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Hematological profile of pulmonary tuberculosis patients before and after 1 month of taking anti-TB drugs

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Abstract: Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium tuberculosis*. *(MTB)* Indonesia ranks third in the number of global TB cases. Studies in Indonesia have shown reduced levels of Hgb (Hemoglobin), Hct (Hematocrit), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Hemoglobin), and leukocytosis in newly diagnosed and untreated TB patients. Further investigation is needed to evaluate the combined use of hematological markers to assess the inflammatory response before and after treatment.This study was conducted in several publice health center (Puskesmas) in Semarang to determine the hematological profile of TB patients before and after 1 month of treatment. This study used a quasi-experimental design with one-group pre-test and post-test methods. The study population included all TB patients in the third area of the puskesmas. Non-probability sampling technique with quota sampling is used to select a sample, consisting of newly diagnosed TB patients (aged 20-60 years, both male and female, and not cases of retreatment). A total of 30 samples were taken (10 from each Puskesmas). Analysis of blood samples is performed using the automated hematology device Sysmex (KX21-N). Data were analyzed with descriptive statistics and paired t-test was used to compare hematologic profiles before and after treatment. The results showed that anemia often occurred in TB patients and the number of patients who experienced anemia after treatment decreased from 16 patients to 13 patients. The study also found significant changes in white blood cell ($p = 0.004$) and platelet ($p = 0.005$) counts in TB patients before and after treatment. The increase in white blood cell count after treatment shows clinical improvement, while the decrease in platelets may be due to the action of anti-TB Drugs. Normocytic normochromic anemia is the most common form of anemia in TB patients before treatment, while microcytic hypochromic anemia is more common after 1 month of treatment.

Keywords: Hematological; Tuberculosis; Anti TB Drugs; Intensive Phase; Anemia.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by bacteria *Mycobacterium tuberculosis (MTB)*. TB is an airborne disease. Transmission is through airborne particles called droplet nuclei, with a size of 1-5 microns. TB is one of the oldest infectious diseases in the world.[1] About a quarter of the global population is estimated to have been infected with TB. About 90% of these cases are adults, with men having more cases than women.[2] Based on WHO data Indonesia ranks third in terms of the highest number of cases in the world.[3] The number of TB cases found and treated in Indonesia in 2020 was recorded at 393,323 cases, then increased in 2021 with 443,235 cases.[2]

Data from the 2021 Indonesian Health Profile states that TB in Central Java occupies the third position with the highest number of TB cases in Indonesia at

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54,640 cases.[4] Data obtained from the Semarang City Health Office, the number of new discoveries of TB cases as of early October 2022 is 1,989 cases. Kedungmundu District ranked first with the highest number of TB cases of 186 cases in the January-November 2022 period. The second highest ranking is Bangetayu District with a total of 158 cases. The success rate of TB treatment in Indonesia is 73% in 2021, not yet reaching the national target that should be achieved is 90%.[5] WHO recommends multi-drug first-line anti-TB drugsconsisting of Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin.[6,7]

Infection MTB is characterized by a cellular response that includes various manifestations reflecting the interaction between the MTB bacillus and the main effector cells of the host's cellular defense defense mechanism. Host immune responses to infections are thought to play an important role in the pathophysiology of TB resulting in a wide variety of immunopathologies, ranging from asymptomatic infections to disseminated disease and ultimately patient death. Systemic inflammation facing pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB) and characterized by increased concentrations of various inflammatory markers in peripheral blood and the spectrum of proinflammatory cytokines, as well as chemokines.[8]

