Factors Associated with Depression Scores in Patients with Pulmonary Tuberculosis at Dr. Pirngadi General Hospital Medan

Risni Nanda[1]*, Bahagia Loebis[1], Vita Camellia[1]

Departement of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara

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***Abstract*- Objectives:** It is known that the prevalence of depression is quite high in pulmonary tuberculosis patients, associated with poor adherence leading to irregular treatment and low treatment success rates. **Method:** This study is a multivariate predictive conceptual framework study with a cross-sectional approach to 111 subjects at the Dr. Pirngadi General Hospital, Medan in June 2020 to August 2020. This study aims to determine what factors are associated with depression scores. The measuring instrument used is the Hospital Anxiety and Depression Scale-Depression (HADS-D). **Results**: After the multivariate test, the variables that were statistically significant to the total HADS-D score were age (p = 0.001), total cigarette consumption (p = 0.005), length of TB treatment (p <0.001), gender (p <0.001), employment status (p = 0.029), HIV status (p <0.001) and DM status (p <0.001). **Conclusion:** That there are several factors that are associated with depression scores in pulmonary tuberculosis patients, namely age, total cigarette consumption, length of TB treatment, gender, employment status, HIV status and DM status.

***Index Terms*-** pulmonary tuberculosis, depression, Hospital Anxiety and Depression Scale-Depression.

I. Introduction

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium Tuberculosis and generally attacks the lungs. Tuberculosis is a public health problem due to high morbidity and mortality worldwide in all age groups. Although all age groups are at risk of developing tuberculosis, tuberculosis affects adults in productive age more.[1] Globally in 2016 there were 10.4 million incidents of tuberculosis (CI 8.8 million - 12 million) which is equivalent to 120 cases per 100.000 population. The five countries with the highest incidence of cases are India, Indonesia, China, the Philippines and Pakistan.[2]

Depression is a mental disorder generally characterized by loss of interest or excitement, feelings of guilt or low self-esteem, disturbed sleep or appetite, decreased energy and poor concentration, insomnia or hypersomnia and occasionally suicidal thoughts.[3] The World Health Organization (WHO) estimates that more than 350 million people suffer from depression and that nearly 1.0 million people end their own lives each year. It is well known that the prevalence of depression is high among people with chronic disease, and several studies have reported that psychiatric morbidity is common in tuberculosis patients.[4]

An increase in proinflammatory cytokines in response to a medical illness can trigger depression, even in individuals with no history of psychiatric disorders. Tuberculosis infection produces an inflammatory and dysregulated response of the hypothalamic-pituitary-adrenal (HPA) axis. If a person is exposed to tuberculosis, T Helper 1 (Th1) cells will produce interferon γ, TNF α and cytokines such as interleukin 2 which interact to activate the function of antibacterial macrophages. These cytokines are important for cells to mediate the immune response against tuberculosis so that it can trigger depression through several biological mechanisms.[5]

Neurotransmitters such as 5 hydroxytryptamine (5HT), dopamine, norepinephrine play an important role in the pathogenesis of depressive symptoms and interact with inflammation. Proinflammatory cytokines reduce the bioavailability of dopamine and norepinephrine by inhibiting the enzyme phenylalanine 4 hydroxylase (PAH), which promotes the synthesis of Tyrosine (Tyr), which is a precursor to dopamine and norepinephrine. Low bioavailability of dopamine and norepinephrine, exacerbating somatic symptoms of depression such as fatigue and weakness. 5HT affects the polarization of macrophages, through 5HT2B and 5HT7 receptors to induce anti-inflammatory processes.[5]

From a study conducted by Dasa et al in 2019 in Ethiopia using the Patient Health Questionnaire (PHQ-9) measurement tool, it was found that age (p = 0.047), employment status (p = 0.04), family income (p <0.001) , type of TB treatment (p = 0.010), and length of TB treatment (p = 0.003) were associated with risk factors for depression in pulmonary TB patients.[6] From a study conducted by Kehbila et al in 2016 in Cameroon using the Patient Health Questionnaire (PHQ-9) measurement tool, it was found that gender (p <0.001), comorbidity (p <0.001), body mass index (BMI) (p < 0.001), treatment status (p = 0.001), family history with mental disorders (p <0.013) associated with risk factors for depression in pulmonary tuberculosis patients.[3] From a study conducted by Koyanagi et al in 2017 in Spain using measuring instruments Short Form 12, the health Utilities Index Mark 3, and EuroQol 5D found that age (p <0.0001), gender (p <0.0001), family income (p <0.0001), smoking (p <0 , 0001) and diabetes mellitus (p <0.0001) were associated with risk factors for depression in pulmonary TB patients.[7]

From the description above, there are several factors that influence depression in pulmonary TB patients, such as gender, age, place of residence, marital status, length of education, employment status, number of cigarette consumption, body mass index (BMI), HIV status, Diabetes Mellitus status, duration of TB treatment. Therefore, researchers need to conduct a study to determine what factors are associated with depression scores in pulmonary TB patients.

