JURNAL MEDIA PENELITIAN DAN PENGEMBANGAN KESEHATAN
Vol 32 No 4, Desember 2022

IMMUNOLOGICAL AND HEMATOLOGICAL STATUS PROFILE IN TUBERCULOSIS-HUMAN IMMUNODEFICIENCY VIRUS COINFECTED PATIENTS

Profil Status Imunologis dan Hematologi Pada Pasien Koinfeksi Tuberculosis-Human Immunodeficiency Virus

Rizana Fajrunni'mah [1*], Niniek Dwi Febriyana [1]
[1] Department of Medical Laboratory Technology, Politeknik Kesehatan Kementerian Kesehatan Jakarta III, Indonesia
*Email: rizana.fajrunnimah@gmail.com

ABSTRAK

Infeksi oleh Human Immunodeficiency Virus (HIV) merupakan masalah di seluruh dunia termasuk Indonesia. Tuberkulosis (TB) adalah infeksi oportunistik tersering pada penderita AIDS. Status imun pada penderita terinfeksi HIV dapat dinilai melalui pemeriksaan jumlah absolut limfosit T CD4+, dan ini merupakan standar untuk menilai dan menentukan derajat imunodefisiensi. Penurunan progresif limfosit T CD4+ berhubungan dengan progresifitas penyakit. Penelitian ini bertujuan mengetahui profil status imunologis yang dilihat dari jumlah CD4 dan hematologi yang dilihat dari jumlah leukosit, hitung jenisnya, hemoglobin, laju endap darah, dan trombosit. Penelitian ini menggunakan rancangan kuantitatif dengan desain analitik observasional (cross sectional).Jumlah data yang diambil sebanyak 45 data. Data dianalisis menggunakan analisis korelasi. Jumlah CD4+ pasien ko-infeksi TB-HIV terbanyak menunjukkan imunodefisiensi berat (jumlah CD4+ <200 sel/ mm3) yaitu 73,3% pasien dengan rerata 118,4 sel/ mm3. Terdapat 86,5% mengalami anemia. Hitung jumlah dan jenis leukosit terbanyak yaitu jumlah leukosit normal sebanyak 59,5%, sebanyak 61,5% mengalami neutrofilia, sebanyak 65,4% mengalami limfopenia, monosit dalam rentang normal yaitu sebesar 57,7%. Sebanyak 73,7% mengalami peningkatan dengan rerata laju endap darah pasien mencapai 46,58 mm/jam. Jumlah trombosit terbanyak dalam rentang normal yaitu sebesar 68,6%. Terdapat korelasi yang signifikan antara kadar hemoglobin, hitung jumlah neutrofil, limfosit, dan monosit dengan hitung jumlah CD4+ dengan nilai p berturut-turut yaitu 0,001; 0,000; 0,000; 0,012. Status imunologis dan hematologi pasien koinfeksi TB-HIV mengalami penurunan, dan terdapat korelasi yang signifikan antara kedua profil tersebut, sehingga perlu meningkatkan pemeriksaan laboratorium secara menyeluruh.

Kata kunci: CD4+, hemoglobin, hitung jenis leukosit, HIV-TB, laju endap darah, trombosit

ABSTRACT

Human Immunodeficiency Virus (HIV) is problem throughout the world, including Indonesia. Tuberculosis (TB) is the most common opportunistic infection in AIDS sufferers. The immune status of HIV-infected sufferers can be assessed by examining the absolute number of CD4+ T lymphocytes, and this is the standard for assessing and determining the degree of immunodeficiency. Progressive decline in CD4+ T lymphocytes is associated with disease progression. This study aimed to determine the profile of immunological status as seen from the CD4 count and hematology as seen from the number of leukocytes, count of types, hemoglobin, erythrocyte sedimentation rate and platelets. This research used quantitative design with an observational analytical design (cross-sectional). The amount of data taken was 45 data. Data were analyzed using correlation analysis by statistical tests. The results showed 73.3% severe

immunodeficiency (CD4+ count <200 cells/mm3) with an average of 118.4 cells/mm3. There were 86.5% anemia. The number of normal leukocytes was 59.5%, 61.5% had neutrophilia, 65.4% had lymphopenia, 57.7% monocytes were in the normal range. 73.7% experienced an increase with the average erythrocyte sedimentation rate of patients reaching 46.58 mm/hour. The highest number of platelets was within the normal range, namely 68.6%. There was a significant correlation between hemoglobin levels, neutrophil, lymphocyte and monocyte counts and CD4+ counts with p-values respectively of 0.001; 0,000; 0,000; 0.012. The immunological and hematological status of TB-HIV co-infected patients has decreased, so it is necessary to increase comprehensive laboratory examinations if the facilities and infrastructure are available so that treatment is more effective.

Keywords: CD4+, erythrocyte sedimentation rate, hemoglobin, HIV-TB, leukocyte count, platelets

INTRODUCTION

Infection by Human Immunodeficiency Virus (HIV) is a worldwide problem, including Indonesia. Globally there are an estimated more than 36 million people living with HIV and AIDS in the end of 2017.[1] In Indonesia until Desember 2017 there were 28,623 HIV sufferers and 102,667 AIDS sufferers. The highest number of HIV infections was in DKI Jakarta with 51,981, followed by East Java with 39,633, Papua with 29,083, West Java with 28,964, and Central Java with 22,292. HIV infection in Indonesia is likely to continue to increase in the next five years due to the increasing number of unprotected sexual relations and HIV transmission through injecting drug abusers, psychotropic substances and addictive substances. It is feared that a new epidemic will spread and the number of AIDS cases being treated will increase. Deaths from AIDS among the productive age population will increase [2].

People living with HIV (PLWH) can develop opportunistic infections. This happens because of the vulnerable conditions in HIV patients [3]. Tuberculosis (TB) is the most common opportunistic infection in AIDS patients. The mortality proportion of HIV/AIDS patients hospitalized in Cipto Mangunkusumo Hospital Jakarta is 23.4%. The cause of AIDS-related mortality was 92.3% with the most common cause being pulmonary tuberculosis [4]. The HIV/AIDS pandemic in the world adds to the TB problem. Co-infection with HIV will increase the risk of TB incidence significantly. In addition, TB is the main cause of death in people living with HIV (about 40-50%). This high mortality, especially in smear-negative pulmonary TB and extra-pulmonary TB, is most likely due to delays in TB diagnosis and therapy. Most people who are infected with TB germs (*Mycobacterium tuberculosis*) do not get TB because they have a good immune system. This infection without becoming sick is known as latent TB infection. However, in people whose immune systems have decreased, such as people living with HIV-AIDS (PLWHA), the latent TB infection can easily develop into active TB disease. Only about 10% of people who are not infected with HIV if infected with TB germs will become ill with TB throughout their life; while in PLWHA, about 60% of PLWHA infected with TB germs will become sick with active TB [5]. Based on WHO estimates, the number of TB-HIV co-infected patients in the world is estimated to be as many as 14 million people. Approximately 80% of TB-HIV co-infected patients are found in Sub-Saharan Africa, but there are about 3 million TB-HIV co-infected patients in Southeast Asia. From this description it is clear that the HIV epidemic is very influential on the increase in TB cases.

