM were included in the study. The average age was 38.5 ± 6.7 years in HIV-negative patients and 32.5 ± 5. years 5 in HIV-positive patients. Among the total, 240 out of 260 (92.30%) were HIV-negative, while 20 out of 260 (7.69%) were HIV-positive. In the HIV-negative group, 130 out of 240 (54.16%) were male, and 110 out of 240 (45.83%) were female (Figure 1).

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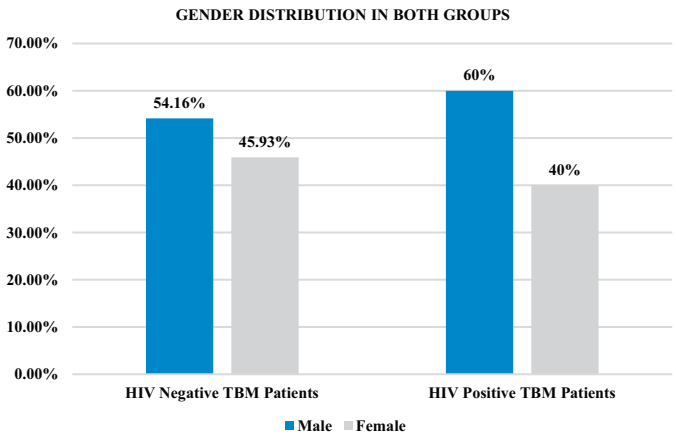

Figure 1 : Distribution of Gender According to HIV Status of TBM Patients

Mortality among tuberculosis meningitis (TBM) patients showed significant variation across stages and HIV status. In Stage 1(n=145, 55.8%), HIV-positive patients had a higher mortality rate (20%) compared to HIV-negative patients (3.57%), with a significant difference (p=0.012). In Stage 2 (N=59, 22.7%), mortality was 50% in HIV-positive patients versus 18.18% in HIV-negative patients (p=0.020). Stage 3 (N=56, 21.5%) recorded the highest mortality rates, with HIV-positive patients at 90.9% and HIV-negative patients at 88.88% (p=0.024). Overall, HIV-positive patients had significantly higher mortality (65%) compared to HIV-negative patients (22.9%), with an overall p=0.031. These findings underscore the increased risk of mortality in HIV-positive TBM patients, particularly in advanced stages. (Table 1).

Table 1: Mortality Among TBM Patients by Staging and HIV Status

TBM Stage	HIV-Positive Patients	HIV-Negative Patients	p-value
Stage 1 n=145 (55.8%)	1/5 (20%)	5/140 (3.57%)	0.012
Stage 2 n=59 (22.7%)	2/4 (50%)	10/55 (18.18%)	0.020
Stage 3 n=56 (21.5%)	10/11 (90.9%)	40/45 (88.88%)	0.024
Total	13/20 (65%)	55/240 (22.9%)	0.031

DISCUSSION

Tuberculosis meningitis (TBM) is a lethal disease resulting in death and disability. TBM with HIV-positive patients is increasing. Mortality in HIV-negative patients was 40% and in HIV-positive patients of TBM had a mortality of 70% [11]. In this study mortality in HIV-positive patients was 65% and HIV negative patients was 22.91%. A study conducted in South Africa showed 15-90% of patients had TBM with HIV positive and had more than twice the mortality than HIV-negative TBM patients [12]. So significant high mortality was found in HIV-positive TBM patients. The same findings were presented in this study. The mean age was 36.75 years in HIV-positive TBM patients and 29.35 in HIV-negative patients. Most patients presented in stage 2 and stage 3. Mortality was 87.5% in HIV-positive patients and 25% in HIV-negative patients in a study concluded in Mumbai, India [13]. In this study age was 38 ±5 years in negative HIV TBM patients and 32±5 years in HIV positive patients. In this study 7.69%were HIV positive patients of TBM. The most common symptom is altered sensorium so they are diagnosed usually in stage 2 and stage 3. Stage 2 and stage 3 had high mortality as compared to stage 1 so mortality must be decreased if TBM is diagnosed in stage 1. The involvement of HIV-positive patients by TBM is 15-21 times more than HIV HIV-negative patients globally [14]. and 37.7 million people are HIV-positive [15]. so TBM in these patients causes high mortality. ART can lead to severe immune syndrome so should start after 2 months of treatment [16]. ART can be reduced but still high mortality in HIV positive patients even after ART treatment. The same result was found in this study. TBM in HIV-positive patients had very low sodium which causes death [17]. In this study, hyponatremia was positive in all patients of TBM who expired. So preventing HIV infection can prevent TBM and reduce mortality. So in Pakistan HIV HIV-positive patients can be reduced by public awareness programs because TBM is 21 times more in HIV-positive patients. Patients of TBM with HIV-positive infection in a study in Europe revealed high mortality and ART-receiving patients also had high mortality [18]. HIV-infected TBM patients had high morbidity as well. 50-70% of patients developed disability and prognosis related to the stage of TBM and patients of GCS less than 10 had high mortality. Increased resistance to drugs also is a risk factor for complications in patients infected with TB. Then HIV infection can activate the silent TBM so HIV infection is a predisposing factor for the activation of TBM [19]. In stage I, TBM brain damage is less as compared to the other two stages. There is no infarction of the brain in stage I so if the diagnosis is made earlier then it could lead to the prevention of morbidity and mortality in patients. In stage II morbidity like cranial nerve palsy is less common so early diagnosis would be essential to prevent further complications of TBM leading to death of the patient. So health education of patients for the prevention of HIV spread and TB spread is important to prevent mortality. Early diagnosis of TBM in stage 1 is important to prevent morbidity and mortality. CSF analysis, GeneXpert and some modern tests like Fuji film can detect TBM in 80% of patients [20]. Prevention of HIV infection is mandatory. Some patients of TBM may have lost to follow-up and their outcome was not recorded so they can slightly affect the result. The sample size of HIV-infected Patients was low and further study was needed to exactly know the mortality in HIV-infected patients. Moreover, the non-probability consecutive sampling may introduce selection bias and a single-center study limits the generalizability of the findings to the broader population.

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CONCLUSIONS

It was concluded that HIV-infected patients in our setup experience higher mortality rates compared to HIV-negative TBM patients. Furthermore, TBM patients presenting in Stage 3 have a significantly higher mortality rate in both HIV-positive and HIV-negative groups, indicating that TBM is indeed linked to higher mortality among HIV-infected patients.

Authors Contribution

Conceptualization: SH
Methodology: SH, MA, WA, AA, MK
Formal analysis: BM
Writing review and editing: MA, WA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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