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Research article

Degree of anaemia based on treatment period, type of OAT, and BTA status in intensive-phase pulmonary tuberculosis patients

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Abstract

Pulmonary tuberculosis can cause anaemia. Anti-tuberculosis Medications (ATM) are divided into 2 types namely Fixed Dose Combination (FDC) and release. The intensive phase of ATM can cause side effects in mild, moderate, or severe anaemia. This study aims to describe the degree of anaemia in intensive-phase pulmonary TB patients based on the duration of treatment for ATM, type of ATM, and smear status. This research is a retrospective descriptive using secondary data in the form of medical records and the results of the Hb examination in the laboratory. The sampling technique used purposive sampling with inclusion criteria including drug-sensitive pulmonary TB, currently undergoing intensive phase treatment, experiencing anaemia based on the degree of anaemia according to WHO. Exclusion criteria included extrapulmonary TB, drug-resistant TB, and pregnant women. A total of 134 samples and data analysis using univariate analysis. Based on the degree of anaemia, the highest percentage of mild anaemia was during the 2nd week of treatment (60.9%), the type of ATM release (60.0%), and smear-positive (55.3%). The highest percentage of moderate anaemia was in the 6th week (100%), ATM FDC (43.6%), and smear-negative (48.4%). The highest percentage of severe anaemia was at week 8 (50.0%), ATM FDC (6.4%), and smear-negative (6.5%). Worsening of the degree of anaemia as the treatment period progresses, in patients with pulmonary TB who are taking FDC and are smear-negative.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis*. Indonesia is in third place as the country with the highest TB disease in the world after India and China. The incidence of this disease increased from 2020 by 351,936 to 397,377 cases in 2021, and as of 1 July 2022, the number of TB cases recorded was 205,927.

Pulmonary TB is a type of TB that has the highest percentage in Indonesia among other types of TB, namely 92%.[1] Central Java is one of the 3 provinces that has the highest number of TB cases in Indonesia from 2018 to 2021.[2–5] The number of TB sufferers in Semarang in 2022 as of July was recorded at 1,487 TB cases.[6] The results of a preliminary study at the KRMT Wongsonegoro Regional General Hospital

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found data on pulmonary TB cases in the period January 1 2022 to 4 October 2022 as many as 2,229 cases.[7]

Pulmonary TB disease can cause hematological disorders, one of which is anaemia. The prevalence of pulmonary TB sufferers who experience anaemia is 71.8%.[8] Tuberculosis can cause mild, moderate, or severe anaemia. Around 25% of pulmonary TB patients experience anaemia, including mild anaemia (75%) and moderate anaemia (30%). Another study stated that 40.5% of TB sufferers had mild anaemia, 48.1% had moderate anaemia and 11.4% had severe anaemia**.**

One of the factors that can contribute to the incidence of anaemia in Pulmonary TB sufferers is the high number of BTA. Anti-Tuberculosis Drugs (OAT) is a treatment therapy for TB sufferers that consists of 2 phases, namely the intensive phase and the advanced phase**.** The initial phase of treatment is carried out during the first 2 months of treatment consisting of the drugs *isoniazid, rifampicin, pyrazinamide, and ethambutol.*[9] 96.6% of intensive-phase OAT causes side effects, especially in the first week of treatment. The perceived side effects will decrease as the intensive phase of treatment progresses**.**

Research results show that OAT can cause a decrease in Hb levels. Other side effects of intensive phase OAT include digestive system disorders, such as nausea, vomiting, and anorexia. Nausea, vomiting, and anorexia are risk factors for anaemia. The research results show that 57.14% of TB sufferers who took OAT for 2 months experienced anaemia**.** Another study also revealed that 54% of the hemoglobin (Hb) levels of pulmonary TB sufferers who took OAT were abnormal. The intensive phase OAT content such as *isoniazid* and *pyrazinamide* can cause sideroblastic anaemia. Another ingredient, namely *rifampicin,* can cause hemolytic anaemia.