Opportunistic infections can also cause anemia in people with HIV. Tuberculosis infection is the most common opportunistic infection in HIV infection and is known to cause anemia on chronic disease (ACD). Anemia is a complication that often occurs in people with HIV [6]. Anemia in people with HIV/AIDS has a huge impact on the quality

of life of patients. Research shows a decrease in quality of life in HIV patients with anemia. Anemia is also independently associated with disease progression and decreased survival. Interventions to prevent anemia can increase the survival of HIV-infected patients. The decrease in hemoglobin levels reflects the speed of disease progression and the predicted prognosis in cohorts with different demographics [7].

An increased erythrocyte sedimentation rate (ESR) (≥100mm/hour.) is associated with TB, Hodgkin's disease, multiple myeloma, and chronic inflammatory or infectious conditions. In a study in Nigeria, the ESR in TB-HIV co-infected patients was 105-165 mm/hour. The mean higher ESR values in TB-HIV coinfected patients [8]. Research by Vazques, showed that there was no significant relationship between erythrocyte sedimentation rate and clinical status of patients and CD4 levels. However, a study by Ndakotsu, showed the opposite result where the erythrocyte sedimentation rate can be used in monitoring HIV/AIDS [9]. In Wesnawa's study [10] the majority of TB-HIV coinfected patients experienced an increase in ESR values, namely 34 patients (97.1%). Thrombocytopenia is also the most common complication of HIV infection [11].

Lymphoid organs are the main reservoir of HIV, and monocytes and macrophages are the main targets of HIV infection. CD4+ T lymphocytes, both infected and uninfected with HIV, migrate to lymph nodes when an immune response occurs. In this situation, uninfected CD4+ lymphocyte cells will come into contact with HIV-infected Antigen Presenting Cells (APCs) causing activation of CD4+ T cells. After activation, CD4+ T cells are recirculated to the periphery and undergo apoptosis. Thus, APCs such as monocytes and macrophages play an important role in immunosuppression due to HIV infection [12].

Immune status in adult HIV-infected patients can be assessed by examining the absolute number of CD4+ T lymphocytes, and this is the standard for assessing and determining the degree of immunodeficiency. A progressive decrease in CD4+ T lymphocytes is associated with disease progression and an increase in opportunistic infections and mortality [13]. CD4 lymphocyte counts are expensive, and are often not available in district hospitals. Laboratory tests are needed to help clinicians predict disease progression and monitor the patient's disease course. According to WHO guidelines, if the CD4 lymphocyte count is not available, the total lymphocyte count (1200/mm^3) can be used as a substitute for CD4 in starting ARVs in patients with HIV. There are several studies in patients with HIV that have shown an association of total lymphocyte count (<1200/mm^3) with mortality. However, CD4 counts remain the best in the management of patients with HIV [9].

In dealing with TB-HIV cases, knowledge about the characteristics of TB-HIV co-infected patients is also required. Based on this background, this study aims to determine the profile of immunological status seen from CD4+ levels as well as hematology seen from the number of leukocytes and their type count, hemoglobin, platelets, erythrocyte sedimentation rate in TB-HIV coinfected patients because the parameters may be different in patients with TB-HIV coinfection.

METHODS

This study used a quantitative research design with descriptive and analytical observational design (cross-sectional). The subjects or population of the study were TB-HIV co-infected patients at Tarakan Hospital, Central Jakarta, Indonesia in Juni-September 2018. The sample was data on TB-HIV co-infected patients at Tarakan Hospital, Central Jakarta in the period January-December 2017 totaling 45 data. Data was collected through laboratory data and patient medical record data. The data obtained from the results of examinations in the laboratory are as follows: Venous blood samples are processed using an automated blood analyzer to determine hemoglobin levels, count leukocytes, platelets, and ESR. The number of CD4 T lymphocytes was

determined using a flow cytometry technique to quantify the number of CD4+ T lymphocytes. WHO made an immunological classification to assess the degree of immunodeficiency into four categories: no significant immunodeficiency (CD4+ > 500 cells/mm3), mild/mild immunodeficiency (CD4+ 350-499 cells/mm3), advanced immunodeficiency (CD4+ 200-349 cells/mm3), and severe/severe immunodeficiency (CD4+ < 200 cells/mm3). Progression of disease to AIDS stage or death has increased with CD4 cell count < 200 cells/mm3 [13]. In conducting the research, the ethical clearance to the Jakarta Health Polytechnic Ethics Commission III and asked for permission to the relevant research agency or institution to obtain research approval and had obtained an ethical permit with no. KEPK-PKKJ3/182/IV/2018. The data collected were analyzed descriptively, both in the form of percentage and mean, median, mode, and standard deviation. After that, correlation analysis was carried out, because the data distribution was normal, then Spearman correlation analysis was used.

RESULT

The sample of this study is data on HIV patients with confirmed TB coinfection from medical records. The number of TB-HIV coinfected patients recorded for the 2017 period was 119, but in this study only 45 patient data were obtained in the laboratory results records, and not all of them had complete records of examination parameters. The following is the result of the descriptive analysis.

Table 1. Characteristics of HIV-TB Coinfected Patients

Variable	Frequency (n=45)	%
Gender		
- Men	30	66.7
- Women	15	33.3
Age (years old)		
- <15	3	6.7
- 15-35	26	57.8
- >35	16	35.6

Table 1 shows HIV/AIDS patients with Tuberculosis coinfection suffered more men as much as 66.7%. The age of HIV/AIDS patients with TB coinfection was highest at the age of 15-35 years, namely 26 people (57.8%). The average age of the patients was 33.6 years with the lowest age being 8 years and the highest being 56 years.

The CD4 count of HIV/AIDS patients with TB coinfection tends to be low. From table 2, a total of 73.3% of patients had severe immunodeficiency (CD4 count <200 cells/mm3). The average CD4 cell count in these patients was 118.4 cells/mm3. The highest percentage of Hb levels in 37 HIV/AIDS patients with TB coinfection was 86.5% had anemia with Hb levels <12 g/dL. The patient's average Hb level reached 10.51 g/dL with the lowest level of 4.2 g/dL and the highest level of 14.4 g/dL. The highest number of leukocytes in 37 HIV/AIDS patients with TB coinfection was 59.5% in the normal range (4000 – 11,000 cells/mm3 blood). The average leukocyte is 7172.9 cells/mm3 of blood. The data, which is complete with the count of leukocyte types, namely the count of neutrophils, lymphocytes, and monocytes is only 26 data.

