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IMMUNO-PATHOLOGICAL PROFILE OF HIV INFECTED PATIENTS WITH TUBERCULOSIS: A RETROSPECTIVE DATABASE STUDY

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Abstract

Objectives: To assess and correlate the hematological and immunopathological profiles of HIV patients with pulmonary TB.

Study Design: A prospective observational study was conducted at the Punjab AIDS Control Program (PACP) and provincial reference TB control laboratory in Lahore.

Place and Duration of the Study: 15th August 2015 to 8th March 2018

Methodology: A data collection form was generated, and socio-economic and demographic information was collected from enrolled subjects. The total number of patients identified was 560, of whom n=510 got HIV. All patients aged 4 to 80 years were included. Blood profiles of the patients were collected, and the Immuno-chromatographic (ICT) Technique was performed for the screening of blood samples; for that, Alere DetermineHIV-1/2 Ag/Abs Combo strips were used. This strip could detect *HIV-1/*2 antigen (p24) and *HIV1/2* antibodies simultaneously. The Gene Xpert detects the DNA sequences that are specific for *M. tuberculosis* and RIF resistance by PCR. The data was entered into an Excel sheet and then analyzed with the help of Statistical analysis tools Statistical Package for Social Science (SPSS).

Results: A total number of five hundred ten (n=510) HIV patients, including males (n=381), females (n=116), and transgender (n=13). Among the enrolled individuals, 64.90% were married, being the highest, and 2.15% were widowed/divorced and were the least. The prevalence of HIV with T.B was significantly higher among male patients. The mean $CD4^+$ and $CD8^+$ count in *HIV* patients was 429.5 cells/mm^3 and 808.4 cells/mm^3. CD8+T cell means were high in newly diagnosed and recurrent *TB* patients. The mean $CD4^+$and $CD8^+$ count in *HIV* patients co-infected with TB was 200.7 cells/mm^3 and 941.6 cells/mm^3. It was also recorded that, as compared to a female, the male populations have a lower mean CD4+T cell count.

Conclusion: The findings of this study have revealed that *HIV/TB* co-infection results in the depletion of $CD4^+$ cells, resulting in susceptibility to other infections. In the current scenario, most

cases of *TB-HIV* co-infection have CD4+ count and Hb lower compared to only *HIV*-infected patients. Male has a high prevalence of *TB-HIV* co-infected compared to females. For optimal therapy, the research suggests that HIV patients co-infected with TB be evaluated regularly.

Keywords: *Tuberculosis, HIV,* CD4+, Co-infection, Acquired immune deficiency syndrome (AIDS), Erythrocytes sedimentation rate (ESR), Differential leukocytes count (DLC)

Introduction

Human immune deficiency virus (HIV) is one of the main diseases causing higher economic burden across the globe due to the immunodeficient nature of HIV chances of other infections like Tuberculosis (TB). HIV and TB co-infection have resulted in an increased rate of mortality by destroying the immune system in the past few years in Asian developing countries (Bruchfeld et al., 2015). In developing countries, the rate of co-infection of *Mycobacterium tuberculosis* and HIV is 90% due to the compromised immune system. It has taken more than 35 million lives approximately (McShane and AIDS, 2005; Riou et al., 2019).

HIV belongs to the *Retroviridae* family, and it is an RNA virus having a diameter of 80 nm to 120 nm. Special features of the virion are reverse transcriptase, integrase and protease enzymes, and cellular transfer RNA (tRNA). They encode *gag*, *pol,* and *env* genes, which are involved in their pathogenesis. HIV directly attacks CD4 cells (Murray et al., 2020; Riou et al., 2020). *Mycobacterium tuberculosis,* on the other hand, is a strict aerobe, acid-fast, and intracellular microbe causing chronic illness when inhaled via respiratory droplets and subsides within macrophages (Obeagu et al., 2020). TB is the 13th leading cause of mortality worldwide and the second leading infectious disease after COVID-19 (Ahmed et al., 2020; Rizvi et al., 2022; Yusof et al., 2021). The prevalence and incidence of *HIV* with *TB* are increasing day by day and worsening the situation. *HIV-TB* co-infection prevalence was 41.25% recorded (WHO, 2022). HIV weakens the immune system of the host and increases the risk of developing TB and in the presence of HIV and creates difficulty in the management of TB (Javed et al., 2018a; Khuawar et al., 2019). Once HIV is transmitted (Akinbami et al., 2013; Mba et al., 2019), it renders severe deterioration of the immune system of an infected person, causing acquired immunodeficiency syndrome (AIDS). *HIV* targets immune cells, particularly helper T cells (CD4+), dendritic cells, and macrophages, and destroys their activity (Setty et al., 2014). Once an *HIV* patient is infected with TB, poor generation and maintenance of antigen processing and presentation, widespread loss of CD4+ T cells, and selective clonal depletion of M-TB specific CD4+ T lymphocytes are observed (Siddiq et al., 2023). Bothe *HIV* and *TB* together make the situation more worsen by further weakening the immune system (Nosik et al., 2021; Ștefanescu et al., 2021).