Several other studies explain the opposite, that the intensive phase of OAT has an impact on increasing Hb levels. Hb levels increase after undergoing intensive phase OAT treatment. The increase in Hb levels occurred significantly starting in the first 4 weeks of intensive phase OAT treatment until treatment was completed. The success of TB treatment influenced the increase in Hb levels, the number of anaemia patients decreased from 43% at week 0 to 6.8% at week 16.

Hb levels determine the severity of TB disease**.** Anaemia can have a bad impact and can affect the results of treatment and the recovery process of TB sufferers**.** Identification of the degree of anaemia in pulmonary TB sufferers needs to be done to determine appropriate management to improve the quality of health and reduce the morbidity and mortality rates of TB sufferers undergoing the intensive phase of OAT treatment.

Based on the description above, researchers are interested in researching "Description of the Degree of Anaemia Based on Treatment Period, Type of OAT and BTA Status in Intensive Phase Pulmonary Tuberculosis Patients at the KRMT Wongsonegoro Regional General Hospital".

METHODS

This research is a retrospective descriptive study that aims to see the degree of anaemia in pulmonary tuberculosis patients who take OAT in the intensive phase. The research used secondary data sources in the form of medical records and laboratory examination results to view data on pulmonary TB patients and the results of Hb examinations during treatment in inpatient units in the period 1 January 2022- 30 November 2022. The research was conducted from July 2022 to January 2023. Data collection was conducted in December 2022. The research location is at the KRMT Wongsonegoro Regional General Hospital.

The population in this study was 353 patients who were all pulmonary tuberculosis (TB) sufferers in the KRMT Wongsonegoro Hospital inpatient room in the 2022 period. 134 research samples had been determined using a *purposive sampling technique*. Inclusion criteria included patients with drug-sensitive pulmonary TB 72(SO), in the intensive treatment phase and experiencing anaemia. Exclusion criteria include extra-pulmonary TB sufferers, and drug resistance, during pregnancy.

Researchers apply research ethics, including respecting basic rights by respecting the privacy and confidentiality of research subject data, treating all research subject data fairly, and considering the benefits and harms. The research was carried out after obtaining *ethical clearance* no. B/070/588/VIII/2022.

The process of searching for pulmonary TB data uses a *computerized system* by inputting the ICD code (A15 and A16), and then recording all medical record numbers (No. CM) of pulmonary TB patients being treated in the inpatient room. Researchers then searched the CM numbers one by one to see biodata, doctor's notes, and treatment history. CM No. is also used to trace the history of Hb examinations while undergoing treatment in the inpatient room.

Assessment of the degree of anaemia is based on the results of checking hemoglobin (Hb) levels. The research instrument uses the classification of anaemia degrees according to *the World Health Organization* (WHO) in 2011 with units of g/dL.

Data input and processing uses *Microsoft Excel* and *IBM SPSS Statistics 20 applications*. Data analysis uses univariate analysis to describe variables. Data managed include age, gender, comorbidity status, Hb levels, and degree of anaemia based on the intensive phase OAT treatment period, type of intensive phase OAT, and bacteriological status (BTA). The normality test in determining the mean value of age, Hb levels, and treatment period uses the *skewness method* (statistical value: standard *error*).

RESULT

The research results are presented in the form of a statistical description table and frequency distribution of 134 research samples. Table 1 shows that male respondents had a higher percentage, namely 67.2%, compared to women, namely 32.8%. The majority of respondents were in the elderly group with a percentage of 31.3%. The oldest is 87 years old and the youngest is 9 months.

The average Hb level from 134 samples was 10.8 g/dL. The highest Hb level is 12.9 g/dL and the lowest is 4.9 g/dL. The degree of anaemia has the highest percentage of *mild anaemia* namely 53.0%. On average, respondents underwent the 1st week of treatment. The longest treatment period was at week 8 and the latest at week 1. Types of OAT FDC (*Fixed Dose Combination*) dominate the total respondents with a percentage of 70.1%. The majority of respondents had BTA-positive status with a percentage of 76.9% and had comorbidities with a percentage of 74.6%.