Table 2. CD4 Count, Hb levels, the Number And Type of Leukocytes, Erythrocyte Sedimentation Rate, Platelet Count in HIV-TB Coinfected Patients

Variable	Frequency	%
CD4+ count		
- <200 cells/mm3	33	73.3
- 200-349 cells/mm3	10	22.3

Variable	Frequency	%
- 350-500 sel/mm3	1	2.2
- >500 cells/mm3	1	2.2
Total	45	100
Hb levels		
- Anemia	37	86.5
- Normal	8	13.5
Total	45	100
Leukocytes		
- Leukopenia	8	21,6
- Normal	22	59,5
- Leukocytosis	7	18,9
Total	37	100
Neutrophils		
- Neutropenia	7	26,9
- Normal	3	11,5
- Neutrofilia	16	61,5
Total	26	100
Lymphocytes		
- Lymphopenia	17	65,4
- Normal	2	7,7
- Lymphocytosis	7	26,9
Total	26	100
Monocyte		
- Monocytopenia	2	7,7
- Normal	15	57,7
- Monocytosis	9	34,6
Total	26	100
Erythrocyte sedimentation rate		
- Normal	5	26.3
- Increase	14	73,7
Total	19	100
Platelet count		
- Normal	24	68.6
- Trombocytopenia	11	31.4
Total	35	100

Table 2 shows that the majority of HIV/AIDS patients with TB coinfection, as many as 61.5% had neutrophilia, 65.4% had lymphopenia, and 57.7% had monocytes in the normal range. The highest percentage of erythrocyte sedimentation rate in 19 HIV/AIDS patients with TB coinfection was 73.7% experiencing an increase in erythrocyte sedimentation rate. The patient's average erythrocyte sedimentation rate reached 46.58 mm/hour. As many as 35 patients who did the platelet count examination, the highest percentage was in the normal range, namely 68.6% with an average of 242,458.24 / L and a lower limit of 65 / L.

Table 3. Correlation Results of Hematological Status with Immunological Status

Variable		p-value	r
CD4+ count	Hb levels	0.001	0.510
	Leukocytes	0.092	0.281
	Neutrophils	0.000	-0.720
	Lymphocytes	0.000	0.744
	Monocyte	0.012	0.485

Variable		p-value	r
	Erythrocyte sedimentation rate	0.868	0.041
	Platelet count	0.373	0.151

Based on the table 3, it can be seen that there is a correlation between hemoglobin levels and CD4 cell count with a p value of 0.001, a correlation between the number of neutrophils and lymphocytes with a CD4 cell count with a p value of 0.000, a correlation between monocyte count and CD4 cell count with a p-value of 0.012. The data used for this correlation analysis did not all 45 sampel, but some of them only 26.

DISCUSSION

1. Characteristics of HIV-TB coinfected patients

Based on the results of the study, the highest percentage of sex was male (66.7%) compared to female (33.3%). Several studies showed almost the same results, among others, that the majority of TB-HIV patients at Cipto Mangunkusumo Hospital Jakarta were male (81.2%)[14]. Likewise, the group of HIV-TB coinfected patients at Sanglah Hospital Bali in 2013 was mostly found in men with 21 people (77.7%) [15]. However, somewhat different results were obtained in Widiyanti's study [16] which stated that the group of HIV-TB coinfected patients at Mitra Masyarakat Hospital in Timika Papua was more common in women as much as 78.8%. This is also in accordance with the condition of HIV prevalence in Indonesia until the end of 2017 which has a ratio between men and women of 2:1, and the prevalence of AIDS in men is 57% [17].

The group of TB-HIV coinfected patients aged 15-35 years had the highest percentage of 26 people (57.8%). A total of 35.6% in the age group > 35 years. The average age of the patients was 33.6 years with the lowest age being 8 years and the highest being 56 years. Most HIV sufferers are in the 25-49 year age group by 69.2% [17]. The results of this study are the same as Soraya's [15] study which stated that TB-HIV patients were more commonly found in patients aged 15-35 years by 15 people (55.5%) compared to those aged >35 years, namely 12 people (44.5%). The mean age of the patients was 34.7 years. Likewise with Permitasari [18] who reported that TB-HIV co-infected patients at dr. Kariadi Hospital Semarang in the age group 15-35 years had the highest percentage of 49 people (59%) and the age group >35 years (41%) . In Widiyanti's study [16] it was found that the age group of 15-35 years was the largest age group, as many as 35 people (87.5%) patients who were co-infected with tuberculosis - HIV. Jayakody [19] reported that there were more pulmonary TB patients aged <45 years than those aged ≥45 years. Pulmonary tuberculosis is common at the age of <45 years due to high mobility so that the risk of contracting it is high. It is estimated that globally about 10 million people (range, 9.0-11.1 million) had TB disease in 2017 consisting of 5.8 million men, 3.2 million women and 1.0 million children. There were cases in all countries and age groups, but overall 90% were adults (age 15 years), 9% were people living with HIV (72% in Africa) and two thirds were in eight countries: India (27%), China (9%), Indonesia (8%), Philippines (6%), Pakistan (5%), Nigeria (4%), Bangladesh (4%) and South Africa (3%)[3].

2. Count CD4 of HIV-TB coinfected patients

TB-HIV coinfected patients showed the most rates of 73.3% severe immunodeficiency (CD4 count <200 cells/mm3). A total of 22.2% with advanced immunodeficiency (CD4 count 200-349 cells/mm3). The average CD4 cell count in these patients was 118.4 cells/mm3. The study of Nzou [20] also showed that 72% of the CD4 cell counts of HIV-coinfected HIV patients were below 200 cells/μL, with the mean CD4 cell count of patients being 104.5 cells/μL. This is similar to what was stated [14] that the

majority of TB-HIV co-infected patients had a low CD4 count < 200 cells/mm3 which was 78%. In Widiyanti's study [16] patients with HIV/AIDS coinfected with tuberculosis showed the most CD4 count values <100 cells/μL (87.3%), with an average CD4 cell count of 49.17 cells/μL. The mortality rate of TB/HIV patients during hospitalization was 29.8%. Most of the patients had CD4 levels <200 cells/uL [21]. The CD4 count of HIV positive patients in the Rajkondawar study [22] was found to be <100 cells/μL (6%), 101-200/μL (34%), 201-350/μL (43%), >350/μL (17%). The majority of patients with opportunistic infections are <350 cells/μL.

CD4 count is a way to assess the immune status of HIV/AIDS patients. A CD4 count complements the clinical examination to determine which patients require prophylactic treatment, opportunistic infections and ARV therapy. The average CD4 decline is about 70-100 cells/mm3/year, with an increase after ARV administration of between 50-100 cells/mm3/year [5]. TB accelerates the severity (progressivity) of HIV infection and when TB is diagnosed, almost all patients with advanced HIV infection are characterized by low CD4 cell count and high viral load or stage 3 and 4 HIV according to WHO [23]. CD4 which is a helper T lymphocyte is the coordinator of the body's immune response, in preparation for B cells to produce antibodies, in helping cellular immune responses to antigens. CD4 is the primary target of the HIV virus. The presence of HIV infection causes a weak immune response and the body's ability to fight foreign antigens, so that the body is susceptible to infection characterized by the emergence of various types of opportunistic infections including TB. This TB infection lowers CD4 cells and worsens immune status so that AIDS progresses more quickly [24].

