ORIGINAL ARTICLE

CD 4 count stratification and its accuracy in predicting the HIV-Tuberculosis co-infection

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ABSTRACT

Background: Co-infection of HIV and TB is a significant public health concern. The relationship between increased HIV replication and low CD4+-TLC in HIV-positive patients with treatment interruptions is well documented. Moreover, TB preventive therapy is highly effective in reducing TB incidence and mortality among HIV-positive patients. The objective of this study was to stratify in terms of different ranges and see the association of CD4+ T-lymphocyte count with different presentations of TB in HIV-positive patients.

Material and Methods: This observational cross-sectional study was conducted from October 2022 to March 2023. A total of seventy-four outdoor and indoor patients were enrolled. Patient data were collected using a structured questionnaire. The MTB gene Xpert, screening for HIV, and CD4+ T-lymphocyte count testing was performed. All the patients aged> 18 years who were found to have positive HIV rapid tests and microbiologically confirmed tuberculosis were included in the study. The CD 4 count was stratified in terms of ranges. The data was analyzed using SPSS 29. The association was established by Spearman's coefficient and odd ratios keeping the significance level <0.05.

Results: 74 patients were enrolled in the study, out of which 67 (90.5%) were males and 7 (9.5%) were females. The mean age of study participants was 38.33 ± 11.43 years (21-78 years) and the mean CD4 count was 85.7 ± 59.48. Most frequent was pulmonary TB; 43 (44.5%) followed by disseminated TB; 11 (24.3%), pleural TB; 9 (9.4%), and TB meningitis 6 (8.1%). There was no association between CD4+ T-lymphocyte count and the site of involvement of TB (p>0.05). Pulmonary TB, miliary TB, TB brain abscess, tuberculomas, and disseminated TB were found more at CD 4 count <100 as signified by the Odd Ratios (1.1, 1.3, 1.3, 1.3, 1.01 within 95% CI)). On the other hand, Pleural TB, Spinal TB, TB lymph adenitis, and TB meningitis were found at CD4 count >100 (4.5, 2.3, 1.51 respectively within 95%CI.

Conclusion: Among HIV-TB co-infected individuals, the frequency of pulmonary TB was found to be highest followed by disseminated TB and pleural TB. No association was found between CD4+ Lymphocyte count and different presentations of TB in this study. The CD4 count is a poor predictor of HIV/TB co-infection unless it is <100. Mostly tuberculosis occurred at count <100 as depicted by odd ratios.

Keywords: CD4+ T-lymphocyte count, Extrapulmonary tuberculosis, HIV-TB co-infection, Pulmonary tuberculosis

BACKGROUND

Human Immunodeficiency Virus (HIV) is a global health issue, affecting millions of people worldwide. HIV is a retrovirus that attacks the immune system and targets CD4+ T-lymphocytes (CD4+) which weakens the body's ability to fight against infections and diseases. This eventually leads to "acquired immunodeficiency syndrome" (AIDS), a condition in which the immune system is severely compromised, leaving individuals susceptible to various opportunistic infections and certain types of cancer. Globally 36.7 million cases of HIV/AIDS have been recorded. Every year 2.1 million people are infected with HIV leading to mortality in 1.1 million cases.[1] In Pakistan, HIV infections were first described in 1987, and from that point onward, the number of positive cases has expanded to 0.18 million.[2] In 2013, the number of HIV-positive patients in Pakistan was only 4,500. With 20,000 new HIV infections in 2017, Pakistan has the second fastest-growing HIV epidemic in the Asia Pacific.[2] By June 2020, the National AIDS Control Program (NACP) had registered 42,563 HIV-positive patients. Tuberculosis (TB) is a major global public health problem with an estimated 10.4 million newly emerging active TB cases worldwide in 2016.[3] Previously due to a lack of diagnostic options, diagnosis