II. Methods

Patient Sample

This research is a predictive type of multivariate study with a cross-sectional approach, namely analyzing the relationship between several independent variables and the dependent variable using the Hospital Anxiety Depression Scale - Depression (HADS-D) instrument. It was carried out in the outpatient installation of Dr. Pirngadi Medan, North Sumatra from June to August 2020. The inclusion criteria included (1) recurrent cases of pulmonary TB patients who came to the pulmonary polyclinic of Dr. Pirngadi Medan; (2) 20-60 years old; (3) Taking anti-tuberculosis drugs for 1 month or more; (4) minimum education has completed junior high school; (5) the patient uses health insurance from the social security administering agency; (6) willing as a respondent and can be interviewed. The exclusion criteria were (1) comorbid with other psychiatric disorders; (2) physical weakness such as blindness, deafness and so on; (3) a family history of mental disorders. This study was approved by the Research Ethics Committee at the Faculty of Medicine, Universitas Sumatera Utara. Pulmonary TB patients who come for treatment at the Lung Polyclinic Dr. Pirngadi Medan who meets the inclusion and exclusion criteria will be given an explanation of the research then fill out the informed consent and be asked to sign the informed consent. After that, interviews were conducted and assessed the depression score using the HADS-D questionnaire. After that, the research data were collected and interpreted and processed further.

III. Statistical Analysis

Analysis of the data collected was performed using a statistical package for service solution software program (SPSS ver 23). Multivariate linear regression analysis can only be used if the requirements of the linear regression test are met, while the linear regression requirements include the distribution of normal residues (evidence with histogram graphs), mean residue = 0 (proving descriptively), no outliers (proof by Case Wise) Diagnostic), constant (proof with a scatter graph between the residue and the dependent variable), independent (proof by the Durbin-Watson test), no multicollinearity (proof with the Pearson correlation test and tolerance test) on independent variables, and the relationship between independent and dependent variables is linear (evidence with a scatter graph between independent variables and dependent variables).

Linear regression test steps for numerical independent variables are to test for normality using the Kolmogorov-Smirnov test, if at least one of the independent variables or numerical variables is normally distributed, the Pearson test will be performed. If the numerical independent variable correlation has a p value <0.25, the independent variable meets the requirements for inclusion in the multivariate linear regression analysis. After that, if the comparison of categorical independent variables has a p value <0.25, then the independent variable meets the requirements to be included in the multivariate linear regression analysis.

IV. Results

Table I. Demographic characteristics

	n (%)	Mean ± s.d.	Median (min-max)
Gender			
- male	68 (61.3%)		
- female	43 (38.7%)		
Age		36.84 ± 10.24	
Residence			
- Medan	89 (80.2%)		
- Outside Medan	22 (19.8%)		
Marital status			
- married	73 (65.8%)		
- not married	38 (34.2%)		
Length of education			12 (9-16)
Employment status			
- work	65 (58.6%)		

- does not work	46 (41.4%)		
Total consumption of cigarettes			8 (0-12)
BMI			19,85 (18,53-21,37)
HIV Status			
- yes	17 (15.3%)		
- not	94 (84.7%)		
DM status			
- yes	30 (27%)		
- not	81 (73%)		
Durations of TB treatment			4 (2-8)
Total HADS-D score		11.08 ± 4.79	

The characteristics of the study sample are presented in Table I. The categorical variables discussed in table I are gender, place of residence, marital status, employment status, HIV status, and diabetes mellitus status. Categorical data are presented in numbers (n) and percentages (%). The numerical variable discussed in table I is age, which is presented in terms of concentration (mean) and distribution (standard deviation) where data is normally distributed with the Kolmogorov-Smirnov test (n = 111) where p> 0.05. While the numerical variables of length of education, total cigarette consumption, BMI and duration of TB treatment, are presented in concentration (median) and distribution (minimum and maximum) because the data were not normally distributed with the Kolmogorov-Smirnov test (n = 111), where p <0.05 for each variable.