3. Hemoglobin levels of HIV-TB coinfected patients

The hemoglobin levels of the HIV-TB coinfected patients in this study were mostly anemic with Hb levels <12 g/dL of 86.5%. The patient's average Hb level reached 10.51 g/dL, which was below the normal limit for both men and women. Even the lowest level is up to 4.2 g/dL and the highest is 14.4 g/dL. The sample with the lowest Hb level had CD4+ count <200 cells/mm3. This is almost the same as Permitasari's study [18] which found that the majority of HIV patients with TB coinfection also had Hb levels <12.5 g/dL as much as 97.3% with an average Hb of 9.7 g/dL. Hb levels of 10-12.49 g/dL are the highest percentage of Hb levels found in TB-HIV patients, namely 13 people (48.1%), Hb levels <10 g/dL as many as 9 people (33.3%) with The patient's average Hb level reaches 10.5 g/dL. A total of 55.5% of HIV-TB coinfected patients had Hb levels <12 g/dL [16].

There are various causes of anemia. Its pathophysiology involves three mechanisms: (1) decreased red blood cell (RBC) production: opportunistic infections, direct effects of HIV infection itself, myelosuppressive drugs, decreased erythropoietin production, hypogonadism; (2) increased RBC destruction: autoimmune hemolytic anemia, thrombotic microangiopathy, disseminated intravascular coagulation; and (3) ineffective red blood cell production: folic acid and vitamin B12 deficiency. Nutrient deficiencies such as vitamins and iron deficiency are common in developing countries [25]. Anemia can occur in all phases of HIV infection. Incidence and severity correlate with disease progression. Anemia was stated if the hemoglobin concentration was less than 12 g/dL for women and 14 g/dL for men [25]. The prevalence of anemia in HIV-AIDS is quite high with the risk factors that play a role are low BMI, CD4 <150/mm3, and oral candidiasis. Hemoglobin level less than 10 g/dL is also an independent predictor of mortality in HIV/AIDS patients hospitalized in RSCM [4].

Anemia in HIV/AIDS can be a marker of HIV disease progression because it is one of the clinical features of most opportunistic infections. This occurs partly because of micronutrient deficiencies and impaired erythropoietin production. In addition, various drugs used by HIV patients also play a role in the onset of anemia, for example the antiretroviral Zidovudine [26]. In Puspitasari's study [4] of 211 patients who had a

hemoglobin level of less than 10 g/dL, 76.8% of them were treated for opportunistic infections. Taha [27] states that anemia will exacerbate immune deficiency and increase the risk of tuberculosis. The Kufa study [28] stated that hemoglobin levels below 10 g/dL increase the likelihood of developing tuberculosis three times.

4. The number and count of leukocyte types in HIV-TB coinfected patients

Counting the number of leukocytes in this study, the majority had a normal number of 59.5% with an average leukocyte count of 7172.9 cells/mm3 of blood. This is similar to the study of Rajkondawar [22] that the mean leukocyte count in HIV patients ranged from 5788 cells/L to 8736 cells/L. Leukopenia or a decrease in the number of leukocytes in this study was found to be 22.9%. Leucopenia was seen in 20.8% of cases. Things that can cause leucopenia are bone marrow failure, severe infections, and vitamin B12 and iron deficiency. While the patients who experienced leukocytosis were 18.9%. Circumstances that can cause an increase in the total leukocyte value (leukocytosis) are one of the conditions of infection in which leukocytes will increase to initiate and maintain the body's defense mechanism to overcome infection [29].

An increase in the number of leukocytes in TB patients indicates the formation of a lot of leukocytes to fight the bacteria that cause TB disease in the overall phagocytosis process [5]. The leukocyte profile of pulmonary TB patients showed leukocytosis in 44.34% of patients, leukopenia in 3.90% of patients, neutrophilia in 63.21% of patients, eosinophilia in 3.77% of patients, monocytosis in 23.58% of patients, and lymphopenia in 69 ,81% of patients. The conclusion is that an increase in leukocytes, neutrophils and monocytes as well as a decrease in lymphocytes is commonly found in pulmonary TB patients at the Respira Lung Hospital, Yogyakarta [30].

Table 2 shows that the majority of HIV/AIDS patients with TB coinfection, as many as 61.5% had neutrophilia. Goyal [31] obtained neutrophil examination results in HIV/AIDS patients, namely 27 patients had normal neutrophils, 10 showed neutropenia and 13 had neutrophils (27.87%). An increase in the number of neutrophils or neutrophilia can be caused by an inflammatory response to bacteria and an immunological reaction with T-lymphocyte mediators [32]. The main function of neutrophils is phagocytosis (killing and digesting microorganisms). Acute bacterial infection and trauma trigger the production of neutrophils. This increase in the number of neutrophils can be referred to as “shift to the left” which indicates an acute bacterial infection [29].

Patients who experienced neutropenia were 26.9%. Neutropenia (neutrophils < 1000 cells/mm) often occurs in HIV-infected patients with a prevalence of 13% to 44%. Neutropenia is more common with low CD4+ lymphocyte counts. However, in Suastika's study [33] , neutropenia was not found. This is the same as the study of Dikshit et al, but different from the study of Attili et al where 22.7% of cases had neutropenia. Decreased neutrophils can be caused by nutritional deficiencies [29]. Neutropenia as well as anemia are frequently observed in patients with HIV infection. Up to 70% of patients in the advanced stage of AIDS show a low neutrophil count. Worsening HIV disease, indicated by decreased CD4 cell counts and increased levels of HIV-1 RNA, has been associated with the development of neutropenia [25]. Neutropenia may result with disease progression or opportunistic infections eg acute or chronic bacterial infection due to inhibition of granulopoiesis by the virus itself, marrow infiltration by infectious organisms or neoplasia, drug side effects, autoimmune neutropenia, and hypersplenism. This is in agreement with the previously reported literature [31].

This study found that 65.4% of HIV-TB coinfected patients had lymphopenia (a decrease in lymphocytes to <25%). An increase in lymphocytes above 33% in 26.9% of patients. This is similar to Wesnawa's study [10] that the total lymphocyte count value in HIV patients with TB infection was found to be the majority experienced a decrease in the total lymphocyte count <1000 cells/mm3 (62.9%) [10]. According to Soraya's

research [15] the number of lymphocytes in HIV/AIDS patients with TB coinfection was less than 15 as many as 48.1%, between 15 and 40 as many as 48.1%, while those with more than 40 were only 3.8%. Goyal [31] stated that in HIV/AIDS patients, 15 patients had normal lymphocyte counts, 27 showed lymphopenia and 8 had lymphocytosis. A total of 45.9% had lymphopenia. Meanwhile, Agustina's research (2012) on TB patients found that the number of lymphocytes < 15% was 8 people (38.1%), between 15% to 40% were 10 people (47.6%) and > 40% were 3 people (14.3%) [34].

