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Original Article

A Marker for Progression of Latent Tuberculosis Infection to Active Tuberculosis Infection in HIV Positive Individuals: CD4/CD8 Ratio

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ABSTRACT

Objective: We aimed to determine the utility of CD4 T lymphocyte counts and percentages and CD4/CD8 ratios as markers for the progression of latent tuberculosis infection (LTBI) to active tuberculosis (TB) infection in HIV-positive patients followed in the Acquired Immunodeficiency Virus (HIV) Polyclinic of our hospital.

Methods: The files of 530 HIV-positive patients were retrospectively analyzed. "Tuberculin skin test" (TST) was applied after the anti-HIV test was positive. Asymptomatic patients with a TST ≤5 mm were considered TB negative, patients with a TST ≤5 mm were considered LTBI, and all symptomatic patients (fever, cough, night sweats, weight loss) regardless of TST result were considered as active TB infection. CD4 counts and percentages and CD4/CD8 ratios were calculated and the relationship between LTBI and active TB infection was evaluated using Mann-Whitney U test and independent sample t-test.

Results: During the specified period, 530 patients were admitted to the HIV Outpatient Clinic. There were 43 (8.11%) patients in the LTBI group, of whom 4 (9.3%) were female and 39 (90.7%) were male. CD4 was <200 mm³ in 7 (16.3%) patients and >200 mm³ in 36 (83.7%) patients. The mean CD4/CD8 ratio was 0.55 (0.08-1.45). 21 (3.96%) patients had symptoms of fever, cough, night sweats and weight loss and were diagnosed with active TB infection. Among these patients, 1 (4.8%) was female and 20 (95.2%) were male. CD4 was <200 mm³ in 5 (23.8%) patients and >200 mm³ in 16 (76.2%) patients. The mean CD4/CD8 ratio was 0.38 (0.07-1.8). The difference in CD4 counts between patients with LTBI and active TB infection was not significant, but the difference in CD4/CD8 ratio was significant ($p<0.05$).

Conclusion: Immune dysfunction that occurs in HIV and TB co-infection facilitates the activation of LTBI. While CD4 counts and CD4 percentages were not significant as risk markers, CD4/CD8 ratio was found as significant.

INTRODUCTION

We aimed to determine the demographic characteristics, prevalence of persons with latent TB infection (LTBIs) and active TB infections, CD4 T lymphocyte counts, CD4 T lymphocyte percentages, and CD4/CD8 ratios as markers for the progression of LTBI to active TB infection in 530 HIV-positive patients who were admitted to one of the HIV outpatient clinics of our hospital.

MATERIALS AND METHODS

We retrospectively evaluated 530 HIV-positive patients admitted between October 2018 and June 2023. TST (0.5 mL of purified protein derivative was administered subcutaneously in the anterior forearm, and the induration at 72 h was recorded in mm) was performed when HIV positivity was detected. Some patients were diagnosed with HIV infection after TB diagnosis. Demographic data, reasons for testing, bacillus calmette-guerin (BCG) vaccination scars, and complaints such as weight loss, fever, night sweats, and cough were recorded. Asymptomatic patients with a TST ≤5 mm were considered TB negative; patients with a TST ≤5 mm were considered LTBI; and all symptomatic patients, regardless of the TST result, were considered to have an active TB infection. Mortality rates in

LTBI and active TB infections were recorded. CD4 counts, CD4 percentages, and CD4/CD8 ratios were calculated. A Mann–Whitney U test and an independent sample t-test were used to determine the relationship between these markers and the progression of LTBI to active TB infection.

RESULTS

During this period, 530 patients were admitted to the HIV Outpatient Clinic. A total of 64 patients with TST >5 mm or complaints of fever, cough, increased sweating at night, and weight loss were included in the study because they were immunosuppressed. TST was <5 mm in 4 symptomatic patients.