Table 2 displays the degree of anaemia based on treatment period, type of OAT, and BTA status. The treatment period, week 1 had the highest percentage of *mild anaemia* (56.6%). The 2nd week of the treatment period had the highest percentage of *mild anaemia* (60.9%). The 3rd week of the treatment period had the highest percentage of *mild* and *moderate anaemia* (42.9%). The 4th week of treatment had the highest percentage of *moderate anaemia* (71.4%). The 5th week of treatment period had the highest percentage of *moderate anaemia* (66.7%). The 6th week of the treatment period has the highest percentage of *moderate* anaemia (100%). The 7th week of treatment period had the

highest percentage of *mild anaemia* (50.0%). The 8th week of the treatment period had the highest percentage of *severe anaemia* (50.0%). Based on the degree of anaemia, the highest percentage of *mild anaemia* was in the 2nd week of treatment (60.9%), *moderate anaemia* was in the 6th week (100%), and *severe anaemia* was in the 8th week (50.0%).

Types of Anti-Tuberculosis Drugs (OAT) FDC and release have the highest percentage of *mild anaemia*. *Mild* anaemia in FDC is 50.0% and in discharge is 60.0%. Based on the degree of anaemia, FDC has the highest percentage of *moderate* and *severe degrees of anaemia*. The highest percentage of *mild anaemia* in the loose type was 60.0%, *moderate anaemia* in the FDC type was 43.6%, and *severe anaemia* in the FDC type was 6.4%.

BTA-positive status has the highest percentage in *mild anaemia* (55.3%). BTA negative has the highest percentage in *moderate anaemia* (48.4%). Based on the degree of anaemia, the highest percentage of *mild anaemia* is in BTA positive status (55.3%), *moderate anaemia* in BTA negative status (48.4%), and *severe anaemia* in BTA negative status (6.5%).

Table 1
Characteristics of intensive phase pulmonary TB sufferers for the period 1 January 2022-30 November 2022 in the inpatient ward of KRMT Wongsonegoro Regional Hospital, (n=134)

Characteristics		n	%	Med	Std	Min	Max	CI 95%	*Skewness*
Age (years)				51.0	20.9	0.8	87.0	43.13-50.30	-2.82
0-1	Baby	8	6.0						
>1-6	Toddlers and pre-schoolers	2	1.5						
>6-18	School and youth	6	4.5						
>18-45	Matrue	41	30.6						
>45-59	Pre elderly	35	26.1						
≥60	Elderly	42	31.3						
Gender	Man	90	67.2						
	Woman	44	32.8						
Hemoglobin (g/dL)				10.80	1.49	4.90	12.90	10.33-10.85	-5.41
Degree of anaemia	*Mild*	71	53.0						
	Moderate	55	41.0						
	Severe	8	6.0						
Treatment period (weeks)				1.00	1.84	1	8	1.72-2.35	9.75
	1	83	61.9						
	2	23	17.2						
	3	7	5.2						
	4	7	5.2						
	5	3	2.2						
	6	1	0.7						
	7	6	4.5						
	8	4	3.0						
Types of OAT	FDC (*Fixed Dose Combination*)	94	70.1						
	Release	40	29.9						
BTA status	Positive	103	76.9						
	Negative	31	23.1						
Comorbidity	Yes	100	74.6						
	No	34	25.4						

Table 2
Frequency distribution of anaemia degrees based on treatment period, type of O, AT and BTA status in intensive phase pulmonary TB sufferers for the period 1 January 2022-30 November 2022 in the inpatient ward of KRMTWongsonegoro Regional Hospital, (n=134)

Variable		Degree of anaemia						Total	
		Mild		*Moderate*		*Severe*			
		n	%	n	%	n	%	n	%
Treatment Period (weeks)	1	47	56.6	33	39.8	3	3.6	83	100
	2	14	60.9	8	34.8	1	4.3	23	100
	3	3	42.9	3	42.9	1	14.3	7	100
	4	2	28.6	5	71.4	-	-	7	100
	5	1	33.3	2	66.7	-	-	3	100
	6	-	-	1	100	-	-	1	100
	7	3	50.0	2	33.3	1	16.7	6	100
	8	1	25.0	1	25.0	2	50.0	4	100
Types of OAT	FDC (*Fixed Dose Combination*)	47	50.0	41	43.6	6	6.4	94	100
	Release	24	60.0	14	35.0	2	5.0	40	100
BTA status	Positive	57	55.3	40	38.8	6	5.8	103	100
	Negative	14	45.2	15	48.4	2	6.5	31	100

DISCUSSION

The results of this study show that anaemia in pulmonary TB sufferers is predominantly found in men and the elderly group. This is not in line with the theory which states that women generally experience anaemia compared to men. For women who experience heavy menstruation, pregnancy, childbirth, and breastfeeding, inappropriate dietary habits can often cause anaemia.

