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Clinical and Laboratory Characteristics and Mortality Factors in HIV- Infected Patients with Tuberculosis Meningitis at a Tertiary Care Hospital in Karachi

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A B S T R A C T

Objective: To assess the clinical features, laboratory and cerebrospinal fluid (CSF) characteristics, and to determine the factors associated with mortality among HIV-infected patients diagnosed with tuberculosis meningitis (TBM).

Methodology**:** A retrospective observational study was conducted at the Indus Hospital, Karachi, including all HIV-positive adult patients (aged 14–75 years) diagnosed with TBM on clinical, radiological, or microbiological grounds between January 2008 and December 2024. Demographic, clinical, laboratory, and treatment related data were retrieved from hospital records, and patients were followed for in-hospital outcomes. The associations between clinical/laboratory variables and mortality were analyzed using chi-square exact tests, with $p \leq 0.05$ taken as statistically significant.

Results: The majority of males around 70%, with an overall median age of 32 years, mostly presented with headache (85%), fever (80%), altered consciousness (65%), and neck stiffness (60%), with seizures reported in around 25% of patients. Most of the cases (75%) were with advanced HIV disease. GeneXpert positivity was in 10.4% and AFB culture positivity in 12.5% of patients. Concurrent pulmonary TB was identified in 45% and extra-pulmonary TB in around 20% of cases. Around 40% of patients had BMRC Grade III and the overall mortality rate was 30%. Overall mortality was significantly higher in patients with a CD4 count below 100 cells/µL, BMRC grade III, delayed ATT initiation beyond 2 weeks, lack of corticosteroid uses and concurrent pulmonary or extra-pulmonary TB ($p>0.05$), along with TBM plus extra-pulmonary TB, as key predictors of poor outcomes.

Conclusion: HIV-infected TBM patients typically presented as young males with advanced immunosuppression, headache, fever, and altered consciousness, with low CD4 count, high BMRC grade, delayed treatment, opportunistic infection and concurrent TB emerging as the principal mortality predictors and corticosteroid use associated with better outcomes, collectively highlighting the need for early diagnosis and strengthened TB-HIV collaborative care.

Key words: TBM, HIV co-infection, CD4 count, GeneXpert, corticosteroids, Predictors, Mortality

Introduction

There are various form of Tuberculosis (TB) and among all Tuberculosis Meningitis (TBM) is the most severe form of TB, with a notably high mortality rate, especially among individuals with Human Immunodeficiency Virus (HIV).[1,2] Approximately these patients are five times more likely to develop central nervous system (CNS) involvement, such as seizures and epilepsy, which can result in severe morbidity or death if left untreated. As per 2019 who data tuberculosis cause 30% of death in HIV patients.[3] As per 2020 WHO data HIV patients are 15-21 times more prone to develop Tuberculosis and even on Anti-Retroviral therapy there are still 3 times more chances of death.[4] Particularly, although only about 8% of all tuberculosis patients worldwide are HIV-positive, this subgroup accounts for a disproportionate 23% of TBM cases and an estimated 35% of all adult TBM deaths, underscoring HIV co-infection as one of the strongest known risk factors for both the morbidity and Mortality.[5] According to a national study from Karachi conducted to compare the mortality of tuberculosis meningitis in HIV and non HIV patients and found 65% mortality of tuberculosis meningitis patients in HIV and 22.9% in non HIV patients.[6]

HIV attacks the immune system and cause a syndrome known as Acquired Immune Deficiency Syndrome (AIDS). In which the human body is susceptible all other opportunist infection which usually does not cause any harm to our body.[7] In HIV-positive patients, TB Meningitis-related mortality can reach up to 50% or above.[8] Some of the reasons of increased mortality of HIV patients with TBM includes, high disease burden, low CD4 counts, MDR TB, poor drug penetration and paradoxical IRIS.[9] Even in this modern era of technology, it is still very difficult to diagnose TBM prior to any complication and usually before starting empiric treatment it requires the need for a combination of clinical evaluation, radiological imaging, and cerebrospinal fluid (CSF) for diagnosis. The Gene-Xpert, a major advancement in tuberculosis diagnostics, plays a crucial role but has limited sensitivity in cerebral spinal fluid (CSF),