43 patients (8.11%) were diagnosed with LTBI, and INH prophylaxis was initiated (Table 1). Among these patients, 4 (9.3%) were female and 39 (90.7%) were male. The mean TDT value was 10.09 (5–18) mm. Three patients had no BCG vaccination scar. 11 patients had 1, 27 patients had 2, and 2 patients had 3 BCG scars. The number of scars decreased with decreasing age. CD4 count was <200 mm³ in 7 (16.3%) patients and >200 mm³ in 36 (83.7%) patients. The mean CD4 percentage was 23.56 (7–42%) and the CD4/CD8 ratio was 0.55 (0.08–1.45). While 8 patients (18.6%) were tested due to suspicious sexual intercourse, it was detected in 5 (11.6%) patients during preoperative tests. These were followed by 4 (9.3%) patients who were examined for diarrhea and weight loss. While the CD4 count was <200 mm³ in one of these 4 patients, it was >200 mm³ in 3 of them. The other patients were diagnosed while being examined for different reasons. One patient died due to lung cancer, and another patient died due to Kaposi's sarcoma.

21 (3.96%) patients were diagnosed with active TB infection with symptoms of fever, cough, sweating, and weight loss and received quadruple anti-TB treatment (isoniazid, rifampicin, ethambutol, and pyrazinamide) (Table 1). Among these patients, 1 (4.8%) was female and 20 (95.2%) were male. The mean TDT value was 12.95 (0–30) mm. TST was <5 mm in 4 (19%) symptomatic patients. Three patients had no BCG scar. 8 patients had 1 BCG scar, 9 patients had 2 BCG scars, and 1 patient had 3 BCG scars. In this group, the number of scars was decreasing with decreasing age. CD4 count was <200 mm³ in 5 (23.8%) patients and >200 mm³ in 16 (76.2%) patients. The mean CD4 percentage was 18.42 (5–32%), and the mean CD4/CD8 ratio was 0.38 (0.07–1.8). 9 (42.8%) patients were diagnosed with HIV after the diagnosis of pulmonary TB. Seven (33.3%) patients were tested because of suspicious sexual intercourse. Four patients were diagnosed during periodic examinations at the workplace, and three patients were diagnosed after preoperative tests. Other patients were tested for different reasons. One patient with a very low CD4/CD8 ratio was diagnosed with pulmonary TB and died before cART was initiated.

CD4 counts were compared in both LTBI and active TB infection, and there was no significant difference (p=0.099).

Table 1. Demographic data of TB patients

	LTBI		Active TB Infection	
	n	%	n	%
Gender				
Male	39	90,7%	20	95,2%
Female	4	9,3%	1	4,8%
Marital status				
Single	21	48,8%	10	47,6%
Married	22	51,2%	11	52,4%
Educational status				
Primary School	16	37,2%	7	33,3%
Middle School	2	4,7%	1	4,8%
High School	12	27,9%	7	33,3%
University	13	30,2%	6	28,6%
Route of Transmission				
Sexual intercourse	42	97,7%	20	95,2%
Needle Prick	1	2,3%	0	0,0%
IV Medicine	0	0,0%	1	4,8%

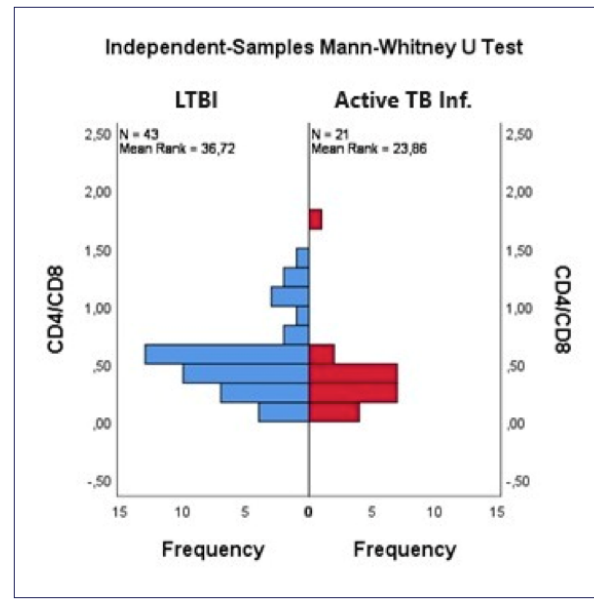

Figure 1. CD4/CD8 ratios in LTBI and Active TB Infection.

No significant difference was also found in CD4 percentages (p=0.066). When the CD4/CD8 ratios in these two groups were analyzed, it was observed that they did not exhibit a normal distribution, and nonparametric tests were applied to look for significance between the values (Figure 1). The null hypothesis was accepted as there was no significant difference in CD4/CD8 ratios between the groups. The non-parametric Mann-Whitney U test showed that the CD4/CD8 ratio was significantly higher in LTBI than in active TB infection (p<0.05).