This research shows that elderly people have the highest proportion compared to other age groups. The elderly experience a process of cell degeneration, causing a decrease in the number of bone marrow erythroid progenitors, and an increase in *hematopoietic stem cell resistance* to *erythropoietin*. The process of cell degeneration that occurs in the elderly also results in a decrease in the kidney's ability to produce sufficient. This can cause a decrease in plasma hemoglobin levels that occurs when entering the fifth decade of life.

Elderly people who experience anaemia can also be caused by comorbidities (comorbidities). The results of other studies state that anaemia has the highest percentage in TB sufferers who have comorbidities compared to those who do not have comorbidities. Comorbidities commonly experienced by elderly people include gastric atrophy which causes malabsorption of nutrients, gastrointestinal bleeding, *myelodysplastic syndrome*, and chronic conditions (eg chronic inflammation or chronic kidney disease).

The results of this study show that the majority of anaemia in pulmonary TB sufferers in the intensive treatment phase during the inpatient treatment period have comorbidities. These comorbidities include cardiovascular disease (hypertension, *congestive heart failure*), DM, hypoalbumin, HIV, *chronic kidney disease*, renal insufficiency, etc.

The results of this study show that pulmonary TB sufferers in the intensive treatment phase who underwent treatment in the inpatient room had an average Hb level of 10.8 g/dL. One other study even stated that the average Hb level for pulmonary TB sufferers was 9.65 g/dL. The highest percentage is found in *mild* anaemia and the lowest percentage is in *severe anaemia*. Several other research results reveal that TB disease without OAT treatment has the highest percentage of *mild anaemia*[8,10–13] and the lowest percentage of *severe anaemia.* TB sufferers

who take intensive phase OAT and those who do not take intensive phase OAT have the same degree of anaemia.

Mycobacterium tuberculosis (MTB) infection can cause *anaemia of chronic disease* (ACD). ACD can be diagnosed based on Hb levels. One study stated that the percentage of ACD in TB sufferers was 49.82%. This is supported by one study which stated that ACD in TB sufferers was 97.7%.

ACD may result from the role of *pro-inflammatory cytokines* in altering iron metabolism and reducing erythrocyte production and lifespan. Research results suggest that the risk factor for anaemia in adult TB sufferers is high levels of. *Pro-inflammatory cytokines* also stimulate the *hepcidin synthesis process* in the liver. High levels of IL-6 increase *hepcidin synthesis* which causes storage disorders and disrupts the process of iron absorption in the duodenum. Cytokines and other inflammatory mediators such as TNF-α, IFN- and *Y*, *hepcidin* contribute to the development of anaemia in B.[14] A high MTB load causes increased *hepcidin levels* and is associated with severe TB symptoms.[15]

Infectious diseases such as TB can also cause anaemia through various mechanisms, including impaired nutrient absorption and metabolism, ineffective. Manifestations of TB disease can also include nausea, vomiting, anorexia, or *hemoptysis*, which can lead to the risk of developing anaemia. Other studies show different results, that intensive phase OAT can cause a decrease in Hb levels. The content of intensive-phase oats such as *rifampicin, isoniazid,* and *pyrazinamide* affect the incidence of anaemia.

Worsening the degree of anaemia in TB sufferers can be caused by increased metabolic demands and duration of anaemia. On average, TB sufferers who take the intensive phase of OAT also experience mild to severe side effects. This can contribute to differences in the degree of anaemia among TB sufferers. Intensive phase OAT can cause an increase or decrease in Hb levels. The ingredients in intensive phase OAT such as *rifampicin, isoniazid,* and *pyrazinamide* reduce MTB proliferation so that the body's metabolic needs and inflammatory mediators are reduced to fight infection. This has an impact on increasing Hb levels.