White blood cell count (WBC), platelet and various relative ratios of white blood cells, such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and monocyte/lymphocyte ratio (MLR), have been widely studied in chronic inflammatory diseases including TB. TB is associated with reversible changes in hematological parameters. Some changes occur also associated with anti-TB drugs.[9,10] Changes in hematological parameters include anemia, leukocytosis, neutrophilia, thrombocytosis, and increased erythrocyte sedimentation rate (ESR), lymphocytosis, thrombocytopenia or lymphopenia depending on severity and comorbidities.[7] In addition, other hematological parameters in chronic inflammatory diseases such as mean corpuscular volume (MCV), red blood cell distribution (RDW), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobinconcentration (MCHC), MPV, platelet distribution (PDW) and erythrocyte sedimentation rate (ESR) have been investigated.[11] Research in Indonesia on TB such as the Yuniza et all (2022) study on healthy patients and newly diagnosed TB patients who have not received treatment found a decrease in Hgb, Hct, MCV and MCH levels and leukocytosis, while Asa (2022) research on the erythrocyte index, found TB patients to have anemia by 60%.[12,13] However, the use of these combined hematologic markers that may reflect a systematic inflammatory response before starting treatment and after 1 month of treatment in TB patients has not been fully investigated. The aim of the research is to determine the morphological abnormalities of blood cells in pulmonary TB patients and to find out the type of anemia that most often occurs in pulmonary TB patients.

MATERIAL AND METHOD

The research was conducted between January 2024 - Mei 2024 at 3 public health center (puskesmas) locations in Semarang City, namely Kedungmundu Health Center, Bangetayu Health Center and Tlogosari Wetan Health Center. Quasi experimental one-group pre-test and post-test to determine hematological profile in TB patients before and after administration of anti-TB drugs over a period of 1 month. The study population included all TB patients in the Kedungmundu Health Center, Bangetayu Health Center and Tlogosari Wetan Health Center, Semarang City. The sampling technique used is non-probability sampling with the type of quota sampling for determine the sample of the population that has certain characteristics up to the desired number (quota). Sampling. Quota sampling was used, including all patients who met the inclusion criteria: men and women aged 20–60 years, newly diagnosed with TB, and not undergoing retreatment. Researchers set 30 samples, with details of 10 patients from Kedungmundu Health

Center, 10 Bangetayu Health Center patients and 10 patients from Tlogosari Wetan Health Center. Approximately 5 ml of venous blood was collected aseptically using EDTA tubes from each selected study patient. after collection, EDTA tubes are labeled with a code number. Blood tests are performed on the same patient, the patient's blood sample is taken twice when the patient has not received treatment and after undergoing anti-TB drug therapy (OAT) for one month. The analysis was performed using the Sysmex automatic hematology tool (KX21-N) using fresh venous blood samples anti-coagulant EDTA, by: EDTA blood is mixed, placed on the sample probe. Press the start button. The device will perform an automatic analysis and display the results on the LCD screen. The analysis results displayed include WBC, RBC, HGB, HCT, MCV, MCH, MCHC, PLT, LYMP, NEUT, and MXD.[14] The reason for using automated blood counts is that automated blood counts can quickly produce accurate and precise blood counts. [15]