Lymphopenia (absolute lymphocyte count less than 1500 cells/mm3) is seen in 65% of cases. Treacy et al reported lymphopenia in 14 cases. However Tripathi et al observed a lower number of cases of lymphopenia (25.6%) [35]. In the study Guadagnino [36] found that absolute lymphocyte counts were lower in patients with active TB than in other HIV-uninfected patients. Regarding statistical analysis, uninfected active tuberculosis patients had a significantly lower absolute number of lymphocytes compared to latently infected patients. Decreased lymphocytes may be due to sepsis and immunodeficiency disease [29]. Lymphopenia increases with reduction in CD4+ cell count with progression of opportunistic disease or infection [31].

Each clinical stage significant difference in progression to AIDS and mortality was predicted by a total lymphocyte count above or below 1250 cells/L. Survival and progression to AIDS occurred at similar rates in patients with a total lymphocyte count of 1250 cells/μL. Overtime CD4 count patterns are more important than single CD4 cell counts. CD4 cell counts generally decline as HIV progresses. Therefore, it is more valuable to evaluate a series of CD4 counts than a single CD4 count [22].

Lymphocytes consist of 2 types, namely T cells (thymus) and B cells (bone marrow). T cells play a major role in cellular-type immune reactions, while B cells play a role in humoral immunity (antibody production). T cells are killer cells, suppressor cells, and T4 helper cells. An elevated lymphocyte count indicates the presence of a chronic bacterial infection or an acute viral infection [29]. An increase in the number of lymphocytes or lymphocytosis is accompanied by a decrease in the number of neutrophils or neutropenia. Neutropenia can be caused by the influence of drugs such as anti-inflammatory drugs, antibiotics and severe anti-bacterial infections [32]. An increase in the number of lymphocytes or lymphocytosis can indicate an inflammatory response to the bacteria that cause TB disease and indicate a TB healing process. Interleukin-2 which has stimulated T lymphocytes that become reactive T cells against *Mycobacterium tuberculosis* will then produce IFN, TNF, IL-2, IL-4, IL-5, IL-10 similar to cytokines produced by T cells, in addition to supernatant T cells stimulated by *Mycobacterium tuberculosis* will increase macrophage aggregation and subsequently play a role in the formation of granulomas. Activated macrophages show increased function in phagocytosis [37].

Counting the types of monocytes in this study, the majority were in the normal range, namely 57.7% and 34.6% had monocytosis. Monocytes are phagocytic cells that can fight bacteria just like neutrophils. Monocytes produce interferon, which is the body's endogenous immunostimulant. Monocytes can be produced rapidly and last longer than neutrophils [29]. The absolute monocyte count was higher in patients with active tuberculosis than in other uninfected HIV patients. Regarding monocytes, uninfected active tuberculosis patients had significantly higher absolute numbers than healthy subjects [36].

An increase in the number of monocytes or monocytosis can be caused by bacterial infection by *Mycobacterium tuberculosis* [32]. The increase in the number of monocytes can occur because monocyte cells play an important role in the immune response to TB infection, so that when the bacteria that causes TB disease enter the body, monocytes multiply to phagocytize it. The bacterium *Mycobacterium tuberculosis* that causes TB disease has phospholipids in its cells, so that some of the phospholipids from Mycobacterium tuberculosis are degraded by monocytes and macrophages in the

tissue, causing the transformation of these cells into epithelioid cells. Monocytes are the main cells in the formation of tubercles. The activation of tubercles formation can be illustrated by the presence of monocytosis in the blood [38].

5. The erythrocyte sedimentation rate of HIV-TB coinfected patients

The results of laboratory examinations that the erythrocyte sedimentation rate in this study were 14 patients (73.7%) experienced an increase (>15 and 20 mm/hour) with the mean erythrocyte sedimentation rate of 46.58 mm/hour. This was also conveyed by Wesnawa (2016) that the majority of TB-HIV coinfected patients experienced an increase in the ESR value, namely 97.1% and 51.4% experienced an increase in ESR >100mm/hour, while an increase in ESR <100mm/hour was 16 people (45.7%).

An increased erythrocyte sedimentation rate (ESR) (≥100mm/hour) is associated with TB, Hodgkin's disease, multiple myeloma, and chronic inflammatory or infectious conditions. In a study in Nigeria, the ESR in TB-HIV co-infected patients was 105-165 mm/hour. The mean ESR value was higher in TB-HIV co-infected patients [8]. Research by Vazques, showed that there was no significant relationship between erythrocyte sedimentation rate and clinical status of patients and CD4 levels. However, a study by Ndakotsu, showed the opposite result where the erythrocyte sedimentation rate could be used in monitoring HIV/AIDS [9].

Increased ESR also occurs in tuberculosis patients because it is a chronic infection. This infection is the first intracellular bacterial infection encountered by neutrophils. Neutrophils phagocytize bacteria by using mats containing a number of antibacterial factors such as elastase, catephsin, myeloperoxidase, and lactoferrin. Phagocytosis activity will activate proteins from the complement system which are acute phase proteins that will increase erythrocyte aggregation to form rouleaux thereby increasing the erythrocyte sedimentation rate [39]. In Ningrum's study [40] it was found that the ESR value in new cases of pulmonary TB patients increased by 94.3% with a median value of 68 mm/hour. This study is similar to that of Rohini [41] ho got an average LED value of 75.85 mm/hour or Niu [42] which got an average LED value of 31.5 mm/hour.

6. Platelet levels of HIV-TB coinfected patients

The results of this study showed that patients with TB-HIV coinfection had platelets in the normal range of 68.6%. There were 31.4% experiencing thrombocytopenia with an average of 242,458.24/µL and the lowest value was 65/µL. The mean platelet count was 239.8 ± 101.3 × 103/µl (range 13.6–685 × 103/µl). Similar results were also obtained from Pramudianti's study [43] which found that most of the subjects (16 people) of HIV/AIDS patients still had normal platelet counts. Subjects with thrombocytopenia found only one woman with a platelet count of 143×103/µL, a diagnosis of HIV and had not received ARV treatment. The mean platelets obtained in the study of Santis [25] was 218,639 / L. Patients with more severe disease (CD4 <200/ml) had slightly lower platelet counts. In Suastika's study [33] , the frequency of thrombocytopenia was 6 (5.5%).

Certain infections can be associated with thrombocytopenia, as they can affect both platelet production and lifespan. Cytomegalovirus and Epstein-Barr virus infection can cause transient thrombocytopenia. HIV infection is probably the most important infection causing thrombocytopenia in North America. Thrombocytopenia is thought to be related to viral toxicity to the bone marrow directly or also mediated by immune mechanisms [44].

Thrombocytopenia affects about 40% of HIV-infected patients. A low platelet count may be the only haematological abnormality and does not appear to affect the prognosis. Thrombocytopenia is the first clinical manifestation of HIV infection, and is not expected to result in significant immunodeficiency. The prevalence of thrombocytopenia

has been reported to be higher in people with AIDS, the elderly, homosexuals, and injecting needle users [25]. Decrease in the number of platelets or thrombocytopenia in HIV patients/patients can be caused by immune and non-immune factors, as well as a combination of autoimmune and prevention of producing (inhibition of production) of platelets. Thrombocytopenia in HIV-1 patients, if without leukopenia or anemia, may be caused by increased nuclear destruction (nuclear destruction) and intracytoplasmic platelets. Patients do not show clinical symptoms and the incidence increases with the duration of the disease and the progression of AIDS [45].