Treatment Period

The results of this study show that the majority of pulmonary TB sufferers in the intensive treatment phase are in the 1st week. The 1st and 2nd weeks of the treatment period had a high percentage of *mild anaemia*. The 3rd week of the treatment period has the same percentage of *mild* and *moderate anaemia*. The 4th, 5th, and 6th week of treatment has a high percentage of *moderate anaemia*. The 8th week of treatment has a high percentage of *severe anaemia*. The degree of anaemia worsens as the intensive phase of OAT treatment progresses.

The results of this study are in line with the results of the Liver study which stated that the duration of OAT treatment was related to the incidence of anaemia. Another study shows that taking OAT in the intensive phase can cause a decrease in Hb levels. The average Hb level of pulmonary TB sufferers before taking OAT was 15.17 g/dL, but after taking OAT for 2 months the Hb level decreased to 12.73 g/dL. One of the side effects of intensive-phase OAT is hepatotoxicity. This is characterized by an increase in SGOT/SGPT of 22% which occurs during 2 months of treatment. Hepatoxicity can cause nausea and vomiting. This also plays a role in worsening the degree of anaemia.

Intensive phase OAT content such as *isoniazid* and *pyrazinamide* can cause sideroblastic anaemia. Another ingredient, namely rifampicin, can cause hemolytic anaemia. Intensive phase OAT in *rifampicin, isoniazid,* and *pyrazinamide* has side effects

such as nausea and vomiting. Decreased intake in TB patients can cause disturbances in the electrolyte balance of calcium, sodium, and potassium, resulting in changes in cell metabolism and causing anaemia.

The results of this study are not in line with several other research results which state that the intensive phase of OAT has an impact on increasing Hb levels. One research result stated that TB sufferers who took intensive phase OAT experienced an increase in Hb. Hb levels increased after undergoing OAT treatment for 2 months. Hb levels before intensive phase OAT treatment averaged 11.1 g/dL and after intensive phase OAT treatment averaged 12.8 g/dL. The increase in Hb levels occurred significantly starting in the first 4 weeks of intensive phase OAT treatment until treatment was completed. The results of the study explained that *hepcidin* levels and the incidence of ACD decreased significantly after undergoing intensive phase OAT. Anaemia cases decreased as the treatment period progressed.

Types of OAT (Anti Tuberculosis Drugs)

The results of this study show that the majority of pulmonary TB sufferers on intensive phase OAT treatment consume the FDC type of OAT. Based on the degree of anaemia, the highest percentage of *mild anaemia* is found in Removable OAT, and *moderate anaemia as well as severe* anaemia are found in FDC. The ingredients in the intensive phase of FDC-type OAT include *rifampicin, isoniazid,* and *pyrazinamide* which can cause anaemia. *Rifampicin, isoniazid,* and *pyrazinamide* have side effects such as anorexia, nausea, and vomiting.

Pulmonary TB sufferers experience increased metabolic needs during the infection and inflammation process of the disease so they require adequate nutritional intake in the healing process. Conditions of anorexia, nausea, and vomiting can cause a decrease in nutritional intake so that the body experiences nutritional intake, one of which is iron. This can result in a worsening of the degree of anaemia. The mechanism of anaemia can also occur due to side effects of *rifampicin, isoniazid,* and *pyrazinamide*.

content that depends on *rifampicin* will direct to antigen I on the surface of erythrocytes. Drug-antidrug antibody complexes attach to the surface of erythrocytes and cause lysis by complement activation. The second mechanism is that *rifampicin* coats the surface of the cell membrane and drug-specific IgG antibodies attach to the drug, causing extravascular hemolysis, macrophages destroy erythrocytes that have been coated with IgG antibodies. Another mechanism occurs when the structure of the erythrocyte membrane can be influenced by the nonimmunological association of the drug with its membrane. *Rifampicin-dependent antibodies* interact with the I-antigen expressed on the erythrocyte surface and form immune complexes that cause complement-mediated hemolysis of erythrocytes. *Rifampicin-associated* IgG or IgM antibodies cause erythrocyte lysis.