DISCUSSION

TB is a disease caused by Mycobacterium tuberculosis

complex (M. tuberculosis, Mycobacterium bovis, Mycobacterium Africanum, and Mycobacterium microti) bacilli, which are transmitted through respiratory and droplet transmission. Although it primarily affects the lungs, it can affect any organ and can be seen in all age groups. While 95% of individuals exposed to tubercle bacilli remain LTBI, 5% progress to active TB infection in the first 2 years. In general, the risk of activation of LTBI is 5–10%.[1] TB disease, which is still an important public health problem, is the leading cause of mortality when co-infected in HIV-infected individuals.[2,3] Increasing international migration contributes to a higher incidence of HIV and TB infections in both host communities and refugees.[4,5]

HIV infection facilitates the progression of LTBI to active TB infection, independent of the CD4 T lymphocyte count.[6,7] The fact that both HIV and TB infect immune system cells mutually gives each other an advantage. M. tuberculosis ingested via aerosols is phagocytosed by macrophages in the alveoli. The macrophage environment provides a favorable environment for the bacillus to survive and grow. CD4 T lymphocytes responsible for humoral immunity and cytotoxic T lymphocytes responsible for apoptosis (CD8), which are stimulated by the activation of infected macrophages, are responsible for granuloma formation and limiting the infection.[7]

Once HIV enters the body, it infects CD4 T lymphocytes, which are its primary target cells. The functions of both TB bacilli-infected macrophages and HIV-infected CD4 T lymphocytes are affected at varying rates. Macrophage apoptosis is affected by the involvement of CD8-cytotoxic T lymphocytes. This immune impairment affects each patient differently, so the prognosis is different, and LTBI may progress to an active TB infection. The incidence of TB in HIV-positive patients is 30 times higher than in HIV-negative patients.[8] TB co-infection increases mortality more than twofold in HIV-positive patients.[9] The World Health Organization (WHO) stage III/IV, CD4 <200 mm³ and hemoglobin value <10 mg/dL have been reported as independent risk factors.[10] In this study, the CD4/CD8 ratio was determined as a risk factor rather than the CD4 count.

Among 530 HIV-positive patients, 55 (10.4%) were female and 475 (89.6%) were male. 64 (12.1%) patients were diagnosed with LTBI or active TB infection. TB is the most common infection in HIV-positive individuals. The WHO has recommended TB screening in HIV-positive patients since 2004.[11] Starting prophylaxis for LTBI after diagnosis prevents progression to active TB infection and reduces the rate of mortality.[12] 466 (87.9%) patients had a TST result of ≤5 mm, no TB symptoms, and no suspicious lesions on PA (posterior-anterior) chest radiographs; therefore, LTBI or active TB infection was not suspected.

Interleukins released from macrophages infected with M. tuberculosis stimulate CD8 cytotoxic T lymphocytes and lead to the release of interferon-gamma, which causes macrophage apoptosis.[13] Interferon gamma also plays a role in the positivity of TST, which is a type IV hypersensitivity reaction. The stimulating effect of M. tuberculosis-infected macrophages on the immune system may be impaired, especially in the acquired immunodeficiency syndrome (AIDS) presentation in which the CD4 T lymphocyte count is extremely low, and this affects the functions of CD8 T lymphocytes. In advanced AIDS patients with low CD8 T lymphocyte counts and an inability to release interferon-gamma, as in our four symptomatic patients, TST may remain negative, and imaging methods (PA chest radiography, thorax CT) may not detect TB and other infection-specific lesions in the lung parenchyma. In this condition, the patient's epidemiologic data and symptoms become important for making a diagnosis.

According to the WHO's data for 2021, 10.6 million people globally are infected with TB, which corresponds to 134 cases/100000. While 45% of cases are seen in Southeast Asia, 23% in Africa, 18% in the Western Pacific, and 8.1% in the Eastern Mediterranean.[11] Since TB infection is so common worldwide, patients with complaints such as fever, cough, weight loss, night sweats, and fatigue should be considered to have TB until proven otherwise.