HIV badly influences the hematopoiesis process by destroying hematopoietic stem cells and results in anemia, neutropenia, thrombocytopenia, and leucopenia, and rarely in thrombocytosis, monocytosis, and lymphocytosis. Hematological changes occur during both HIV and TB but differ depending upon the virus replication, viral load, immune status, and phase of infection (Amilo et al., 2013; Tan, 2016). HIV results in the reactivation and activation of latent TB and failure of treatment of TB (Bukhari et al., 2021; Ramzan et al., 2022). Tuberculosis affects various organs, particularly the lungs and hematopoietic system. Thus, Hematological profiles undergo various changes that can be used to diagnose a disease. Co-infection of *HIV-TB* where all cell lines are involved may result in mortality and is quite difficult to cure (Javed et al., 2018b).

There is a strong need to use serological markers for screening of HIV and TB, although non-specific, to prevent co-morbidity and mortality (Marrazzo et al., 2014). HIV and TB represent a serious threat to public health and the economy worldwide (Khan et al., 2006; Ogunmola et al., 2014). In low-middle-income countries, particularly Pakistan, there has been few research on the hematological and immunopathological profiles of HIV patients co-infected with pulmonary TB patients. To the best of our knowledge, there is a shortage of data in Pakistan assessing the hematological and immunopathological profiles of HIV with pulmonary TB patients to analyze changes in parameters and track their treatment results. This study may pave the way for public

health organizations in Pakistan to take correct preventive measures by proper screening of *HIV* patients for *TB* and decrease mortality.

Methodology

A cross-sectional retrospective study was conducted at the Punjab AIDS Control Program (PACP) and provincial reference TB control laboratory, 6 Bird Wood Road, Lahore, Pakistan. The study period was from 15th August 2015 to 8th March 2018. All HIV patients visiting the PACP lab during this study time frame were included in the data collection in this study. A data collection form was generated. Socio-economic and demographic information was collected from enrolled subjects.

Study Population:

A universal sampling method was used to identify the study population. The total number of patients who visited the PACP lab was 560. Of whom n=510 were HIV+ subjects, and their entire data in line with the aims of the study was extracted from the electronic database.

Sample collection

Blood samples of enrolled subjects were collected from the Institute of Public Health (IPH) and Tertiary Care Mayo Hospital, Lahore. To determine the hematological profiling, which included CD4+, Hb, CD8+, PCV, and T lymphocyte count, a total of 3 cc of blood was collected in EDTA tubes.

Screening of blood samples

The immuno-chromatographic (ICT) Technique was performed for the screening of blood samples, and for that, Alere DetermineHIV-1/2 Ag/Abs Combo strips (MedicalDeviceDepot) were used. This strip could detect *HIV-1/2* antigen (p24) and *HIV1/2* antibodies simultaneously.

HIV viral load determination through PCR

Upon collection of the blood sample, a quantitative polymerase chain reaction (PCR)(Lallemand et al., 2000; Shen et al., 2011) test was performed after plasma separation through centrifugation. After extraction of RNA, it was quantified by nano drops. Extracted RNA was subjected to RT PCR for *HIV-1* viral load determination. Three RT PCR primers were used for the optimization process. It undergoes four steps: reverse transcription, initial denaturation, annealing, and extension. It also finds out the levels of HIV in the blood by multiplying them up to 1000000 copies per ml as a high level. RT-PCR was performed on all research samples. The RT-PCR products were confirmed by 1% agarose gel electrophoresis using ethidium bromide solution and visualized under UV light in a gel documentation system (Barletta et al., 2004).