Isoniazid (INH) consists of a synthetic derivative of nicotinic acid. INH can inhibit *aminolevulinate synthase-214*, thereby disrupting the process of erythrocyte formation and causing sideroblastic anaemia. INH can also cause suppression of blood cell precursors in the bone marrow, which can cause severe anaemia. INH directly inhibits *erythroid aminolevulinate synthase* (ALAS $_2$), altering the structure of ALAS $_2$ and blocking the binding of the cofactor *pyridoxamine 5-phosphate* (PLP) to ALAS $_2$. PLP is a phosphorylated derivative of vitamin B6. *Pyridoxamine 5-phosphate* is an active coenzyme form of vitamin B6, which plays a role in the metabolism of amino acids, glycogen, hemoglobin synthesis, and nucleic acids. The binding of the PLP cofactor will inhibit the formation of *human erythroid 5-aminolevulinate synthase* (hALAS $_2$). Inhibition of *pyridoxal kinase* or reaction with *pyridoxal* to form *pyridoxal*

isonicotinoyl hydrazone. So *isoniazid* inhibits the action of pyridoxine in the pyridoxine metabolism function.

Pyrazinamide can cause side effects such as anorexia, nausea, vomiting, and sideroblastic anaemia. Sideroblastic anaemia is a type of anaemia resulting from abnormal use of iron during erythropoiesis during *heme production.*[16] 55.8% of TB patients experienced serious side effects when taking *pyrazinamide*, of which 44.5% experienced hepatotoxicity and 23.% experienced gastrointestinal intolerance. Hepatotoxicity can cause nausea and vomiting. The risk of serious side effects from *pyrazinamide* increases with age and comorbidities. Nausea and vomiting can cause nutritional deficits, thereby increasing the risk of anaemia.

BTA Status

The results of this study show that BTA positive has the highest percentage in *mild anaemia*, while BTA negative has the highest percentage in *moderate anaemia*. Based on the degree of anaemia, the highest percentage of *mild anaemia* in BTA positive, and *moderate* and *severe anaemia* in BTA negative. The results of this study are not in line with one study which stated that positive BTA status dominates *moderate* and *severe anaemia*.

BTA status indicates the number of MTB in the body. Positive BTA can indicate a high number of BTA. The results of this study indicate that the worsening degree of anaemia occurs in TB sufferers who have negative BTA status. This is not in line with several previous research results which explained that the higher the number of BTA in the body of TB sufferers, the lower the Hb level in the blood. BTA positive worsens the degree of anaemia.

TB bacteria that invade the body cause an infection and inflammation process, thereby activating macrophages to release cytokines. *Pro-inflammatory cytokines* such as TNF-α, IFN-γ, and IL-6 affect disorders of iron metabolism and the erythropoiesis process. Another impact of *pro-inflammatory cytokines* is that they stimulate the synthesis of *hepcidin*, which is an acute phase protein and inhibits *ferroportin-1* (responsible for the release of iron into the blood from the digestive tract, macrophages, and hepatocytes).

Anemic TB sufferers have higher *hepcidin levels* than those without anaemia. The higher the number of MTB, the higher the levels of *hepcidin* which will affect the severity of anaemia. The TB infection process will cause an increase in the body's metabolism. Increased metabolic demands of the body may influence the development of anaemia. The impact of increasing the body's metabolism is loss of nutrients. Increased metabolic demands and nutritional loss can influence the development of anaemia in TB sufferers.

CONCLUSION

Intensive-phase pulmonary TB sufferers have the highest percentage of *mild anaemia.* The degree of anaemia worsens as the intensive phase of OAT treatment progresses. Intensive phase pulmonary TB sufferers who take FDC type OAT have a high percentage of worsening anaemia. Patients with intensive phase pulmonary TB who have BTA negative status experience worsening degrees of anaemia.

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CONFLICT OF INTEREST

Neither of the authors has any conflicts of interest that would bias the findings presented here.

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