The data obtained were analyzed using stastical programme. Frequency and cross-tabulation are used for descriptive statistics. Descriptive analysis to describe the frequency and percentage of research variables such as sex, hemoglobin, hematocrit, leukocyte count, platelet count, erythrocyte count, differential count, MCV, MCH, MCHC. Criteria for anemia in men, HgB <13 g / dL and female HgB < 12 g / dL.[16] Normal Hct values Nonpregnant women age > 15 years.< 36% Men > 15 yrs.<39%. Normal leukocyte count 5000-10000/ µl. Leukocytosis is a condition characterized by a very high total number of circulating leukocytes (> 10000/ µl). Leukopenia is a condition characterized by a very low total number of circulating leukocytes (< 5000/ µl). Normal platelet count 150,0000-400,000/ µl. Thrombocytosis is a high platelet count in the blood (>400,000/ µl). Thrombocytopenia is a very low level of platelets in the blood (<150,0000/ µl). Normal erythrocyte count 4-5 x 10^6 per mm^3. Erythrocytosis is a high number of erythrocytes in the blood 4-5 x 10^6 per mm^3). Low erythrocyte count is < erythrocyte count of 4-5 x 10^6 per mm^3. Normal lymphocytes 20-40%. Lymphocytosis is > 40% lymphocyte count. Lymphocytopeny is < 20% lymphocyte count. Monocytes 2-8%, monocytosis is the number of lymphocytes >8%, low lymphocytes < 2%. Normal neutrophils are 50-70%, neutrophils are the number of neutrophils >70%, neutropeni is the number of neutrophils <50%.[17] Anemia can be classified by morphology into Normochromic normocytic (MCV 76–96 fL, MCHC 30–35 gm/dL), Macrocytic (MCV >96, MCHC 30–35 gm/dL), Microcytic (MCV <76 fL, MCHC 30 gm/dL).[16] The paired t-test was used in the analysis to compare hematological profile values before and after 1-month TB treatment. A P value of < 0.05 is considered statistically significant, which means that there are differences in hematological profile values before and after treatment. This research has obtained ethical approval from the ethics committee of the Health Polytechnic of the Ministry of Health Semarang No. 0575/EA/KEPK/2024

RESULTS AND DISCUSSION

TB is an infectious infectious disease caused by *Mycobacterium tuberculosis* (MTB). Tests that can be used in the diagnosis of TB include sputum examination for acid-resistant bacilli, chest CT scan, chest X-ray, tuberculin culture and skin test, PCR test used for TB diagnosis and blood tests.[18] Blood examination is one of the supporting methods carried out to examine patients suffering from TB. Assessment of hematological parameters/profiles plays an important role in designing treatment strategies and influencing patient prognosis. This is very important in planning treatment strategies and can have an impact on a patient's prognosis. Using hematological markers as a guide in treatment can not only improve treatment outcomes, but also improve patient survival and quality of life.[19]

Hematological profile is a parameter that has a normal range or value as a reference value to determine whether blood morphology (red blood cells, white blood cells, platelets) is normal or not. When infected with pulmonary TB, certain

changes occur in the blood due to bacterial infection secreting substances that cause certain effects.[18] Hematological parameters such as hemoglobin (HgB), Packed Cell Volume (PCV), red blood cell count (RBC), erytrocyte index, platelet count, white blood cell count (WBC), erythrocyte sedimentation rate (ESR) can be used for diagnosis, prognosis, and follow-up of TB patients.[20]

Table 1. Distribution of TB cases by gender

Gender	Number of cases	Percentage (%)
Male	16	53.33
Female	14	46.67
Total	30	100

In Table 1, the gender of male patients is 53.33% more than female. Our findings are in line with previous studies by the Ministry of Health (2023) and Situmorang (2020), which reported similar findings, showing that pulmonary TB cases are dominated by men.[21,22] Men mostly have smoking habits, smoking as a major risk factor for TB can inhibit the target of reducing the incidence and death from TB.[23] In addition, men's lifestyles such as drinking alcoholic beverages and doing a lot of activities outside the home are at risk of exposure to air that has been contaminated with bacteria so it is easy to contract TB.[24]

Table 2. HgB, Hct and RBC levels before and after 1 month of TB treatment

Parameter	Before treatment Mean ± SD	After treatment Mean ± SD	p-value
HgB (g/dl)	12,450 ± 2,30	12,343 ± 2,10	0.768
Hct (%)	37.865 ± 9,57	35.868 ± 8.58	0.195
RBC (cel//µl)	4,81 ± 0,21	4,63 ± 0,11	0.138

"HgB : hemoglobin, Hct : hematocrit, RBC : red blood cell count."