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of TB was missed in many instances. These days due to advancements in molecular and microbiological techniques, diagnosis of TB has been made relatively easy leading to a significant increase in the number of diagnosed TB patients.[4] The co-infection of TB and HIV is particularly problematic because each condition can worsen the other. TB can accelerate the progression of HIV to AIDS, and HIV can increase the risk of developing active TB disease in individuals with latent TB infection. This co-infection can lead to more severe symptoms, increased mortality rates, and more challenges in managing both diseases. In Pakistan, the prevalence of HIV-TB co-infection might vary based on several factors, including the prevalence of HIV and TB in the general population. Around 33% of 39.5 million HIV-positive patients were infected with TB and up to half of people living with HIV are supposed to develop TB.[5] The presence of other infections including TB tends to increase the rate of HIV replication in HIV-positive people. This may result in high replication of HIV along with a more rapid progression to develop AIDS. Of the 8.8 million TB cases around the world, an expected 1.1 million (13%) were also co-infected with HIV. Treatment with antiretroviral therapy (ART) suppresses HIV replication, this allows the immune system to recover and reduces the chances of death and illness associated with TB. The low CD4+-TLC remains an important risk factor for TB mortality in HIV-positive patients receiving first-line ART.[6] The relationship between increased HIV replication and low CD4+-TLC in HIV-positive patients with treatment interruptions is well documented.[7] HIV-positive patients with TB and low CD4+-TLC (<100 cells/mm3), often have atypical chest X-rays and negative acid-fast bacilli (AFB) sputum smears, compared to the HIV-negative patients.[8] TB preventive therapy is highly effective in reducing TB incidence and mortality among HIV-positive patients. Although it is well established that tuberculosis can occur at any CD4 count value, CD4+-TLC stratification has not been evaluated previously as a strategy to guide the testing and treatment of active TB infection for HIV-positive patients.[9] In a resource-limited country like ours where already prevalence of tuberculosis in the general population is very high, screening patients of HIV for TB co-infection below a specific cut-off of CD 4 count will have a positive impact on reducing morbidity and mortality. The CD 4 count is easily performed, rapid, and cost-effective for the initial assessment of patients living with HIV. CD 4 count assessment is though provided at almost all the centers of national and provisional Aids Control programs free of cost, but its excessive ordering will of course create a burden on HIV care continuum services. This idea also supports the rationale of the study i.e. defining cut-off and stratifying CD 4 count into ranges.

MATERIAL AND METHODS

This cross-sectional observational study was conducted over 6 months from May 2023 to October 2023 after approval from the Ethical Review Board (F.1-1/2015/ERB/SZABMU/1117 dated 17-04-2023). The convenience sampling technique was followed. Sample size of seventy-four was calculated by using the World Health Organization (WHO) calculator, keeping the significance level at 5%, power of test (1-β) at 90 %, anticipated value of population proportion of 0.78[10] and specified relative precision at 0.12. Patients from the inpatient and outpatient facilities of the Department of Infectious Diseases of Pakistan Institute of Medical Sciences (PIMS), Islamabad, also registered with the National Aids Control Program (NACP) were enrolled. All adult (>18 years) HIV-positive patients with confirmed tuberculosis (either by AFB smear, Xpert MTB, or AFB Culture) irrespective of the site of involvement, and regardless of CD4+-TLC were included. The data was collected using a structured questionnaire that included demographic details, CD4 count and status of AFB smear, Gene Xpert MTB, and AFB Culture positivity. Informed consent was taken from the patient or attendant before collecting the information with assurance to maintain confidentiality and anonymity. The patients who were found to be HIV-positive at the regional ART center of PIMS and had any symptom or sign that directed the workup of TB were identified. The AFB smear, MTB gene Xpert (PCR-based test for mycobacterium tuberculosis) and AFB Culture were sent to the laboratory. The MTB gene Xpert test was performed with the device “Gene Xpert GXIV-4”. Moreover, those patients who were already on anti-TB therapy for TB involving any site and presented to the departmental clinic or emergency were also screened for HIV and included in the study if found positive. The screening for HIV was done using the WHO three test protocol (Bio Alere HIV 1/2, Ag/Ab Combo test followed by Uni- Gold HIV kit of Trinity

Biotech & Abott and SD bio line kit as a third test). The baseline CD4+-TLC of every patient was noted at the time of diagnosis of co-infection. The CD4+-TLC was performed on analyzer by "Alere Pima" at the ART Centre of PIMS. The data was analyzed by IBM SPSS, Statistics 29.0 software. The demographic details of patients like gender, marital status, education, occupation, residential area, mode of transmission, history of foreign travel and types of TB in HIV-positive patients were presented as percentages. The association of different ranges of CD4+-TLC with different sites of TB was assessed.

A CD4 count cut-off of 100 was kept for analysis assuming that most TB cases occur at the CD4 count of <100. A 2×2 contingency table was constructed for each site of TB involvement. The Spearman coefficient (r) and ODD ratios were calculated as a measure of association and a level of significance was identified keeping p=value < 0.05 as significant. Fischer's Exact probability test was used to calculate odd ratios.

RESULTS

The demographic characteristics of 74 patients are summarized in Table-I. Pulmonary involvement was found to be highest in all co-infected patients followed by TB Meningitis, Pleural TB, and TB Lymphadenitis. There was only one case of Bone Marrow tuberculosis, one case of TB pericarditis, and two cases of tuberculous arthritis in whom TB was also diagnosed from other sites and was counted as disseminated tuberculosis. The frequency and proportions of sites of tuberculosis involvement are given in Table-II.