Table II. Bivariate analysis of independent variables with a categorical scale

	mean ± s.d.	Median (min-max)	p
Gender			
-male		8 (3-18)	< 0.001[a]
-female		16 (10-19)	
Residence			
-Medan	10.78 ± 4.77		0.177[b]
-Out of Medan	12.32 ± 4.79		
Marital status			
-married		11 (3-19)	0.468[a]
-not married		12 (3-19)	
Employment status			
-work		10 (3-18)	< 0.001[a]
-does not work		14 (3-19)	
HIV status			
-yes	14.65 ± 2.37		0.001[b]
-not	10.44 ± 4.84		
DM status			
-yes		16 (8-19)	< 0.001[a]
-not		9 (3-18)	

a = *Mann Whitney U test*

b = *t test independent test*

For the independent variables with a categorical scale, namely the variable gender, place of residence, marital status, employment status, HIV status, diabetes mellitus status consisting of only 2 groups for each variable. On the independent variables of residence and HIV status, an independent t test was carried out because the data were normally distributed (Kolmogorov-Smirmov test). The Mann Whitney U test was carried out on the independent variables of gender, marital status, employment status, and diabetes mellitus because the data were not normally distributed (Kolgomorov-Smirnov test), even though log transformation efforts had been made. From these data, using bivariate analysis shows that the independent variable has a p value <0.25, namely gender, place of residence, employment status, HIV status and diabetes mellitus status, so that the categorical independent variable data deserves to be included in the multivariate linear regression analysis test predictive conceptual framework.

Table III. Bivariate analysis of independent variables with numerical scale

Independent variable	Depression score
Age	r = 0.66 p = <0.001 n = 111
Length of education	r = -0.04 p = 0.67 n = 111
Total consumption of cigarettes	r = 0.29 p = 0.002 n = 111
BMI	r = -0.29 p = 0.002 n = 111
Duration of TB treatment	r = -0.67 p = <0.001 n = 111

Pearson Correlation Test

Other independent variables with a numerical scale are age, length of education, total cigarette consumption, BMI, length of TB treatment. Pearson test was performed because the depression score variable was normally distributed (Kolgomorov-Smirnov test). The Pearson correlation test was carried out because it fulfilled the requirements for the Pearson test, which is one of the normally distributed variables (with the Kolmogorov-Smirnov test) p> 0.05 and the linearity was met with a scatter graph. From table III it can be seen that for each independent variable the p value is <0.25 , except for the length of education variable, namely p = 0.67. Therefore, based on statistical considerations, the variable length of education can be considered not related to depression scores, so that the variable length of education is considered ineligible for inclusion in the multivariate linear regression analysis with a predictive conceptual framework.
Table IV. Resume of multivariate linear regression analysis

Second Multivariate		
Model	Obtained a model consisting of age, total cigarette consumption, duration of tuberculosis treatment, sex, occupational status, HIV status and diabetes mellitus status.	This model is obtained after the variables of residence and BMI are gradually removed using the backward method.
Assumption Test	Linearity: fulfilled Normality : fulfilled Residual mean zero: fulfilled. Residue of no outliers: fulfilled. Residual constant: fulfilled. Independent: fulfilled. There is no multicollinearity: fulfilled	Scatter gives a linear impression. The histogram and plot graphs give a normal impression. Average = 0. Residue value ranges from -3 to d. 3 standard deviations. Graphics do not form a specific pattern. The Durbin-Watson score is close to 2. Tolerance> 0.4.

Regression Equation	Depression score = 11.69 + 0.09 * age + 0.17 * total cigarette consumption - 0.49 * length of treatment TB + 3.52 * gender - 0.98 * employment status + 3.53 * HIV status + 2.32 * DM status	
***Adjusted* R^2**	79.4 %	The ability to relate age, total cigarette consumption, length of tuberculosis treatment, sex, work status, HIV status, diabetes mellitus status to explain depression score was 79.4%
Correlation Coefficient	Age = 0.19	The strength of the correlation is very weak and positive direction.
	Total consumption of cigarettes = 0.13	Very weak correlation strength and positive direction.
	Duration of TB treatment = - 0.21	Weak correlation strength and negative direction.
	Women than men = 0.36	Weak correlation strength and positive direction.
	Working versus not working = - 0.10	The strength of the correlation is very weak and the direction is negative.
	HIV positive compared to HIV negative = 0.27	Weak correlation strength and positive direction.
	DM positive compared to negative DM = 0.22	Weak correlation strength and positive direction.