making it unreliable for ruling out TBM just on the basis of gene-xpert.[10] There are many challenges in managing TBM patients including, adherence to treatment, low efficacy of drugs due to poor penetration in CSF, multi-drug resistant TB and also the data for number of patients having TBM and HIV as co-infection is scarce.[9] There are only few studies that evaluated the outcomes of TBM patients in HIV and negligible in our country. So given high mortality of TBM in HIV and with less number of studies specifically at local level, it is important to study this topic and look at the outcomes of study like mortality in our setting, any disability post treatment, delayed response of treatment to guide further for optimal treatments and future management plans.[9]

This study was aimed to analyze the clinical presentation, CSF findings, treatment outcomes, and risk factors contributing to mortality, with the goal of identifying areas for improving TBM management in HIV-infected patients. This study explores the potential causes of mortality and morbidity in our setting, with the aim of identifying preventable factors that, if addressed, could help save lives and reduce the adverse outcomes among patients.

Methodology

This retrospective observational study was conducted on patients treated from, 2008, to 2024, at the Indus Hospital, Karachi, Pakistan, a tertiary care center serving to large a population area. The study was conducted following the approval by the IRB and CPSP. All record of adult patients aged >14 years; both male and female, HIV-positive patients, diagnosed with TBM on the basis of clinical findings plus radiological or microbiological evidence (GeneXpert positive or AFB culture positive), and who had received treatment at The Indus Hospital during the study period, were incorporated, while the recorded of patients aged <14 years or >75 years, and patients who were transferred out, was not studied. Data were collected, following IRB approval, from the medical records of patients using a structured questionnaire. The following variables were documented: demographic information (age, sex, socioeconomic status); clinical history, including symptoms at presentation (headache, altered mentation, focal deficit, seizures) and signs at presentation (fever, meningeal irritation, visceromegaly, lymphadenopathy); disease severity as graded by the British Medical Research Council (BMRC) staging system (Grade I: non-specific symptoms and signs, no clouding of consciousness, and no neurologic deficits; Grade II: lethargy or behavioral changes, meningeal irritation, or minor neurologic deficits such as cranial nerve palsies; Grade III: stupor or coma, abnormal movements, seizures, or severe neurologic deficits such as paresis); previous history of TB; HIV staging as per WHO criteria; smoking and alcohol use; and the presence of anemia and comorbidities such as chronic kidney disease (CKD), malignancy, chronic liver disease, and diabetes mellitus (DM). Laboratory data recorded included complete blood count (CBC), estimated CD4 count, sputum AFB smear, GeneXpert (GXP), GXP-XDR, AFB culture and sensitivity, CSF analysis (differential count, AFB smear, GXP, GXP-XDR, AFB culture), HIV PCR, CD4 count, HbA1c, creatinine, liver function tests (LFTs), and CT/MRI brain imaging. Details of the treatment regimen, including the type of drugs used, duration of treatment, and adherence to treatment, were also recorded.

TBM was diagnosed using a standardized scoring system comprising clinical criteria (maximum score 6), CSF criteria (maximum score 4), cerebral imaging criteria (maximum score 6), and evidence of tuberculosis elsewhere (maximum score 4). Based on the total score, cases were classified as possible TBM (score 6–9 without brain imaging, or 6–11 with brain imaging), probable TBM (score >9 without brain imaging, or >11 with brain imaging), or definite TBM (acid-fast bacilli seen in CSF, or *M. tuberculosis* cultured or detected by commercial nucleic acid amplification test in CSF). All the data were entered and analyzed by SPSS version 20.

Results

Overall 48 patients were enrolled, with mostly were aged between 30–45 years (45.8%), majority of males (70.8%), from urban areas (64.6%), and of low socioeconomic status (75.0%). Most frequent common presenting symptoms were headache (85.4%), fever (79.2%), altered consciousness (64.6%), and neck stiffness (60.4%), while diabetes mellitus (22.9%) was the leading comorbidity. According to HIV profile, the majority was in WHO clinical stage IV (62.5%), had a CD4 count below 100 cells/μL (75.0%), and was not on ART at the time of admission (70.8%), as presented in table I.

