Original article

CD4 Count Stratification, its Accuracy and Association with TB Site Involvement in HIV / TB Co-infection

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ABSTRACT

Background: Co-infection of HIV and TB is a significant public health concern, as these two diseases can interact and worsen each other's effects, leading to more severe health outcomes. The objective of this study was to stratify CD4 count according to different presentations of TB and see their association in HIV/TB co-infected patients. Other objective was to establish the predictive value of CD4 count for different sites of involvement.

Patients and methods: This cross-sectional observational study was conducted from October 2022 till March 2023. A total of seventy-four outdoor and indoor patients were enrolled. Patients aged more than 18 years having confirmed HIV and TB infections were included in the study. Those having any other opportunistic infection and aged less than 18 any having only presumed TB infection were excluded from the study. Patient's data was collected using a predesigned and pretested questionnaire after taking consent and ensuring confidentiality. Baseline CD4 count were recorded and stratified into <100 and >100 CD4 counts. Fischer Exact Test was used to measure association. Prediction was established by calculating CD4 count sensitivity and specificity against the smear microscopy for *Mycobacterium tuberculosis* infection.

Results: Mean age of the patients was 38.33 (range = 21-78 years), out of which 67 (90.5%) were male and 7 (9.5%) were female. Most frequent was pulmonary TB 34 (46.0%) followed by disseminated TB 13 (17.5%), TB meningitis 10 (13.5%), and pleural TB 08 (10.8%) and others 09 (12.2%). There was no association found between CD4+ T-lymphocyte count and site of involvement of TB. Spearman co-efficient showed no relationship between CD4 count and site of involvement. ROC curve showed maximum sensitivity and specificity at CD4 count of 53.5 hence establishing the cut-off value.

Conclusion: The Stratification of CD4 count does not show any specific trend for TB site involvement in TB/HIV co-infected patients. No association was found between CD4+ Lymphocyte count and site of involvement of TB in this study. Cut-off predictive value came out to be 53.3 in our study using receiver operating curve.

Keywords:

HIV/TB co-infection, CD4+ T-lymphocyte count, pulmonary tuberculosis, extrapulmonary tuberculosis

INTRODUCTION

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. The number of HIV patients in Punjab, the region with the highest number of cases, is 75,000, followed by Sindh (60,000), Khyber Pakhtunkhwa (16,322) and Baluchistan (5,275). Till 2017, 97,400 cases of HIV/AIDS have been documented by the National AIDS Control Programme (NACP).[3] Tuberculosis (TB) is a major global public health

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problem with an estimated 10.4 million newly emerging active TB cases worldwide in 2016.[4] It is the most common opportunistic infection occurring in patients with HIV. Previously due to a lack of diagnostic options, diagnosis 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.[5] 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.[6] 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.[7] People with HIV have a greater risk of developing infection with "Mycobacterium tuberculosis" (MTB), the organism responsible for TB owing to the suppression of the immune system by HIV. HIV weakens the immune system by attacking CD4+ Count, which is crucial for mounting an effective immune response. 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. Regardless, low CD4+-TLC remains an important risk factor for TB mortality in HIV-positive patients receiving first-line ART.[8] 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.[9] TB preventive therapy is highly effective in reducing TB incidence and mortality among HIV-positive patients. CD4+ Count stratification has not been evaluated previously as a strategy to guide the testing and treatment of latent TB infection for HIV-positive patients.[10] It has already been shown by many researchers that low CD4 counts increases the chances of TB co-infection specially below 200cells/mm3. But little has been researched about the different presentations of TB and CD4 count. Whether different level of counts result in different kinds of TB or not. So we designed this study to stratify CD4 count against different presentation of the and the see if any association exists between CD4 count and TB site involvement in HIV/TB co-infected individuals. We also tried to establish a cut-off value at which there are increased chances of TB/HIV co-infection.