Screening of pulmonary Tuberculosis:

All subjects were screened for pulmonary tuberculosis by a rapidimmuno-chromatography test (ICT) (Gounder et al., 2002; Shenoy and Mukhopadhyay, 2014)for the detection of antibodies.

Sputum Collection for TB Testing

The sputum is originating from deep within the lungs after a productive cough. Specimens were collected in containers that are sterile, clear, plastic, and leak-proof and should not be saliva and immediately transferred to the laboratory for further testing.

Gene Xpert test Principal and Description

The Gene Xpert of MTB/RIF is an automatic diagnostic test to identify the DNA of *M. tuberculosis* and determine the resistance to rifampicin (RIF). The Gene Xpert detects the DNA sequences that are specific for *M. tuberculosis* and RIF resistant by PCR. This process occurs inside the cartridge, and the results are obtained within one and a half hours.

Hematological profiling:
The patients were tested for RBC index, total red blood cell (RBC) count, hemoglobin (Hb), differential leukocyte counts (DLC), total lymphocyte counts (TLC), CD4+, CD8+, erythrocyte sedimentation rate (ESR) and platelet count using complete blood count (CBC) analyzer. Cut-off values were determined as TLC < 4,000/cumm, platelet count < 1.5 lakh/cumm and Hb < 10 g/dl. With the help of a flow cytometry machine, the CD4+ lymphocyte count was reported to estimate the situation of patients. ESR was measured by the Westergren method to ensure quality results.

Statistical analysis and ethical consideration:
The data was entered into an Excel sheet and then analyzed with the help of Statistical Analysis Tools Statistical Package for Social Science (SPSS). The data was examined using parametric statistics such as frequencies, mean, median, and standard deviation. To compare categorical variables between groups, the Chi-square test was applied, and the independent T-test was used to analyze continuous data across groups. The project was approved by the Institutional Research Board UVAS, city Campus Lahore, and Punjab AIDS Control Program (PACP) and provincial reference TB control laboratory, 6 Bird Wood Road Lahore, Pakistan.

Results
Of the 510 HIV patients, the majority, 381 (74.70%), were male, 116 (22.74%) were female, and 13(2.54%) were transgender. Mos the patients whose information was retrieved from the database were from the age group 15-45 year 416 (93.52%, p=<0.001). They were divided into four groups: gender, age, education, and marital status. Of the 510 patients, 356 (69.8%) HIV patients were without TB, while 154(30.2%) were with HIV and TB (p=<0.001). The majority of 331(64.90%) of the patients who were with a confirmed diagnosis of HIV were married, and 168(32.94%) were single. Details are mentioned in Table 1.

Table 1: Socio-Demographics of Patients

	Total (510) N (%)	**HIV without Tuberculosis (356) N (%)**	**HIV with Tuberculosis (154) N (%)**	**Chi-Square test (p<0.05)**
Gender				$\chi 2$= 8.32, Df=2, p=0.01*
Male	381(74.70)	254(71.34)	127 (82.46)	
Female	116(22.74)	90 (25.28)	26 (16.88)	
Transgender	13(2.54)	12(3.37)	1 (0.64)	
Age				$\chi 2$=107.76, Df=55, P= <0.001*
< 15	11(2.15)	7(1.96)	4(2.59)	
15-30	214(41.96)	140(39.32)	74(48.05)	
31-45	202(41.56)	154(43.25)	48(31.16)	
46+	83(16.27)	57 (16.01)	28 (18.18)	
Education				$\chi 2$ =0.30, Df=2, P=<0.58
Literate	90(17.64)	65(18.25)	25(16.23)	
Illiterate	420(82.35)	291(81.74)	129(83.76)	
Marital status				$\chi 2$=10.07, Df=5, P= 0.27
Single	168(32.94)	117(32.86)	51(33.11)	
Married	331(64.90)	232(65.16)	99(64.28)	
Divorced/Widow	11(2.15)	7 (1.96)	4 (2.59)	

P-value < 0.005 was considered statistically significant.