Another mechanism of thrombocytopenia can be caused by autoimmune, namely antiplatelet antibodies or megakaryocytes that destroy megakaryocytes or their precursors. Thrombocytopenia is typically found without anemia and leukopenia. Laboratory studies are required to look for secondary causes of ITP (Idiopathic thrombocytopenia purpura), including HIV and hepatitis C infection (and other infections if indicated) [44]. Najean and Rain conducted a study in 1994 on platelet kinetics of HIV-1-ITP patients with and without AIDS, which concluded that AIDS patients tend to have decreased platelet counts. Meanwhile, in patients who were initially infected with HIV-1, there was an increase in peripheral (peripheral) platelet destruction.[46] HIV patients with non-thrombocytopenia can be due to a slight decrease in platelet viability due to the direct influence of HIV on platelets or low autoimmune processes that occur, and it can also be due to inadequate platelet yields [45]. In people with pulmonary TB infection according to Lasut's study [47] the distribution of platelet levels was mostly normal in 50 patients (74.62%), but thrombocytopenia was still found in 4 patients (5.97%). Hematologic abnormalities can be caused by a tuberculosis infection process or a preexisting haematological basis abnormality.

7. Correlation results of hematological status with immunological status

This study found a correlation between the hematological status, namely hemoglobin levels, the number of neutrophils, lymphocytes, and monocytes with the immunological status as seen from the CD4 count. Meanwhile, the leukocyte count, erythrocyte sedimentation rate, and platelet count had no correlation with the CD4 count. This is the same as Pramudianti [43] who stated that there was no significant positive correlation between platelet count and absolute CD4 cell count (r=0.456; p=0.066) in HIV/AIDS patients. There was only 5,8% thrombocytopenia in HIV/AIDS patients. In this research there was 11% thrombocytopenia.

Spearman correlation value between hemoglobin level and CD4+ lymphocyte count is 0.51 which indicates the direction of positive correlation with strong correlation strength and statistically significant. This means that there are low hemoglobin levels in patients with low CD4+ lymphocyte counts. There was a significant positive correlation between hemoglobin level and CD4+ lymphocyte count ($r = 0.683$; $p < 0.001$) in HIV-infected patients pre-ARV therapy [33]. Obirikorang's study [48] showed that there was a significant difference between the hemoglobin levels of patients with CD4+ T lymphocyte counts <200 cells/mm3 and HIV/AIDS patients with CD4+ lymphocyte counts between 200-499 cells/mm3 and CD4+ lymphocyte counts of more than 500 cells/mm3. mm3. Dikshit et al also found that 92.4% (n=121) patients with CD4+ counts <200 cells/mm3 while 7.6% (n=10) patients with CD4+ counts >200 cells/mm3 and there was a statistically significant difference ($p<0.001$).

There is a pathogenesis mechanism that can explain the correlation between hemoglobin levels and CD4+ lymphocyte counts. HIV infection will cause the activation of lymphocytes and monocytes which are characterized by an increase in activation markers on the cell surface, an increase in the ratio of memory: naive T cells, and an increase in the production of pro-inflammatory cytokines. Activation of CD4+ T lymphocytes is caused by antigen recognition by APCs at the T cell receptor (TCR) as well as HIV products such as gp120. Activation of CD4+ T lymphocytes causes an

increase in the expression of Fas receptors on their cell surfaces. Fas receptor/APO-1/CD95 is a cell surface receptor molecule, where activation by Fas ligand (FasL) can induce apoptotic signal transduction. Apoptosis occurs in CD4+ T lymphocytes as a result of the interaction between Fas receptors and FasL via fratricide, paracrine death, or autocrine suicide mechanisms. The magnitude of the incidence of apoptosis in CD4+ T lymphocytes is associated with a decrease in the total number of CD4+ T lymphocytes in peripheral blood.

Immune activation due to HIV infection in T lymphocytes and monocytes also affects the cytokine profile in the circulation. There is a change in the cytokine profile in HIV infection, especially an increase in IFN-γ and TNF-α. IFN-γ is the most potent cytokine in causing apoptosis of erythroid progenitor cells where IFN-γ will cause an increase in Fas expression on the cell surface. The interaction between Fas receptors and FasL produced by T lymphocytes and activated macrophages is the main cause of apoptosis in erythroid progenitor cells. Apoptosis of erythroid progenitor cells causes a decrease in erythrocyte production which causes a decrease in hemoglobin levels.[49]

Based on the above, there is the same mechanism as the main cause of the decrease in the total number of CD4+ T lymphocytes and decreased hemoglobin levels in HIV infection where immune activation causes apoptosis in both CD4+ T lymphocytes and erythroid progenitor cells induced by the interaction between Fas receptors and FasL. Tuberculosis (TB) is the most common opportunistic infection in HIV patients. The T cell response to *Mycobacterium tuberculosis* requires the production of IFN-γ. This protective mechanism is related to the formation of granulomas to localize the infection which is dependent on the presence of IFN-γ. In CD8+ T lymphocytes, IFN-γ expression was higher in the TB group than in the TB-HIV group. This indicates that in HIV patients there is a hyporesponsiveness of T lymphocytes in recognizing Mycobacterium tuberculosis antigens which results in impaired IFN-γ production in the TB-HIV group. This T-lymphocyte hyporesponsiveness results from generalized immune activation. As described above, IFN-γ plays a role in causing a decrease in hemoglobin levels through the mechanism of apoptosis of erythroid progenitor cells.[49]

Spearman correlation value between neutrophil count and CD4+ lymphocyte count is -0.720 which indicates a negative correlation direction with strong correlation strength and statistically significant. This means that the higher the neutrophil count, the lower the CD4 count. While the monocyte count with CD4 has a correlation number of 0.485 which indicates the direction of the positive correlation with the strength of the correlation being moderate and statistically significant. This means that there is a low number of monocytes in patients with low CD4+ lymphocyte counts. Included in the innate leukocytes are natural killer cells, mast cells, eosinophils, basophils, and phagocytic cells, namely macrophages, neutrophils, and dendritic cells. These cells in the immune system have the function of identifying and eliminating pathogens that may cause infection [50]. Through complement receptors located on innate leukocytes in the form of macrophages and neutrophils, the complement system can be activated. The complement system can be activated quickly by infection and form complement proteins that opsonize pathogens that enter the tissue. In addition to complement, phagocytes also play a role in fighting infection. If *Mycobacterium tuberculosis* infects the body then phagocytes/macrophages will phagocytize *Mycobacterium tuberculosis*. Broadly speaking, macrophages can be activated in two ways, first directly by M. tb bacteria and second indirectly by various cytokines produced by CD4+ T-helper lymphocytes.