A total of 64 (12.1%) patients, including 60 patients with TDT >5 mm and 4 symptomatic patients with TDT <5 mm, were included in the study. Among these patients, 5 (7.3%) were female and 59 (92.2%) were male. Forty-three (8.11%) asymptomatic patients without lung lesions were diagnosed with LTBI, and 21 (3.97%) symptomatic patients were diagnosed with active TB infection. These data suggest that HIV infection increases the prevalence of TB compared to the normal population.

The mean TST value of 43 patients diagnosed with LTBI was 10.09 (6–18). 3 patients had no BCG scar, 11 patients had 1 scar, 27 patients had 2 scars, and 2 patients had 3 scars. It was observed that as the age of the patients decreased, the number of scars decreased in parallel. The BCG vaccine limits the progression of LTBI to active TB infection and reduces the occurrence of miliary TB and TB meningitis.[14] Considering that young patients are more likely to have HIV and this group did not receive the BCG vaccine, it can be predicted that the incidence of active TB infection will increase in HIV-positive individuals. They were most frequently examined for suspected sexual intercourse, pre-operative blood donation, and generalized lymphadenomegaly. They had no complaints such as fever, cough, sweating, weight loss, weakness, or chronic diarrhea.

Seven (16.3%) patients had a CD4 count <200 mm³, while 36 (85.7%) had a CD4 count >200 mm³. Although the CD4 count was below 200 mm³, TB symptoms were not present, indicating that TB occurs independently of the CD4 count. The mean CD4 percentage was 23.56 (7–42%) and the CD4/CD8 ratio was 0.55 (0.08–1.45). One patient died of Kaposi's sarcoma, and another patient died of lung cancer. The patient with Kaposi's sarcoma was diagnosed with a CD4 count <200 mm³. This shows the correlation between CD4 count and HIV-defining malignancies.[15]

INH prophylaxis and vitamin B6 were given for 9 months

in LTBI.[16] CART was initiated on the 10th day after prophylaxis was started. Rapid initiation of cART helps the patient realize the seriousness of his or her disease, increases treatment compliance and sustainability, is effective in controlling HIV infection and reducing infectiousness, and provides a rapid increase in CD4 counts and CD4/CD8 ratio. However, delay in cART treatment may lead to the patient's loss of trust in the physician, a decrease in treatment compliance, and the continuation of infectiousness.[17] Normalization of the immune system reduces the risk of malignancy and mortality due to TB and other infections. However, the occurrence of HIV-defining malignancies is not associated with the level of CD4 alone.[15] In this study, no correlation was shown between LTBI and CD4 counts and percentages. Exacerbation and mortality were not observed in the patients. The values of patients with CD4 <200 mm³ with cART became >200 mm³ in an average of 1–6 months. Since CD4 counts and CD4/CD8 ratios were very low in 2 patients, CD4 counts exceeded 200 mm³ in the 12th month.

Active TB infection was diagnosed in 21 (3.96%) symptomatic patients, and quadruple anti-TB treatment was administered for 6 months.[18] Among these patients, 1 (4.8%) was female and 20 (95.2%) were male. TST was 0 mm (negative) in 4 patients. The mean value of TST was 12.95 (0–30) mm. This value was 2.86 mm higher than the mean value in LTBI. Three patients had no BCG scar. 8 patients had 1 BCG scar, 9 patients had 2 BCG scars, and 1 patient had 3 BCG scars. In this group, the number of BCG scars decreased with decreasing age. CD4 count was <200 mm³ in 5 (23.8%) patients and >200 mm³ in 16 (76.2%) patients. There was no significant difference compared to LTBI (p=0.099). The mean CD4 percentage was 18.42 (5–32%), which was not significant compared to LTBI (p=0.066). The mean CD4/CD8 ratio was 0.38 (0.07–1.8), which was lower than that of LTBI, and a significant difference was noted (p<0.05) (Figure 1). Patients with a low CD4/CD8 ratio had a higher risk of LTBI progression to active TB infection.