At the presentation, majority of the cases had moderate to severe disease, with BMRC grade II (39.6%) and grade III (39.6%), whereas only 20.8% presented in grade I. The analysis of CSF most commonly showed lymphocytic pleocytosis (83.3%), raised protein (70.8%), and low glucose in (64.6%), with a median cell count around 120 cells/μL (IQR: 60–220). According to the microbiological status, CSF GeneXpert was positive in 5(10.4%) of cases (54.2%), and definite or probable TBM together noted for most diagnoses (85.4%), with only 14.6% classified as possible TBM, as shown in table II.

Around half of the cases had co-existing pulmonary TB (45.8%), while a third had TBM alone with no

concurrent TB involvement (33.3%). Majority of the patients were started on ATT within 2 weeks (64.6%), corticosteroids received by (58.3%), and (70.8%) were initiated on ART during admission, with the standard 4-drug regimen (HRZE) used in the most of he patients (89.6%). According to the outcomes, most patients achieved treatment success (60.4%) with failure arte around 10.4%, while mortality was recorded in 29.2% of the cohort, as presented in table III.

Table 1: Demographic, clinical and HIV characteristics (n = 48)			
VARIABLES		N	%
Demographic and clinical characteristics			
Age (years)	<30	18	37.5%
	30–45	22	45.8%
	>45	08	16.7%
Gender	Male	34	70.8%
	Female	14	29.2%
Residence	Urban	31	64.6%
	Rural	17	35.4%
Socioeconomic status	Low	36	75.0%
	Middle	12	25.0%
Symptoms	Headache	41	85.4%
	Fever	38	79.2%
	Altered Consciousness	31	64.6%
	Neck Stiffness / Meningism	29	60.4%
	Seizures	12	25.0%
	Focal Neurological Deficit	9	18.8%
	Vomiting	22	45.8%
	Weight Loss / Night Sweats	34	70.8%
Comorbidities	DM	11	22.9%
	CLD	08	16.7%
	CKD	05	10.4%
	Malignancy	03	06.3%
HIV Profile			
HIV Stage (WHO)	Stage III	18	37.5%
	Stage IV	30	62.5%
CD4 Count (cells/µL)	<100	36	75.0%
	100–200	09	18.8%
	>200	03	06.3%
On ART at admission	Yes	14	29.2%
	No	34	70.8%

According to the opportunistic infections evaluation, esophageal candidiasis was the most common, present among41.7% of patients, followed by Pneumocystis jiroveci pneumonia (16.7%), cryptococcal infection/meningitis (12.5%), and cytomegalovirus (8.3%), while cryptosporidiosis and Tinea corporis were least common, as presented in figure 1.

Based on post stratification analysis, the mortality was significantly higher in patients with a CD4 count below 100 cells/µL (36.1%, p = 0.001), BMRC grade III (57.9%, p = 0.003), delayed ATT initiation beyond 2 weeks (52.9%, p = 0.012), lack of corticosteroid uses (50.0%, p = 0.028), and concurrent pulmonary or extra-pulmonary TB (37.5%, p = 0.041), indicating all as key predictors of poor outcomes. Moreover mortality rate was lowest in cases with TBM alone (12.5%) and highest among those with TBM plus extra-pulmonary TB (40.0%), while the difference was statistically insignificant (p = 0.195). Table IV.

Table II: BMRC Grading, CSF and Microbiological Findings. (n = 48)		
VARIABLES	N	%
BMRC Grading at Presentation		
Grade I (Alert, no deficit)	10	20.8%
Grade II (Lethargy / cranial nerve palsy)	19	39.6%
Grade III (Stupor / coma / severe deficit)	19	39.6%
CSF Findings		
Lymphocytic Pleocytosis	40	83.3%
Elevated Protein (>1 g/L)	34	70.8%
Low Glucose (<2.2 mmol/L)	31	64.6%
Clear Appearance	38	79.2%
Median Cell Count (cells/µL)	120 [IQR: 60–220]	
Microbiological Findings		
GeneXpert Positive (CSF)	05	10.4%
AFB Culture Positive (CSF)	06	12.5%
AFB Smear Positive (CSF)	05	10.4%
GeneXpert Positive (Sputum)	22	45.8%