In this study, there was a strong and significant correlation between the total lymphocyte count and CD4 cell count ($p=0.000$, $r=0.744$). This is similar to that obtained by Suastika (2013) who found a significant strong correlation between TLC and the number of CD4+ lymphocytes ($r = 0.646$; $p<0.001$) in HIV-AIDS sufferers. Several studies have also shown that there is a good correlation between TLC and CD4+ T lymphocyte counts in HIV-infected patients. Longitudinal studies have also shown that

TLC and CD4+ T lymphocyte count are similar markers in predicting disease progression. This is a strong reason to start antiretroviral therapy based on TLC. There was a very significant correlation between CD4 cell count and total lymphocyte count. CD4 cell count is the gold standard in the assessment of disease progression in HIV-infected persons, the total lymphocyte count can be used as a surrogate marker in resource-poor countries [22].

CONCLUSION

The results of this study indicate that the majority of TB-HIV coinfected patients have decreased immunological status as seen from the decreased CD4 count and hematological status, namely decreased levels of hemoglobin, neutrophilia, lymphopenia, while leukocytes, monocytes, and platelets were in the normal range, as well as an increase in sedimentation rate. blood. There is a significant correlation between hemoglobin levels, neutrophil counts, lymphocytes, and monocytes and CD4 counts. The next suggestion is that more stringent monitoring of laboratory examinations is needed as well as evaluation in administering appropriate medication. There is a need for further research regarding the condition of patients with TB-HIV co-infection based on the history of treatment, length of suffering, and other accompanying opportunistic infections.

ACKNOWLEDGMENT

The author would like to thank the Director of Tarakan Hospital and the staff who have facilitated this research.

REFERENCES

[1] G. A. Roth *et al.*, "Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017," *Lancet*, vol. 392, no. 10159, pp. 1736–1788, 2018.

[2] Kementerian Kesehatan RI, "Laporan Perkembangan HIV AIDS & Infeksi Menular Seksual (IMS)," 2017. [Online]. Available: https://siha.kemkes.go.id/portal/files_upload/Laporan_HIV_AIDS_TW_4_Tahun_2017__1_.pdf.

[3] W. H. Organization, "Global tuberculosis report executive summary," *Geneva World Heal. Organ.*, 2018.

[4] E. Puspitasari, E. Yunihastuti, I. Rengganis, and C. M. Rumende, "Prediktor mortalitas pasien HIV/AIDS rawat inap," *J. penyakit dalam Indones.*, vol. 3, no. 1, pp. 22–28, 2016.

[5] Kementerian Kesehatan RI, "Petunjuk teknis tata laksana klinis ko-infeksi TB-HIV," *Jakarta KemenKes RI*, p. 150, 2012.

[6] M. Meidani, F. Rezaei, M. R. Maracy, M. Avijgan, and K. Tayeri, "Prevalence, severity, and related factors of anemia in HIV/AIDS patients," *J. Res. Med. Sci.*, vol. 17, no. 2, p. 138, 2012.

[7] E. C. Russell, S. Charalambous, L. Pemba, G. J. Churchyard, A. D. Grant, and K. Fielding, "Low haemoglobin predicts early mortality among adults starting antiretroviral therapy in an HIV care programme in South Africa: a cohort study," *BMC Public Health*, vol. 10, no. 1, pp. 1–8, 2010.

[8] C. C. Affusim, E. Kesieme, and V. O. Abah, "The pattern of presentation and prevalence of tuberculosis in HIV-seropositive patients seen at Benin City, Nigeria," *Int. Sch. Res. Not.*, vol. 2012, 2012.

[9] S. Sen *et al.*, "Correlation of CD4+ T cell count with total lymphocyte count, haemoglobin and erythrocyte sedimentation rate levels in human immunodeficiency virus type-1 disease," *Med. J. Armed Forces India*, vol. 67, no. 1, pp. 15–20, 2011.

[10] M. Wesnawa and I. Putra, "Profil Pasien Koinfeksi TB–HIV," *J. Respirologi Indones.*, vol. 36, pp. 175–181, 2016.
[11] F. Kirchhoff and G. Silvestri, "Is Nef the elusive cause of HIV-associated hematopoietic dysfunction?," *J. Clin. Invest.*, vol. 118, no. 5, pp. 1622–1625, 2008.
[12] F. Cottrez, F. Manca, A. G. Dalgleish, F. Arenzana-Seisdedos, A. Capron, and H. Groux, "Priming of human CD4+ antigen-specific T cells to undergo apoptosis by HIV-infected monocytes. A two-step mechanism involving the gp120 molecule.," *J. Clin. Invest.*, vol. 99, no. 2, pp. 257–266, 1997.
[13] World Health Organization (WHO), *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children*. World Health Organization, 2007.
[14] Z. Djoerban, E. Yunihastuti, A. Uyainah, and Z. Amin, "Profil Pasien Tb-hiv dan Non Tb-hiv di Rscm," *Indones. Bull. Heal. Res.*, vol. 41, no. 4, p. 20061, 2013.
[15] D. Soraya and D. M. Artika, "Profil Pasien Koinfeksi TB-HIV Di Rumah Sakit Umum Pusat Sanglah Bali Tahun 2013," *EJURNAL Med*, vol. 5, no. 20, pp. 66–71, 2016.
[16] M. Widiyanti, E. Fitriana, and E. Iriani, "Karakteristik pasien koinfeksi tb-hiv di rumah sakit mitra masyarakat mimika papua," 2019.
[17] Kementerian Kesehatan RI, "Laporan Situasi Perkembangan HIV-AIDS & PIMS di Indonesia," *Jakarta*, pp. 2–21, 2017.
[18] D. A. Permitasari and M. A. U. Sofro, "Faktor Risiko Terjadinya Koinfeksi Tuberkulosis pada Pasien HIV/AIDS di Rsup Dr. Kariadi Semarang." Fakultas Kedokteran, 2012.
[19] W. Jayakody, A. D. Harries, S. Malhotra, S. De Alwis, S. Samaraweera, and N. Pallewatta, "Characteristics and outcomes of tuberculosis patients who fail to smear convert at two months in Sri Lanka," *Public Heal. Action*, vol. 3, no. 1, pp. 26–30, 2013.
[20] C. Nzou, R. A. Kambarami, F. E. Onyango, C. E. Ndhlovu, and V. Chikwasha, "Clinical predictors of low CD4 count among HIV-infected pulmonary tuberculosis clients: A health facility-based survey," *South African Med. J.*, vol. 100, no. 9, pp. 602–605, 2010.
[21] A. J. Sunggoro, Z. Amin, and C. M. Rumende, "Mortality among Hospitalized HIV-Infected Patients with Tuberculosis in Cipto Mangunkusumo Hospital, Jakarta, Indonesia: A Retrospective Cohort Study," 2014.
[22] A. V. Rajkondawar and V. Rodge, "Correlation Between Clinical Profile, Total Lymphocytic Count And CD4 Count In HIV Positive Patients," *Blood Transfus.*, vol. 4, p. 4, 2017.
[23] S. K. Sharma, A. Mohan, and T. Kadhiravan, "HIV-TB co-infection: epidemiology, diagnosis & management," *Indian J. Med. Res.*, vol. 121, no. 4, pp. 550–567, 2005.
[24] J. Elston and H. Thaker, "Co-infection with human immunodeficiency virus and tuberculosis," *Indian J. Dermatol. Venereol. Leprol.*, vol. 74, no. 3, p. 194, 2008.
[25] G. C. De Santis *et al.*, "Hematological abnormalities in HIV-infected patients," *Int. J. Infect. Dis.*, vol. 15, no. 12, pp. e808–e811, 2011.
[26] S. Jam *et al.*, "A cross-sectional study of anemia in human immunodeficiency virus-infected patients in Iran," *Arch Iran Med*, vol. 12, no. 2, pp. 145–150, 2009.
[27] M. Taha, A. Deribew, F. Tessema, S. Assegid, L. Duchateau, and R. Colebunders, "Risk factors of active tuberculosis in people living with HIV/AIDS in southwest Ethiopia: a case control study," *Ethiop. J. Health Sci.*, vol. 21, no. 2, pp. 131–140, 2011.
[28] T. Kufa *et al.*, "Undiagnosed tuberculosis among HIV clinic attendees: association with antiretroviral therapy and implications for intensified case finding, isoniazid preventive therapy, and infection control," *JAIDS J. Acquir. Immune Defic. Syndr.*, vol. 60, no. 2, pp. e22–e28, 2012.
[29] A. S. Atmadja, R. Kusuma, and F. Dinata, "Pemeriksaan laboratorium untuk membedakan infeksi bakteri dan infeksi virus," *CDK-241*, vol. 43, no. 6, pp. 457–461, 2016.
[30] A. A. Maharani, "Profil Leukosit Pasien Tuberkulosis (TB) Paru di Rumah Sakit Paru Respira Yogyakarta," Universitas Islam Indonesia, 2018.
[31] V. Goyal, P. N. Vaish, A. Deshmukh, J. Mishra, and G. Deshmukh, "Hematological Study