Table 3. Proportion of TB patients who experience anemia before and after treatment

Parameter	Criteria	Before treatment	After treatment
HgB	Anemia	16	13
	No anemia	14	17
Erythrocyte index (MCV, MCH, MCHC)	Normocytic and normochromic	17	14
	Hypochromic microcytic	13	16

The number of erythrocytes (RBC) is used as a determinant of the degree of anemia, along with hemoglobin (HgB), and hematocrit (Hct).[6,25] There was no statistically significant difference in hemoglobin levels before and after 1 month of treatment (p-value 0.768), indicating that a longer treatment period may be required for significant hematological improvement. The 1-month period is still within the time range of intensive phase treatment which should be completed within 2 months. Intensive TB treatment lasts for 2 months with the administration of 4 types of anti-TB Drugs, namely Isoniazid, Rifampicin, Pyrazinamid, and Ethambutol and consumed every day. Treatment at this stage aims to lower the number of bacteria *MTB* effectively and minimize bacteria *MTB* who may have been resistant from before treatment.[26]

Most TB patients before and after treatment have low hematocrit levels. According to Kassa (2016), the low hematocrit value is caused by a decrease in hemoglobin levels in erythrocyte cells, causing anemia.[6, 27] Anemia, a decrease in red blood cell mass, is also interpreted as a decrease in the concentration of hemoglobin and hematocrit. The criteria for anemia are based on hemoglobin levels, in men <13 g/dL and women <12 g/dL.[16] Anemia was identified in 16 patients before treatment and 13 patients after TB treatment (Table 3). In our study, the number of anemic TB patients decreased in the number of patients. The results

of this study are different from the results of Come's (2023) study, anemia in TB patients before and after administration of anti-TB drugs for 2 months has increased.[28] Anemia due to chronic diseases such as TB can be caused by inflammatory pathogenesis that causes a short life span of erythrocytes, poor binding of iron and erythrocytes and decreased sensitivity or supply of erythropoietin. Low food intake is one of the causes of iron deficiency anemia. Loss of appetite is thought to be one of the causes of reduced food intake. Malabsorption problems result in decreased iron absorption.[29]

The mechanism of occurrence of anemia in pulmonary TB patients is explained as bacterial invasion causes activation of T lymphocytes and macrophages, which induce the production of cytokines (IFN-ÿ), (TNF-α), Interlukin-1 (IL-1) and interlukin-6 (IL-6) which will cause iron diversion in the reticulo-endothelial system resulting in a decrease in iron concentration in plasma thereby limiting its availability to red blood cells for hemoglobin synthesis, inhibition of erythroid progenitor cell proliferation and erythropoietin production and activity.[6,27]

Table 4. MCV, MCH and MCHC levels before and after 1 month of TB treatment

Parameter	Before treatment Mean ± SD	After treatment Mean ± SD	p-value
MCV (fl)	80.97 ± 1.23	78.61 ± 1.10	0.144
MCH (pg)	25.82 ± 0.51	25.79 ± 0.81	0.968
MCHC (g/dl)	32.08 ± 0.70	33.73 ± 0.61	0.008

"MCV : mean corpuscular volume, MCH : mean corpuscular hemoglobin, MCHC : mean corpuscular hemoglobin concentration (MCHC)."

The erythrocyte index consists of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobinconcentration (MCHC).[30] The results of our research showed that the MCV and MCH values before and after treatment did not change significantly, but there was a significant difference in the MCHC values before and after treatment (p-value 0.008). Average cell volume (MCV) is the most frequently used index. It measures the average volume of red blood cells by dividing the hematocrit by RBCs. MCV categorizes red blood cells based on size. Cells of normal size are called normocytic, smaller cells are called microcytics, and larger cells are called macrocytics. This size category is used to classify anemia.[25] The MCH value usually rises or falls as the MCV increases or decreases. MCHC categorize red blood cells based on their hemoglobin concentration. Cells with a normal hemoglobin concentration are called normochromic; Cells with a lower than normal concentration are called hypochromic.[25] Using accurately determined red blood cell counts, hematocrit, and hemoglobin values, the size and average hemoglobin content of red blood cells in a given blood sample can be calculated. The value obtained is an erythrocyte index that helps in the classification and study of anemia.