9 (42.8%) patients were diagnosed with HIV after a pulmonary TB diagnosis and had symptoms of fever, weight loss, and increased sweating at night. 12 (57.1%) patients had a TST >10 mm, and pre-cART TB treatment was initiated when they had symptoms of fever, cough, sweating, and weight loss. No patient was diagnosed with lymphoma. 7 patients were diagnosed due to suspected sexual intercourse; 4 patients were diagnosed by periodic examination at the workplace; and 3 patients were diagnosed by preoperative investigations. One patient, who started treatment for pulmonary TB, was diagnosed with HIV, had a very low CD4/CD8 ratio (0.07), and died before cART was initiated due to deterioration in general condition.

Conclusion

The most important parameter determining the prognosis of HIV infection is the CD4/CD8 ratio, and one of the treatment goals should be to increase this ratio above 0.5 or even 1. This ratio is a good marker for the progression of LTBI to active TB infection and also indicates immune damage. CD4 count and CD4 percentage are not good parameters to indicate the risk of exacerbation of LTBI.

Ethics Committee Approval

This study approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 12.07.2023, Decision No: 2023/514/253/7).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: B.K., R.D.; Design: B.K., R.D.; Supervision: B.K., R.D.; Fundings: B.K., R.D.; Materials: B.K., R.D.; Data: B.K., R.D.; Analysis: B.K., R.D.; Literature search: B.K., R.D.; Writing: B.K., R.D.; Critical revision: B.K., R.D.

Conflict of Interest

None declared.

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HIV Pozitif Bireylerde Latent Tüberküloz Enfeksiyonunun Aktif Tüberküloz Enfeksiyonuna İlerlemesinde Bir Belirteç: CD4/CD8 Oranı

Amaç: Hastanemizin Edinsel İmmunyetersizlik Virüsü (HIV) Polikliniği'nde takip edilen HIV pozitif hastalardaki latent tüberküloz enfeksiyonu'nun (LTBE) aktif tüberküloz (TB) enfeksiyonuna ilerlemesinde CD4 T lenfosit sayıları ve yüzdeleri ile CD4/CD8 oranlarının bir belirteç olarak kullanılabilirliklerini öğrenmeyi amaçladık.

Gereç ve Yöntem: 530 HIV pozitif hastanın dosyaları retrospektif olarak incelendi. Hastaların anti-HIV testi pozitif geldikten sonra "tüberkülin deri testi" (TDT) uygulandı. TDT ≤5 mm olan asemptomatik hastalar TB negatif, >5 mm olan hastalar LTBE, TDT sonucundan bağımsız olarak tüm semptomatik (ateş, öksürük, gece terlemesi, kilo kaybı) hastalar aktif TB enfeksiyonu olarak kabul edildi. CD4 sayıları ve yüzdeleri ile CD4/CD8 oranları hesaplanıp, bunlarla LTBE ve aktif TB enfeksiyonu arasındaki ilişki Mann-Whitney U testi ve bağımsız örneklem t-testi uygulanarak değerlendirildi.

Bulgular: Belirtilen dönemde HIV Polikliniği'ne 530 hasta başvurdu. LTBE grubunda 43 (%8.11) hasta vardı, bunların 4'ü (%9.3) kadın, 39'u (%90.7) erkekti. Yedi (%16.3) hastada CD4 <200 mm³ iken, 36 (%83.7) hastada >200 mm³'tü. Ortalama CD4/CD8 oranı 0.55 (0.08-1.45) olarak bulundu. 21 (%3.96) hastada ateş, öksürük, gece terlemesi ve kilo kaybı semptomları vardı ve aktif TB enfeksiyonu tanısı aldı. Bu hastalardan 1'i (%4.8) kadın, 20'si (%95.2) erkek idi. Beş (%23.8) hastada CD4 <200 mm³ iken 16 (%76.2) hastada >200 mm³ idi. Ortalama CD4/CD8 oranı 0.38 (0.07-1.8) olarak saptandı. LTBE ile aktif TB enfeksiyonu arasındaki CD4 sayıları arasındaki fark anlamlı değildi fakat CD4/CD8 oranları arasındaki fark anlamlı bulundu ($p<0.05$).

Sonuç: HIV ve TB ko-enfeksiyonunda oluşan immün bozukluk LTBE'nin aktifleşmesini kolaylaştırır. Risk belirteci olarak CD4 sayıları ve CD4 yüzdeleri anlamlı değilken, CD4/CD8 oranı anlamlı bulundu.

Anahtar Sözcükler: Aktif TB enfeksiyonu; CD4/CD8 oranı; HIV; LTBE.