Table III: Co-existing TB, treatment details, clinical Outcomes and Mortality Predictors. (n = 48)		
VARIABLES	N	%
Co-existing Tuberculosis		
Pulmonary TB (PTB)	22	45.8%
Extra-pulmonary TB (EPTB)	10	20.8%
TBM Alone (no concurrent TB)	16	33.3%
Treatment Details		
Initiated ATT within 2 weeks	31	64.6%
Delayed ATT (>2 weeks)	17	35.4%
Corticosteroid Use	28	58.3%
ART Initiated During Admission	34	70.8%
Aspirin Use	14	29.2%
Single Drug Regimen	5	10.4%
Standard 4-Drug Regimen (HRZE)	43	89.6%
Clinical Outcomes		
Treatment Success	29	60.4%
Treatment Failure	05	10.4%
Mortality	14	29.2%
Definite TBM	12	25.0%
Probable TBM	29	60.4%
Possible TBM	07	14.6%

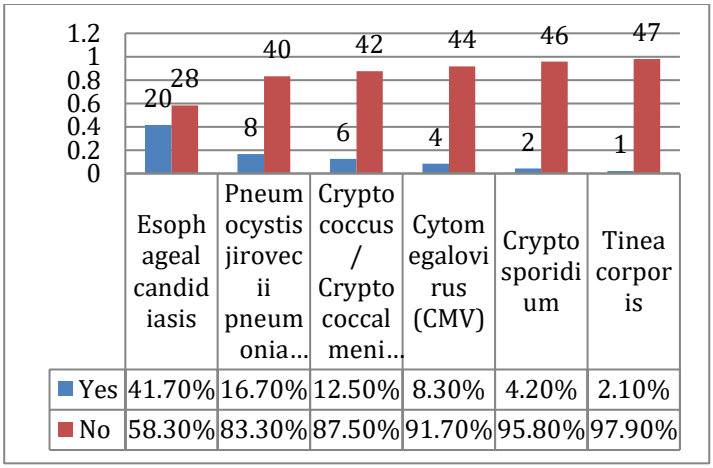

Figure 1. Frequency of opportunistic infection. (n=48)

established clinical spectrum of TBM in HIV-infected individuals, like a retrospective cohort study of 100 TBM patients Maleki Rad M et al reported that the patients were with median age of 36.5 years, majority of males 57.0% were male, with fever (64.7%), headache (63.6%), and altered consciousness (60.0%) being the most frequently reported symptoms.[15] According to Vinnard C et al, who previously noted that HIV-infected patients with TBM are more likely to exhibit altered level of consciousness.[16] Neck stiffness was present in 60.4% of our cases, while seizures occurred in 25%, which is consistent with data from India where predominant clinical features observed were generalized weakness, headache, altered sensorium, and neck stiffness.[17]

Table IV: Suspected mortality predictors. (n=48)

Variables		Mortality		Total	p-value
		Yes	No		
CD4 Count <100 cells/µL		13 (36.1%)	23 (63.9%)	36	0.001
BMRC Grade III		11 (57.9%)	8 (42.1%)	19	0.003
Delayed ATT Initiation (>2 weeks)		9 (52.9%)	8 (47.1%)	17	0.012
Absence of Corticosteroid Use		10 (50.0%)	10 (50.0%)	20	0.028
Concurrent PTB or EPTB		12 (37.5%)	20 (62.5%)	32	0.041
Opportunistic infection	Esophageal candidiasis	12 (60.0%)	8 (40.0%)	20	0.001
	PJP	6 (75.0%)	2 (25.0%)	8	0.006
	Cryptococcal meningitis	5 (83.3%)	1 (16.7%)	6	0.005
Co-existing Tuberculosis	TBM Alone	2 (12.5%)	14 (87.5%)	16	0.195
	TBM + PTB	8 (36.4%)	14 (63.6%)	22	
	TBM + EPTB	4 (40.0%)	6 (60.0%)	10	