Baseline Biomarkers of the HIV and HIV with TB patients
Based on the baseline CBC, it was revealed that the patient with HIV and TB got WBC 9.61± 1.95 [MD 0.91, 0.17 ─ 1.46], and the difference between the HIV alone patients and patient with HIV and TB was statistically significant (p=0.039). Similarly, the erythrocyte sedimentation rate (ESR) was observed to be statistically significantly different between both groups (MD -17.76 [-21.56 ─ -13.97], p=<0.0001). Rest for the other parameters, there were differences among both groups, i.e.

HIV patients and patients with HIV and TB. However, these differences were not statistically significant. The detail is shown in Table 2.

Table 2: Baseline markers for detection of HIV and TB

	HIV Without T.B Mean ± SD	HIV With T.B Mean ± SD		CI 95%		p-value (<0.05)
			Mean Difference (MD)	Lower	Upper	
WBC	8.7±1.96	9.61± 1.95	0.91	0.17	1.46	0.039*
RBC	4.18±0.86	4.0± 0.86	0.18	-0.13	0.18	0.76
HGB	9.63±2.07	9.64± 1.79	-0.004	-0.36	0.35	0.98
HCT	39.28±7.71	39.39± 6.98	-0.11	-1.48	1.25	0.87
MCV	88.35±13.84	86.93± 13.18	1.41	-1.12	3.95	0.27
MCH	26.34±4.17	25.57± 3.95	0.76	0.005	1.53	0.48
MCHC	29.85± 1.7	29.46± 1.7	0.39	0.07	0.71	0.17
PLY	301.86± 87.54	300.96± 93.95	0.9	-16.57	18.38	0.91
ESR	60.41± 16.54	78.18± 21.31	-17.76	-21.56	-13.97	<0.001

P-value < 0.005 was considered statistically significant.

Serology Comparison of HIV patients with TB and without *TB*

The mean $CD4^+$ and $CD8^+$ count in *HIV* patients was 429.5 cells/mm^3 and 808.4 cells/mm^3 with a mean difference of 228.86 [185.84 ─ 271.87, p=<0.001] for $CD4^+$, while for $CD8^+$ the HIV without TB got lower $CD8^+$ level MD -133.16 [-243.67 ─ -22.65, p=<0.001]. In Addition, the viral load was significantly higher among patients with HIV and TB in comparison to those who are with TB [p=<0.001]. Details are described in Table 3. Further analysis revealed that the female population has a significantly lower level of hemoglobin than the male patients (p=0.047). Similarly, the HCT was lower among female patients, and so was the WBC. For the other parameters, there were differences based on gender. However, they were statistically insignificant. The details are mentioned in the given Table 4.

Table 3: Serological indicators of HIV along with the viral load

	HIV Without T.B	HIV With T.B	Mean Difference (MD)	95% Confidence Interval of the Difference		p-value (<0.05)
	Mean ± SD	Mean ± SD		Lower	Upper	
CD4	23.25 ± 8.03	10.97±7.13	12.28	10.87	13.75	<0.001
CD4 count	429.58±247.03	200.72±217.33	228.86	185.84	271.87	<0.001
CD8per	42.68±11.56	69.22± 136.52	-26.54	-48.31	-4.76	0.02
CD8count	808.46± 500.71	941.62± 613.45	-133.16	-243.67	-22.65	0.02
CD4CD8	0.64± 0.37	0.22± 0.21	0.41	0.36	0.46	<0.001
Viral load	1251101± 4531777.9	24658638±7139096	-23407537	-34782392.67	-12032681	<0.001

P-value < 0.005 was considered statistically significant.