(Blood & Bone Marrow) in HIV Patients," *Int. J. Contemp. Med.*, vol. 4, no. 1, pp. 94–99, 2016.

[32] R. Wirawan, *Pemeriksaan Laboratorium Hematologi*. Jakarta: Badan Penerbit FKUI, 2011.

[33] N. Suastika, "Akurasi Diagnostik Kombinasi Total Lymphocyte Count (TLC) Dan Kadar Hemoglobin Untuk Memprediksi Imunodefisiensi Berat Pada Penderita Terinfeksi Human Immunodeficiency Virus (HIV) Pra Terapi Antiretroviral," Universitas Udayana Denpasar, 2013.

[34] P. Agustina, H. Rahmawati, A. Rusli, T. Sundari, and I. B. S. Wiweka, "Profil Pasien Suspek Resistensi Ganda Tuberkulosis HIV/AIDS di Rumah Sakit Penyakit Infeksi (RSPI) Prof. Dr. Sulianti Saroso Tahun 2012.," *Indones. J. Infect. Dis.*, vol. 3, no. 1, pp. 1–7, 2017.

[35] R. Kumar, "Comparison between CD4 count, haematological manifestations and respiratory tract infections in HIV seropositive individuals," *Int. J. Contemp. Med. Res.*, vol. 3, no. 5, pp. 1245–1248, 2016.

[36] G. Guadagnino *et al.*, "Monocyte to lymphocyte blood ratio in tuberculosis and HIV patients: Comparative analysis, preliminary data." Pharmacologyonline, 2017.

[37] S. Longanbach, M. K. Miers, E. M. Keohane, L. J. Smith, and J. M. Walenga, *Rodak's hematology: Clinical principles and applications*. St. Louis: Elsevier Saunders, 2016.

[38] A. Oehadin, *Aspek Hematologi Tuberkulosis*. Bandung: Fakultas Kedokteran Universitas Padjajaran, 2003.

[39] K. Bochen, A. Krasowska, S. Milaniuk, M. Kulczynska, A. Prystupa, and G. Dzida, "Erythrocyte sedimentation rate–an old marker with new applications," *J. Pre-clinical Clin. Res.*, vol. 5, no. 2, 2011.

[40] W. L. Ningrum, "Profil laju endap darah pada pasien tuberkulosis paru kasus baru di RSU Kota Tangerang Selatan." UIN Syarif Hidayatullah Jakarta: Fakultas Kedokteran dan Ilmu Kesehatan, 2017, 2017.

[41] K. Rohini, M. S. Bhat, P. S. Srikumar, and A. M. Kumar, "Assessment of hematological parameters in pulmonary tuberculosis patients," *Indian J. Clin. Biochem.*, vol. 31, no. 3, pp. 332–335, 2016.

[42] W. Y. Niu, Y. G. Wan, M. Y. Li, Z. X. Wu, L. G. Zhang, and J. X. Wang, "The diagnostic value of serum procalcitonin, IL-10 and C-reactive protein in community acquired pneumonia and tuberculosis," *Eur Rev Med Pharmacol Sci*, vol. 17, no. 24, pp. 3329–3333, 2013.

[43] M. I. D. Pramudianti and T. Tahono, "Korelasi Antara Hitung Trombosit Dengan Jumlah CD4 Pasien HIV/AIDS," *Indones. J. Clin. Pathol. Med. Lab.*, vol. 17, no. 2, pp. 102–106, 2018.

[44] N. B. Sianipar, "Trombositopenia dan berbagai penyebabnya," *Cermin Dunia Kedokt.*, vol. 41, no. 6, pp. 416–421, 2014.

[45] K. R. McCrae, *Thrombocytopenia*. New York: CRC Press, 2006.

[46] E.-J. Lee and A. I. Lee, "Thrombocytopenia," *Prim. Care Clin. Off. Pract.*, vol. 43, no. 4, pp. 543–557, 2016.

[47] N. M. Lasut, L. W. A. Rotty, and E. B. I. Polii, "Gambaran Kadar Hemoglobin Dan Trombosit Pada Pasien Tuberkulosis Paru di RSUP. Prof. Dr. Rd Kandou Manado Periode Januari 2014–Desember 2014," *e-CliniC*, vol. 4, no. 1, 2016.

[48] C. Obirikorang and F. A. Yeboah, "Blood haemoglobin measurement as a predictive indicator for the progression of HIV/AIDS in resource-limited setting," *J. Biomed. Sci.*, vol. 16, no. 1, pp. 1–7, 2009.

[49] T. Sokoya, H. C. Steel, M. Nieuwoudt, and T. M. Rossouw, "HIV as a cause of immune activation and immunosenescence," *Mediators Inflamm.*, vol. 2017, 2017.

[50] B. Gunawan, "Stres dan sistem imun tubuh: suatu pendekatan psikoneuroimunologi," *Cermin Dunia Kedokt.*, vol. 154, pp. 13–15, 2007.