Normocytic and normochromic anemia were the most common categories of anemia identified in 17 (57%) TB patients prior to treatment. This is in line with Chavan et al's 2016 research found normocytic and normochromic anemia in new patients.[31] Microcytic hypochromic anemia was found in 16 anemic patients after 1 month of treatment. Mild to moderate anemia, which is common in patients with infectious, inflammatory, or neoplastic diseases and lasts more than 1 to 2 months, is called chronic disease anemia. Anemia in pulmonary TB patients has been reported in 16% to 94%. All chronic infections, including TB, can cause anemia. Anemia usually develops during the first month or two of the disease and does not develop afterwards.[18]

Before treatment, anemia was predominantly normochromic normocytic in 17 (57%) patients followed by hypochromic microcytic in 13 (44%) patients. After treatment 14 (44%) developed normochromic normocytic anemia and 16 (53%)

patients developed microcytic hypochromic anemia. This result is different from Kumar's (2017) study which showed the majority of TB patients (76%) had normochromic normocytic anemia. This may be due to the fact that after treatment with anti-TB drugs, anemia improves but is not completely corrected, reflecting the chronic disease TB anemia.[32]

Table 5. WBC and Plt levels before and after 1 month of TB treatment

Parameter	Before treatment Mean ± SD	After treatment Mean ± SD	p-value
WBC (cel/µl)	9.030 ± 701	6.873 ± 317	0.004
Plt (cel/µl)	352.300 ± 2.179	297.633 ± 18.695	0.005

"WBC : white blood cell count, Plt : platelet."

There was a significant difference in the number of WBC (p-value 0.004) and platelets (p-value 0.005) indicating a hematological effect of tuberculosis treatment (Table 4). Our findings on the number of white blood cells are in line with Sheetal's (2020) study which reported similar findings.[27] This study also found that normal leukocyte counts were found in 17 (57%) patients before treatment and 27 (90%) patients after the treatment phase. The results of our study are in line with previous studies by Reta (2023) and Sheetal (2020) which showed that before starting treatment, TB patients experienced leukocytosis, but after treatment, the leukocyte count decreased to normal. In the early stages of MTB infection, MTB moves and accumulates in lung lesions, increasing the number of white blood cells associated with the host's innate immune mechanism.[27,33]

The significant difference in platelet counts from our findings is in line with the study by Eyuel Kassa et al (2016) which showed similar results.[6] However, our findings differ from the study by Karwiti et al (2021) which stated that there was no difference in platelet counts in TB patients before and after taking anti-TB drugs (p-value.0.728).[34] Although platelet counts were within normal limits in most patients, thrombocytosis was observed in 9 (30%) patients before treatment and 4 (13%) patients after treatment (Table 4). The difference in platelet count in TB patients before and after taking anti-TB drugs can be due to the influence of anti-TB drugs, especially the type of Rifampicin. Rifampicin can cause a decrease in platelet count. This is because Rifampicin can be absorbed into platelets and cause platelets to be recognized as antigens by antibodies, resulting in a mechanism of platelet destruction by the immune system.[35] There were significant differences in white blood cell and platelet counts, indicating the hematological influence of tuberculosis treatment.

Table 6. Proportion of hematology profiles with normal, high, and low values in TB patients before and after 1 month of treatment

Parameter	Criteria	Before treatment (%)	After treatment (%)
Hct	Normal	11 (36%)	10 (33%)
	Low	19 (64%)	20 (67%)
WBC	Normal	17 (57%)	27 (90%)
	High (Leukocytosis)	10 (33%)	2 (6.6%)
	Low (Leukopenia)	3 (10%)	1 (3.4%)
Plt	Normal	21 (70%)	25 (83%)
	High (Thrombocytosis)	9 (30%)	4 (17%)
	Low (Thrombocytopenia)	0	1 (3.4%)
RBC	Normal	18 (60%)	15 (50%)
	High (Erythrocytosis)	9 (30%)	10 (33%)
	Low	3 (10%)	5 (27%)
Lymp	Normal	20 (66%)	24 (80%)
	High (Lymphocytosis)	1 (3.4%)	3 (10%)
	Low (Lymphopenia)	9 (30%)	3 (10%)
Monocytes	Normal	19 (63.4%)	15 (50%)
	High (Monocytosis)	11 (36,6%)	15 (50%)