as a retrospective cohort study by Kagimu E et al[11] from Uganda demonstrated a comparable median age of 36 years among HIV-associated TBM cases, with a near-equal gender distribution (46% female).[1] Haji S et al[6] also consistently reported that among g HIV-positive TBM patients, 12(60%) were male and 8 (40%) were female, with an overall mean age of 32.5 ± 5.5 years. An Indian study by Patel AS et al[12] also similarly documented that among most HIV-positive TBM patients, a predominantly male cohort (72.22%), most patients were aged 21–30 years (38.89%), and from rural areas (55.56%). Moreover the predominance of low socioeconomic status (75%) in our cohort correlated to findings from Kinshasa is the capital and largest city of the Congo and other high-burden countries, where poverty, overcrowding, delayed healthcare access and well-established settings are limited for TB-HIV co-infection.[13,14] Collectively, these comparisons confirm that HIV-linked to TBM predominantly affects relatively young, economically disadvantaged adults across diverse geographic regions, reinforcing the disproportionate of disease burden on populations already facing barriers to healthcare access.

In this study headache (85.4%), fever (79.2%), and altered consciousness (64.6%) were the most frequent presenting symptoms. These findings align well with the

In this study, the most patients in this study were in advanced WHO clinical stage IV with a CD4 count below 100 cells/µL, and the majority of patients were not receiving ART at admission. The pattern of profound immunosuppression at presentation mirrors findings from Uganda, where the median CD4 count among HIV-TBM cases was 74 cells/µL, and from the ACT HIV trial, where approximately over half of patients had a baseline CD4 count of 50 cells/mm³ or below.[11,18] Our findings were also related to recent systematic review and meta-analysis involving 5,210 TB-HIV co-infected patients, found CD4 counts below 200 cells/mm³ and advanced WHO clinical staging as the most consistent predictors of mortality in this population. The pattern, also related to studies from Africa, Southeast Asia, and South Asia where CD4 count underscored as a reliable and reproducible marker for the severity of disease and prognosis in HIV-associated TBM, consistent with its identification as a significant mortality predictor in this study.

In this study the near-equal distribution of grade II and grade III disease at the presentation, with comparatively few patients presenting in grade I, reflects the diagnostic delay that characterizes TBM globally. A retrospective cohort of HIV-infected Brazilian cases admitted with TBM, found with BMRC severity grade as: Grade I was observed in 40 (37%)

patients, Grade II in 43 (40%) patients, and Grade III in 25 (23%) patients.[20] The Vietnamese cohort-based prognostic modeling study also found higher MRC severity grade as one of the most consistent predictors of mortality in both HIV-infected and HIV-uninfected TBM populations, a finding related to Ugandan study, which also found MRC grade significantly linked to early mortality.[11,20] Overall consistency of this link across multiple large cohorts supports BMRC/MRC grading as a robust, low-cost, bedside tool for early stratification of risk, and reinforces the findings of present study that severe grade at presentation independently predicted mortality.

In this cohort the overall mortality rate was observed around 29.2%, which is broadly comparable to, though somewhat lower than, certain other cohorts, possibly reflecting differences in follow-up duration and the case definitions. The study from Ugandan reported a 14-day mortality around 25.9%, comparable to the short-term rate in this series, whereas cohorts with longer follow-up have demonstrated extensively higher cumulative death rate: 31.6% in a Romanian cohort followed to hospital discharge, 44.1% at 12 months in the double-blind, randomized, placebo-controlled trial HIV with MTB patients, and as higher as 51.2% at 12 months and 63.3% in-hospital in other HIV-TBM cohorts from Europe and India correspondingly.[7,18,10.20] Collectively the pattern suggesting that the mortality among HIV-infected patients with TBM continues to accrue well beyond the initial period of hospitalization, and that the true burden of death in this population may be considerably underestimated by studies, including potentially the present one, that explore only in-hospital or short-term outcomes rather than extended follow-up mortality.