PTIENTS AND METHODS

This cross-sectional observational study was conducted over 6 months from October 2022 till March 2023.The convenient sampling technique was followed. Sample size of seventy-four was calculated by using the World Health Organization (WHO) calculator.[11] Patients from the inpatient and outpatient departments of Infectious Disease at the Pakistan Institute of Medical Sciences and the patients registered in the Islamabad Centre of National AIDS Control Programme (NACP) were enrolled. Patients who were more than 18 years old, were HIV-positive, on antiretroviral medicines, and proven to have TB of any site irrespective of which infection was diagnosed first and showed positive MTB gene Xpert or AFB smear microscopy and regardless of their CD4+-TLC were included. The patients of less than 18 years of age, who are HIV-positive but are suffering from opportunistic infections other than TB, and unconfirmed cases of TB were excluded. The patient's data was collected using a predesigned and pretested questionnaire. Questionnaire included questions regarding subject's age, gender, marital status, education, occupation, residential area, IV drug abuse, spouse HIV status, sexual practices, history of foreign travelling, HIV Status, CD4 Count, and type of TB. 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 center of National AIDS Control Programme (NACP) and had any symptom or sign that directed the workup of TB were identified. Patient's Sputum sample were sent for MTB gene Xpert and AFB smear microscopy to the National TB Control Program at the National Institute of Health. The MTB gene Xpert was performed with the device "Gene Xpert GXIV-4". Moreover, those patients who were already on anti-TB therapy due to TB at any site and presented to the departmental clinic or emergency were also screened for HIV/AIDS and included in the study if, they were positive. The screening was done using the "UNI

GOLD HIV" kit by Trinity Biotech and Abbott and gene Xpert for HIV by "Cepheid S/N802318". The baseline CD4+-TLC of every patient was noted at the time of diagnosis of co-infection. The CD4+-TLC was performed by analyzer by "Alere Pima" at the Islamabad Centre of NACP. The data were analyzed by IBM SPSS, Statistics 26.0 software. The demographic details of patients like age, gender, residence, CD4 Count, Source of transmission, foreign travel and compliance to ART were presented as percentages. CD4 counts against different presentation of TB were given in a table for <50, 50-99, 100-199, 200-349 and > 350cells/mm3. A CD 4 count cut-off of 100 was kept for analysis. A 2×2 contingency Table was constructed for each site of TB involvement and keeping the CD 4 cut off either <100 or > 100, as most of the cases lie at the count <100. The Fischer Exact test was implied for the measure of association instead of chi-square distribution because there were many cells where the count in each cell was less than 20%. A p-value of equal to or less than 0.05 was taken as statistically significant.

RESULTS

Pulmonary involvement was found to be highest in all co-infection patients followed by Disseminated TB, TB Meningitis, Pleural TB, and TB Lymphadenitis. The frequency of Tuberculosis according to different sites is given in Table 2. Cases of Miliary TB and disseminated TB were counted only once and they were not included in subsequent counting of isolated site involvement. Demographic characteristics of 74 patients are summarized in Table 1.

The CD 4 count of each patient was collected, it was then stratified to show which TB presentation lies in what ranges of CD4 count. There was no favorite CD4 count range for the involvement of any site in HIV-TB Co-infection, but more distant sites are involved at CD4 counts below 100. Pulmonary tuberculosis occurred at any count ranging from 1-350. This is best depicted in Table. 3

All the p-values are more > 0.05 showing that there is no significant association of CD4 count with any site in the body for TB involvement. The Spearman rank-order coefficient and odd ratios were also calculated for each TB site as given in the Table. 3. 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 with CD4 count.

Similarly, the odds ratio for Pulmonary TB, Disseminated TB, TB Meningitis, Pleural TB, Spinal TB, TB lymphadenitis, Bone marrow TB, TB pericarditis, Tuberculoma are given above in Table 4 for cut-off values of >100 and <100 respectively.

Table 1: Demographic characteristics of the patients.

Demographic Details	Frequency (%)
Age (mean±SD)	38±11.24 years
CD4 count	86±59.4
Gender	
Males	67 (90.5%)
Females	7 (9.5%)
Residence	
Punjab	30 (40%)
KPK	15 (20.6%)
AJK	12 (15%)
Islamabad	10 (13%)
Source of transmission	
Unknown	46 (62.2%)
Sexual	15 (20.3%)
IVDU	13 (17.6%)
Foreign Travel	
Yes	18 (24%)
No	56 (74%)
Compliance to ART	
Yes	72 (97.3%)
No	2(2.7%)

Table 2: Different sites of involvement of tuberculosis.