The CD 4 count of each patient was recorded and then categorized into different ranges for ease of analysis. There was no association found between CD4 count ranges and the site of TB involvement in HIV-TB Co-infection (p>0.05), but it was interesting to note that multiple sites (disseminated disease) were involved at CD4 counts at or below 100. Pulmonary tuberculosis occurred at any CD4 count ranging from 1-350 as depicted in Figure-I.

The Spearman rank-order coefficient and odd ratios were also calculated for each TB site as given in Table III. Most values of the Spearman coefficient were either slightly above zero on the positive side or below zero on the negative side signifying no or negative correlation of site of involvement of TB with CD 4 count.

Pulmonary TB, miliary TB, TB brain abscess, tuberculomas, and disseminated TB were found to occur at CD 4 count <100 as signified by the odd ratios. On the other hand, Pleural TB, Spinal TB, TB lymph adenitis, and TB meningitis developed at CD4 count >100 (Table-III).

Receiver Operating Curve analysis was performed to find sensitivity and specificity and appropriate cut-off CD 4 count keeping Xpert MTB Rif as the gold standard for diagnosis. The sensitivity and specificity of CD 4 count was found to be 68.4% and 41.2% respectively. The appropriate cut-off CD 4 count was found to be 53.5 at a point where maximum sensitivity and specificity (accuracy) was identified. This was calculated using the Youden Index. The Curve with different coordinates is shown in Figure-II.

Table-I: Demographic characteristics of the patients.

Demographic Details		
Age	38±11.24 years	
CD4 Count	86±59.48	
Gender	Males	67 (90.54%)
	Females	7 (9.45%)
Residence	Punjab	34 (45.94%)
	KPK	12 (16.21%)
	AJK & GB	11 (14.86)%
	Islamabad	17 (22.97%)
Source of transmission	Unknown	46 (62.16%)
	Sexual	15 (20.27) %
	IVDU	13 (17.56%)
Foreign Travel	Yes	11 (14.86%)
	No	63 (85.13%)
Compliance to ART	Yes	72 (97.29%)
	No	2 (2.70%)

Table-II: Different sites of involvement of tuberculosis (n=74).

Tuberculous Site	Frequency (%)
Miliary TB	3 (4.1%)
Pulmonary TB	33 (44.5%)
Pleural TB	7 (9.4%)
TB Lymphadenitis	4 (5.4%)
TB Brain Abscess	1 (1.4%)
TB meningitis	6 (8.1%)
Tuberculoma	1 (1.4%)
Spinal tuberculosis	1 (1.4%)
Disseminated tuberculosis	18 (24.3%)

Table-III: Odds Ratios and Spearman Coefficient values along with level of significance.

TB Site	Spearman coefficient (r)	Odd Ratios (OR) for CD4 count		P Value
		<100	>100	
Miliary TB	-0.11	1.3	-	0.34
Pulmonary TB	-0.10	1.1	0.67	0.38
Pleural TB	0.04	0.92	1.27	0.71
TB Lymphadenitis	0.15	0.6	2.3	0.19
Spinal TB	0.21	-	4.5	0.06
TB brain Abscess	-0.06	1.3	-	0.58
TB Meningitis	0.07	0.85	1.51	0.53
Tuberculomas	-0.06	1.3	-	0.58
Disseminated TB	-0.01	1.01	0.95	0.93

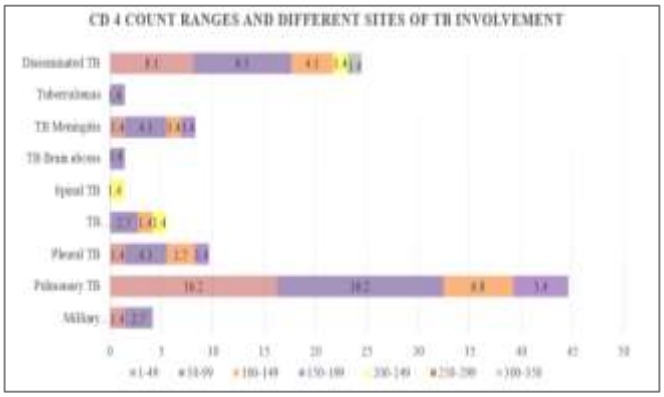

Figure-I: Percentage of involvement of various sites at different CD 4 count ranges.