Additionally, in this cohort, the lymphocytic pleocytosis, raised proteins level, and low glucose to be the dominant CSF abnormalities, consistent with the classical lymphocytic meningitic picture described across the several studies. Though, the association between CSF cellularity and mortality appears more complex compared to a simple linear association: as in a study observed that the 14-day mortality was surprisingly higher among patients with very low CSF white cell counts (<5 cells/μL) than those with intermediate counts, a pattern accredited to a blunted inflammatory response in the most immunosuppressed cases.[11] This pattern raises an important consideration for interpreting CSF findings in HIV-TBM, where a "quiet" CSF profile may reflect severe immune compromise rather than mild condition of disease, an issue that requires attention in future analyses of CSF-mortality associations in similar cohorts.

Moving forward, this study found, around half of the patients with co-existing pulmonary TB and disseminated disease was significantly associated to mortality. The findings aligns with a large European and Argentinian cohort, that found the TBM carried a substantially higher 12-month mortality (51.2%) than either extra-pulmonary TB (19.4%) or pulmonary TB alone (12.3%), emphasizing that meningeal involvement itself, specifically when combined with disease at other sites, signifies a more advanced and immunologically compromised state.[10] Consistently, a paediatric HIV-TBM hydrocephalus cohort identified extra-meningeal TB as an independent predictor of in-hospital mortality.[21] The observation are collectively supporting the disseminated tuberculosis as a marker of both greater bacillary burden and deeper immune failure and endorsing its association with poorer outcomes in this cohort.

In the present study**,** the absence of corticosteroid use was significantly associated with higher mortality rate. The findings were supported by a recent study of Wilt AL et al[22] where thay observed that the HIV infected adults with TBM treated with dexamethasone, mortality showed a strong link to CSF hypo-inflammation; while steroids may benefit those with high inflammatory activity, a more individualized approach to immunotherapy is likely required to improve the outcomes. However an ACT HIV randomized controlled trial found inconsistent findings with statistically insignificant survival benefit of adjunctive dexamethasone among HIV-positive adults with TBM (44.1% mortality with dexamethasone vs. 49.0% with placebo) at 12 months (P = 0.22).[8] Another meta-analysis by Pu J et al[23] also inconsistently observed that the corticosteroid therapy did not significantly decrease all-cause mortality and was not associated with an raised risk of serious adverse events. Observed discrepancy across the studies likely reflects confounding by indication, as the use of steroid likely appeared protective because sicker patients were less able to receive it, so this may reflect patient condition rather than a true treatment effect, a question best answered by randomized trials rather than observational kind of study.

Moreover in this study the delay in ATT initiation beyond two weeks and patients with concurrent PTB or EPTB were significantly linked to high mortality rate (37.5–40%) compared to those with TBM alone (12.5%), an outcome that is biologically plausible and consistent with the broader TBM literature emphasizing that diagnostic and treatment delays worsen neurological consequences and survival rate, the finding are consistent with observations from multiple studies.[19,24] The possible reason is that HIV-infected patients with extra pulmonary tuberculosis may have had extreme immunosuppression, which

could contribute adverse outcomes. Present study possesses numerous limitations like retrospective design introduces inherent risks of incomplete data retrieval and selection bias, relatively very limited sample size and some missing relevant clinical information or inconsistently may limits the statistical power of multivariable analyses, along with absence of a standardized neuropsychological follow-up protocol precludes assessment of long-term neurocognitive outcomes among survivors. Hence future larger, prospective, multi-center studies with longer follow-up and more comprehensive data collection are recommended to validate these findings and to more accurately identify the predictors of mortality in this population.

Conclusion

This study revealed that the, HIV-infected patients with tuberculosis meningitis typically present as young males, with headache, fever, altered consciousness, and neck stiffness, along with late presentation, advanced immunosuppression, low CD4 counts, and often untreated HIV infection, frequently alongside disseminated pulmonary or extra-pulmonary tuberculosis. CSF findings typically showed lymphocytic pleocytosis with raised protein and low glucose, consistent with the usual pattern seen in TBM. Mortality remained high, driven associating by low CD4 count, advanced clinical grade at presentation, delayed treatment initiation, lack of corticosteroid use, opportunistic infection, and disseminated disease, which are largely modifiable, earlier diagnosis, prompt treatment initiation, routine use corticosteroid, and proper integrated HIV-TB care could meaningfully reduce mortality in this high-risk population.

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