Table 4: Baseline Markers for Detection of Anemia in HIV and T.B Patients

	Male	Female	Mean Difference (MD)	95% Confidence Interval of the Difference		p-value (<0.05)
	Mean ± SD	Mean ± SD		Lower	Upper	
WBC	8.90± 1.98	7.64± 1.91	1.26	-0.35	0.95	0.040*
RBC	4.2± 0.81	4.1± 0.96	0.10	-0.93	0.29	0.300
HGB	9.9± 1.95	9.1± 2.07	0.81	-0.03	0.82	0.047*
HCT	40.21± 8.5	38.89± 7.18	-1.32	-3.03	0.39	0.013*
MCV	87.86± 14.05	87.62± 12.07	0.23	-2.39	2.86	0.86
MCH	26.14± 4.22	26.04± 3.82	0.09	-0.72	0.91	0.81
MCHC	29.78± 1.71	29.72± 1.52	0.06	-0.26	0.39	0.70
PLY	304.33± 90.16	293.95± 87.72	10.38	-8.08	28.84	0.26
ESR	65.93± 20.01	66.06± 19.46	-0.12	-4.22	3.69	0.95

P-value < 0.005 was considered statistically significant.

Discussion

In developing countries, TB is a major health problem and one of the leading causes of death among infectious diseases. The current study is unique in various perspectives. One, there is a scarcity of comparison between HIV and HIV+ TB patients based on the blood parameters and serology. Moreover, the comparison based on gender and comorbid TB is another important aspect that makes the findings of this study unique. The incidence of TB among HIV patients was found to be 30.1% among the patients visiting the testing facility in Lahore. This number may be higher than this if proper reporting and testing is ensured. In developing countries, negligence in testing for HIV remains one of the main issues and needs national-level policy measures to ensure its implementation and compliance per the international guidelines, which aim at reducing stigma and discrimination among HIV-positive patients (Ahmed et al., 2019; Parsons et al., 2011; Talati et al., 2009). According to Pakistan's National AIDS Control Program (NACP), the prevalence of HIV-positive patients is around 1.0%, and according to a rough estimate, there are over 150,000 persons in the country, of whom around 15.0% are unaware that they are HIV positive (Hospital, 2022). Regardless of this limitation, the prevalence of TB among HIV patients was observed to be in line with international studies, which also report this incidence to be 30.1% (Gelaw et al., 2019).

Pakistan, the 5th most populous nation around the globe, as of June 2019, 24,331 people living with HIV (PLHIV) were registered with the National AIDS Control Program (NACP). However, the estimates can be seven times this value, which is due to the under-reported and lack of willingness to diagnose. Vulnerable people to HIV in Pakistan are drug addicts (38.4%), transgender sex workers (7.1%), transgender people (5.6%), male sex workers (5.4%)and 2.2% in female sex workers (FSW) (Marfani et al., 2022; Naghavi et al., 2015). In the current study, which was a database analysis of one of the referral centres in Punjab, 2.54 % of the total sample (n=510) were transgender people. In Addition, the results of this study have revealed a significantly higher incidence of HIV and HIV with TB among the younger population ranging from the age of 15-45 years ($p=<0.001$). This growing incidence of HIV-positive cases among youth is alarming. In economically and politically unstable countries, various factors, i.e. poor health facilities, lack of screening, quackery practices with unsterilized surgical/dental equipment and rising IV drug users, can be one of the main factors resulting in HIV infection among the younger population (Khan et al., 2021; Marfani et al., 2022; Nguyen et al., 2001). However, in our records, this information was not disclosed, and due to the lack of synchronization in the national health records, we were unable to identify such information for further analysis and interpretation. This can be included as a recommendation point for the national database so that integration of information can be ensured and the assessment of the risk groups can be done in a timely manner. Another important fact is that most of the patients from our record were married [331(64.90%)], and a majority of 82.3%(n=420) were illiterate. This is an alarming situation and perhaps one of the silent reasons for the progression of HIV from the infected partner to the other one and then to the newborn (Adebayo et al., 2013). It is proven from the literature that patients with a lower education profile were found to have poor knowledge about HIV and its treatment. This emphasizes the need for individualized education programs for the patients so that their understanding of disease, its management and prevention measures can be enhanced.