Types of tuberculosis	Frequency (%)
Pulmonary TB	34 (46.0%)
Disseminated TB	13 (17.5%)
TB meningitis	10 (13.5%)
Pleural TB	08 (10.8%)
Spinal TB	03 (4.0%)
TB lymphadenitis	03 (4.0%)
Bone marrow TB	01 (1.3%)
TB pericarditis	01 (1.3%)
Tuberculoma	01 (1.3%)

Table 3: CD4 count Stratification according to different presentations of TB

Types of tuberculosis	CD4+ T-lymphocyte count stratification				
	< 50 mm³ of blood	50-99 mm³ of blood	100-199 mm³ of blood	200-349 mm³ of blood	>350 mm³ of blood
Pulmonary TB	12 (35.2%)	0 (0.0%)	22 (64.7%)	0	0
Disseminated TB	5 (38.6%)	4 (30.7%)	4 (30.7%)	0	0
TB meningitis	5 (55.5%)	3 (33.3%)	1 (11.1%)	0	0
Pleural TB	4 (50.0%)	3 (37.5%)	1 (12.5%)	0	0
Spinal TB	2 (66.6%)	1 (33.3.0%)	0 (0.0%)	0	0
TB lymphadenitis	1 (33.3%)	1 (33.3%)	1 (33.3%)	0	0
Bone marrow TB	0 (0.0%)	0 (0.0%)	0 (0.0%)	0	1 (100%)
TB pericarditis	1 (100.0%)	0 (0.0%)	0 (0.0%)	0	0
Tuberculoma	0	0	0	0	1 (100%)

Table 4: Odds Ratios and Spearman Coefficient values along with level of significance.

TB Site	Spearman coefficient (ρ)	Odd Ratios (OR) for CD4 count		p-value
		<100	>100	
Pulmonary TB	-0.57	1.06	0.81	0.41
Disseminated TB	-0.07	1.01	0.96	0.60
TB Meningitis	0.13	0.80	1.76	0.22
Pleural TB	-0.09	1.31	-	0.59
Spinal TB	-0.06	1.30	-	0.77
TB Lymphadenitis	0.15	0.72	2.05	0.19
Bone Marrow TB	0.05	0.86	1.48	0.55
TB Pericarditis	-0.06	1.3	-	0.71
Tuberculomas	-0.09	1.3	-	0.59

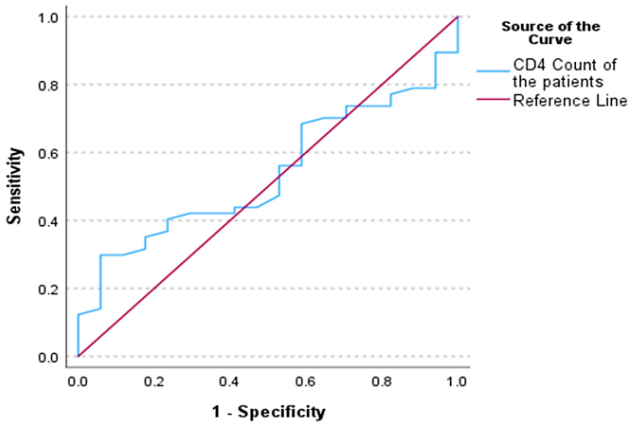

Figure 1: ROC curve for CD4 count keeping Xpert MTB Rif as Gold Standard.

Receiver Operating Curve analysis was performed to find sensitivity and specificity and appropriate cut-off CD4 count keeping Xpert MTB Rif as the gold standard for diagnosis. The sensitivity and specificity of CD4 count is found to be 68.4% and 41.2% respectively. The appropriate cut-off CD4 count was found to be 53.5 at a point where maximum sensitivity and specificity (accuracy) are identified. The Curve with different coordinates is shown in Figure 1.

DISCUSSION

Results of our study are comparable with other studies on the same topic which state that lower the CD4 count, higher the chances of TB infection in HIV infected individuals. But no study has ever compared the CD4 counts with different presentations of TB like we did but results of our study were not significant. 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.[12] HIV-positive patients are estimated to have a 20-30 times higher risk of developing active TB than HIV-negative individuals.[13] Globally, 1.2 million people are diagnosed with HIV-infected TB and are more likely to have TB than people with HIV infection.[14] The overall prevalence of TB in HIV-positive patients is 16%.[15] In this study, more male patients of HIV with TB have been observed as compared to female HIV patients with any type of TB. The higher number of HIV-positive males may be due to more involvement in unsafe sexual activities. The main source of HIV transmission was unclear in this study but still intravenous drug abusers are more prone to develop HIV infection.[16] Like many other local and international studies, most of the patients in our study were uneducated. The educated person may have basic knowledge about diseases and their source of transmission. The lack of education is also a major factor in unemployment.[17]