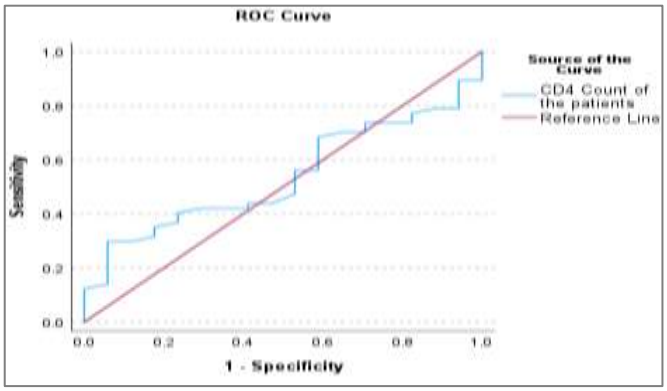

Figure-II: ROC curve for CD 4 count keeping Xpert MTB Rif as Gold Standard.

DISCUSSION

TB is one of the most common opportunistic infections in HIV-positive patients. The co-infection of HIV and TB is spreading across the globe, especially in developing countries.[11] HIV-positive patients are estimated to have a 20-30 times higher risk of developing active TB than HIV-negative individuals.[12] Globally, 1.2 million people are diagnosed with HIV-TB coinfection[13] and the overall prevalence of TB in HIV-positive patients is 16%.[14] In our study, we found that TB coinfection was more prevalent among males, compared to females which may be due to a higher number of male patients with HIV infection enrolled. The main source of HIV transmission was unclear in this study followed by sexual (20.2%) and then IVDU (17.5%).[15] It seems that lack of awareness about routes of transmission is a major risk factor for both HIV and TB infections in Pakistan.[16]

CD4+-TLC has an important role in HIV-TB coinfection, and a low CD4+-TLC has been implicated as a strong predictor of TB in HIV-positive patients in a few studies.[17] The pulmonary was the most common site of TB involvement when calculated frequencies were split at each site.

These results are consistent with other studies[18]. TB infection is normally fought by cell-mediated immunity in the host. Cell-mediated immunity is a limb that is often depressed in HIV-positive patients. Impaired mechanisms to control TB infection among HIV patients lead to unusual presentations of TB. Consequently, TB has become a major contributing factor in the mortality of AIDS patients.[19] This is well-documented that HIV-positive patients are more likely to develop EPTB.[20] However, Click and coworkers, demonstrated that pulmonary TB was more prevalent in HIV-TB coinfection patients in their study.[21] Some of the studies identified that EPTB along with pulmonary involvement was more common than EPTB alone in co-infection patients.[22]

In the Pacific and Asia, India, Myanmar, Thailand, and Indonesia, are among the 41 countries that have the highest burden of HIV-TB co-infection.[23] In a study from South Asia, 4% of HIV-positive TB patients had EPTB, particularly in those with significant immune suppression.[24] Leeds and researchers showed that TB lymphadenitis (28%) was the most widely recognized EPTB, followed by disseminated TB (23%), and cerebrospinal TB (22 %).[16] TB Lymphadenitis and pleural TB were the most common locations of EPTB in the other studies.[25,26] Reports from the US also showed that pleural TB is the second most pervasive sort of EPTB.[27]

A study published in India in 2019 found that the prevalence of all types of tuberculosis was higher when the CD4 cell count was <300 cells in contrast to our study where active TB cases were more common below a CD4 count of 100. They have also studied the impact of ART on the association of CD 4 count with the type of tuberculosis, but the results were insignificant.[28]

In a Chinese study CD 4+ T-cell count was significantly associated with TB at a cut-off of <200 and the odds of developing active Tuberculosis were high (P = 0.002, OR = 3.714, 95% CI: 1.612–8.577) which signifies that CD 4+ T-cell count is a predictor of active TB by lowering cut-offs to < 200. These findings match our study, in which the sensitivity and specificity of CD 4 count is found to be 68.4% and 41.2%, and OR >1 for most forms of TB at CD4 count < 100 (Pulmonary TB, miliary TB, TB brain abscess, tuberculomas, and disseminated TB).[29] Conversely, pleural TB, Spinal TB, TB lymph adenitis, and TB meningitis occurred more at CD4 count >100. Among this group overall TB, prevalence was very low indicating that these results might not have depicted the true association of CD4 count with the site of TB involvement.

CONCLUSION

TB is a common opportunistic infection among HIV-positive patients. Most forms of TB occurred at CD4+-TLC of between 50-99 with a cut-off at 53.3 regardless of the site of involvement. The overall prevalence of tuberculosis was highest below CD 4 count of 100 and there was no significant correlation between sites of involvement and CD4 count.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Hina Sadiq: Conceived the research idea, data collection

Nasim Akhtar: Critical review

Sana Tahir Virk: Data analysis and drafting of manuscript

Kazim Abbas Virk: Literature review and referencing

Abeer Zafar: Data collection.

Lubna Meraj: Data Interpretation and review.

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