Neut	Normal	17 (56,6%)	23 76,6%)
	High (Neutrophilia)	12 (40%)	5 (16,6%)
	Low Neutropenia)	1 (3.4%)	2 (6.8%)

Table 7. Lymphocytes, Monocyte and Neutrophils levels before and after 1 month of TB treatment

Parameter	Before treatment Mean ± SD	After treatment Mean ± SD	p-value
Lymp (%)	24 ± 2	29 ± 2	0.021
Monocytes (%)	8.23 ± 0.49	8.18 ± 0.46	0.928
Neut (%)	65.95 ± 2.82	62.25 ±1.84	0.236

"Lymp : lymphocytes, Neut : neutrophils."

Our study results showed that the average lymphocyte count was different before (24 ± 2) and after TB treatment (29 ± 2). The results of statistical tests on lymphocytes also showed a significant difference between before and after treatment (p-value 0.021). Our findings are in line with the studies of Chedid (2020) and Sheetal (2020) which reported similar things. An increase in lymphocytes indicates general clinical improvement in response to treatment. TB treatment can increase the number of lymphocyte cells to be more or return to normal.[36,27]

Most patients had normal monocyte and neutrophil counts before and after TB treatment. However, statistically the data showed no significant difference in monocyte and neutrophil counts in TB patients before starting treatment and after completing 1 month of TB treatment. Monocytes are an important component of the innate immune response that acts as a link to the adaptive immune system through antigen presentation to lymphocytes. Monocytes are the dominant innate immune cells in the early stages of MTB infection as a host defence against intracellular pathogens. Therefore, any factor that interferes with the function or relative numbers of these cell types has the potential to influence an individual's response to infection.[18,37]

Before starting treatment, 12 (40%) TB patients had neutrophilia, but after treatment, the neutrophil count decreased to normal. The immune system's reaction to TB may be the cause of this increase. Neutrophilia and neutropenia are also found in TB patients but neutrophilia is more common than neutropenia.[38] Neutrophilia is a sign of recurrent and continuous inflammatory reactions and often turns into lymphocytosis when the inflammatory response becomes chronic.[39] Neutrophilia describes a high number of neutrophil granulocytes in the blood. Neutrophils are the primary white blood cells that respond to bacterial infection. Relative or absolute neutrophilia is documented in 29-57 percent of patients with tuberculosis.[40]

The study results underline the importance of routine blood parameter monitoring during TB treatment to assess the response to treatment, whether the patient's condition improves as treatment progresses, or worsens, requiring immediate action.

CONCLUSION

TB treatment does not directly increase Hb levels in a short time, it affects several other aspects of the patient's hematological profile. This indicates that hematological monitoring during TB treatment remains important to detect changes that might affect the patient's condition, especially with regard to the type of anemia and changes in white blood cells and platelets. Overall, this study demonstrates the importance of hematologic profile monitoring in the treatment of TB, which can improve patient outcomes and quality of life. This research has several limitations, such as a relatively small sample size because it is a longitudinal study (the study was only conducted in Semarang) which may affect the generalization of the findings. Patient non-compliance with anti-TB treatment, resulting in some patients

not returning after 1 month of treatment. This research has not yet taken into account the nutritional status or health conditions of the patients that could affect the hematological profile.

AUTHORS' CONTRIBUTIONS
Ririh Jatmi Wikandari and Surati conducted research and prepared research reports. Siti Nuryani and Sistiyono analyzed the data and interpreted the results.

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DATA AVAILABILITY STATEMENT
The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT
The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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