Globally, foreign travel plays an important role in the spreading of sexually transmitted diseases especially HIV. Those individuals who travel to Western countries are more likely to develop HIV infection. In this study, 24% of HIV-positive patients have a history of traveling to foreign countries. The diagnosis of sexually transmitted diseases especially HIV in returning travelers suggests that foreign traveling is an important risk factor.[18] In Pakistan, spouses and intimate partners are at a high risk of HIV acquisition on an ongoing basis due to the high HIV burden and limited access to treatment and prevention. Total 15.87% of spouses of married ones also developed HIV infection in this study. A local study observed that 8.8% of female spouses of HIV-positive drug abusers males were found HIV positive.[2]

CD4+-TLC has an important role in both HIV and TB infection, and a reduction in CD4+-TLC has been implicated as a strong predictor of TB risk in HIV-positive patients.[19] Based on the results of this study, majority of HIV patients developed pulmonary TB (46.0%). The study also shows a link between HIV infection and pulmonary TB. 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. Thus, with an impaired

mechanism to control TB infection, both increased incidences of TB as well as an uncommon form of pulmonary TB in AIDS patients are expected. Pulmonary TB has, consequently, become a pathogen of increased importance in the mortality of AIDS patients.[20] The frequency of extrapulmonary tuberculosis (EPTB) was also evaluated in this study. Many HIV-positive patients had disseminated TB (17.5%), followed by TB meningitis (14.3%), pleural TB (11.1%), spinal TB (4.8%), miliary TB (4.8%), TB lymphadenitis (4.8%), ocular TB (3.2%), TB arthritis (3.2%), abdominal TB (1.6%), hepatic TB (1.6%), cutaneous TB (1.6%), TB brain abscess (1.6%), bone marrow TB (1.6%), TB pericarditis (1.6%), and tuberculoma (1.6%). This is well-documented that HIV-positive patients are more likely to develop EPTB.[21] As indicated by Click and coworkers, HIV reactivity was linked to significantly more pulmonary TB.[22] HIV reactivity was linked to significantly more pulmonary TB. In addition, a similar report found that EPTB with associated pulmonary involvement was more associated with extrapulmonary disease than EPTB alone.[23]

In the Pacific and Asia, India, Myanmar, Thailand, and Indonesia, are among the 41 countries have the highest burden of HIV-TB co-infection.[24] In a study from South Asian, 4% of HIV-positive TB patients had EPTB, particularly in those with significant immune suppression.[25] Leeds and coresearchers showed that the lymphocytic (28%) disease was the most widely recognized EPTB, followed by disseminated TB (23%), and cerebrospinal TB (22%).[16] Lymphatic TB and pleural TB were the most common locations of EPTB in the other studies.[29,30] Reports from US also showed that pleural TB is the second most pervasive sort of EPTB.[26]

In one study published in 2019, the type of tuberculosis was correlated with CD 4 count. It was found that all types of tuberculosis were higher when the CD4 cell count was <300 cells, there was no advantage of one form of tuberculosis over the other form. Thes results were not significant like our study, but they had kept cut off value at 300 counts instead of 100. They have also studied the impact of ART on this association of CD 4 count with the type of tuberculosis, but the results were again insignificant.[27]

In a Chinese study CD 4+ T-cell count was significantly associated at cut-off <200 but the odds of developing active Tuberculosis were less. (p = 0.002, OR = 3.714, 95% CI: 1.612–8.577). This signifies that CD 4+ T-cell count is not an accurate predictor of the development of active tuberculosis. This is like our study, in which the sensitivity and specificity of CD4 count is found to be 68.4% and 41.2%, and OR >1 for more forms of TB.[28]

CONCLUSION

In our study most of the HIV-positive patients with any type of TB infection had CD4+-TLC of between 50-99 with a cut-off at 53.3. Any site of involvement with tuberculosis was not significantly associated with CD4+ TLC count. Hence, CD4+ T lymphocyte count is not a good marker to predict the site of involvement of tuberculosis. Given this conclusion, Our study was limited due to study design being cross sectional hence can't give temporal associations. Moreover, further research is encouraged with larger sample size and prospective study designs to further add to our knowledge on this topic

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