Our result revealed that the CD4+T cell count is lower among *TB-HIV* co-infected subjects compared to *HIV* positive alone, and severe immune suppression has been observed in those with CD4+T cell count <200/ µl. These findings are in accordance with previous studies conducted on national and international geographical locales such as Nepal (27.3%) and Nigeria (34.5%) (Gyar et al., 2014). It has been observed that when the immune suppression is more marked, features of *TB* are presented with a much greater frequency of extra-pulmonary *TB.* The classical picture of TB is seen in immune-competent patients. The decrease of CD4+ indicates immunodeficiency due to the reactivation of latent TB, or a new TB infection occurs if a person is exposed to *M. tuberculosis* (Lawson et al., 2008). Low CD4+ T cell count in subjects was probably due to advanced stages of infection. Instead of antiretroviral therapy, *HIV*-positive individuals with CD4+ T cells < 200 cells/µl of blood are more susceptible to *tuberculosis* than *HIV*-positive individuals with >500

CD4+T cells/µl of blood (Aibibula et al., 2016). This decline of CD4+ T cells and leukocytes may be correlated with the severity of both *tuberculosis* and *HIV*/AIDS and leads to reduced cellular immunity against *M. tuberculosis* and *HIV* -co-infection. Hematological indices such as lymphocytes and their subsets, for example, CD8+T cells and CD4+T cells, have a vital role in humoral immunity and cellular immunity. For opportunistic infections, the prophylactic drugs should be started, and the CD4+T cell count demonstrates stop. Cellular immunity against intracellular microorganisms just like *M. tuberculosis* is depleted due to the reduction of CD4+ cells destroyed by *HIV* (Li et al., 2019). Cell-mediated immunity contains both CD4+ and CD8+ T lymphocytes that play an essential role in controlling intracellular microbes. Studies conducted in low-income countries have reported higher CD4+T cell counts. These variations may depend on diet, ethnicity, gender, geographical area, genetic, and environmental factors. The poor population is more susceptible to TB than the rich one due to their diet and immune status (Lawson et al., 2008). $CD4^+$ is considered a hallmark for the diagnosis and prognosis of HIV and a predictor of immune status. CD4 and CD8 had a high degree of association with the viral load, as shown by our study, portraying a strong correlation observed between CD4+ and viral load (Eggena et al., 2005). CD4+ and CD8+ ratio is considered an independent risk factor for the development of TB, as has been shown by a study performed in 2020 (Wolday et al., 2020). Our study has reported similar findings because the patient has a CD4+/CD8+ ratio of less than 0.3 81.1% and suffers from TB and has the worst survival. CD4+ and CD4+/CD8+ ratios were considered good predictors for the prognosis of HIV.

Erythrocyte sedimentation rate is another biomarker considered while assessing the severity of infection. Results of this study have shown that the ESR was significantly higher among patients with HIV with TB (MD= -17.76; [-21.56 ─ -13.97], p=<0.001) (Batool et al., 2022; Ukpe and Southern, 2006). In Addition, the prevalence of anemia among HIV was 66%, while HIV and TB co-infected persons showed 75.3% anemia (Yaranal et al., 2013). It was also observed that female patients are observed to have significantly lower levels of hemoglobin in comparison to men. Thrombocytopenia is 6.17% in our study of *HIV* patients without TB. Our finding shows a lower rate of thrombocytopenia compared to the previous studies, which show 53.3% thrombocytopenia in *HIV* patients with TB (Baghel et al., 2021).

The prevalence of TB with HIV(WHO, 2022) was quite low in the past years, but now increasing in recent years,41.25% were recorded (WHO, 2022). Poor health literacy and the influence of sociodemographic factors, along with chronic infection, can be the main factor resulting in this increase (Shaw et al., 2018).

Limitations:

This was a retrospective study and one of the main limitations of retrospective study is that the researchers are unable to personally see the outcomes and patient-related parameters. In Addition, we didn't have data related to smoking, drug abuse and other co-morbidities which might have assisted in creating a better association of the pathological and hematological data of the HIV patients with and without TB. we gathered the available data and analyzed it. If this data is available, then the chances are there that we will elaborate the discussion and conclusion efficiently.

Conclusion

The findings of this study have revealed that *HIV/TB* co-infection has an impact on the immune system, resulting in the deactivation of the hosts' immune responses. Thus, *Tuberculosis with HIV* result in the depletion of $CD4^+$ cells and result in susceptibility to other infections. In the current scenario, most cases of *TB-HIV* co-infection have CD4+ count and Hb lower compared to only *HIV*-infected patients. Male has a high prevalence of *TB-HIV* co-infected compared to females. For optimal therapy, the research suggests that HIV patients co-infected with TB be evaluated regularly.

Conflict of Interest:
The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

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