By analyzing the backward method, a linear regression equation is obtained based on the resume above, namely depression score = 11.69 + 0.09 * age + 0.17 * total cigarette consumption - 0.49 * length of tuberculosis treatment + 3.52 * gender - 0.98 * employment status + 3.53 * HIV status + 2.32 * diabetes mellitus status. All linear regression assumptions, namely linearity, normality, mean zero residue, no outliers residue, independent, constant / homoscedasticity and no multicollinearity have been fulfilled.

Table V. Final results of multivariate analysis

Depression score	***Correlation Coefficients***	**Multivariate Regression β**	**p**
Constant		11.69	<0.001
Age	0.19	0.09	0.001
Total consumption of cigarettes	0.13	0.17	0.005
Duration of TB treatment	-0.21	-0.49	<0.001
Gender	0.36	3.52	<0.001
Employment status	-0.10	-0.98	0.029
HIV status	0.27	3.53	<0.001
DM status	0.22	2.32	<0.001

Adjusted R^2 79.4 %

V. Discussion

The results of the study show that the variables gender, age, number of cigarette consumption, length of TB treatment, occupational status, HIV status, and DM status are associated with depression scores in pulmonary TB patients. From the gender variable, namely women than men have a positive correlation coefficient, which means that women are associated with higher depression scores. In this study, the majority of sex was male (61.3%). In this study, after conducting a multivariate analysis of the sex of women compared to men, it was found that there was a relationship between gender and depression scores in pulmonary TB patients (r = 0.36, p <0.001), which means that female gender was associated with depression scores in pulmonary TB patients. This is in line with a study by Kehbila et al. In 2016 in Cameroon, where this study found an association between gender and depression scores in pulmonary TB patients (p <0.001).[3] The occurrence of hormonal changes in women during puberty, the menstrual cycle, postpartum and menopause. Estrogen and progesterone are ovarian steroid hormones that affect sexual development and the menstrual cycle in women. Estrogen also has an important role in the central nervous system, which affects the hypothalamus, hippocampus and cerebellum which largely controls cognitive function, motor skills and mood.[8]

The age variable has a positive correlation coefficient on depression scores, which means that the higher age in pulmonary TB patients is associated with a higher depression score. In this study the mean ± s.d. of age is 36.84 ± 10.24. After doing multivariate analysis, there was a relationship between age and depression score in pulmonary TB patients (r = 0.19, p = 0.001), which means that increasing age is associated with higher depression scores in pulmonary TB patients. This is in line with a study by Dasa et al. In 2019 in Ethiopia, where this study found an association between age and depression scores in pulmonary TB patients (p <0.047). Older age with low economic life, stigma, discrimination, side effects of OAT, stressful life events and chronicity of depression-related TB in pulmonary TB patients.[6]

For the employment status in this study, most of them are working (58.6%). In this study, after conducting a multivariate

analysis of work versus not working, it was found that there was a relationship between work status and depression scores in pulmonary TB patients (r = -0.10, p = 0.029), which means that work was associated with lower depression scores in pulmonary TB patients. This is in line with a study by Masumoto et al in 2014 in Japan, where this study found an association between employment status and depression scores in pulmonary TB patients (p = 0.017). For work status, it is assumed that TB patients who work so that they earn money, increase social interaction, and get support from work colleagues and family, can reduce depression scores in pulmonary TB patients.[9]

For the number of cigarette consumption in this study with the median value (minimum-maximum) is 8 (0 - 12). After conducting a multivariate analysis there was a relationship between the number of cigarette consumption and depression scores in pulmonary TB patients (r = 0.13, p = 0.005), which means that the increasing number of cigarette consumption was associated with higher depression scores in pulmonary TB patients. This is in line with a study by Koyanagi et al. In 2017 in Spain which also found a very significant relationship between smoking status and depression scores in pulmonary TB patients (p <0.0001).[7] The decrease in monoamine oxidase B (MAO B) together with nicotine has an effect on behavior. Nicotine use can increase susceptibility to depression, which is the dysregulation of the dopaminergic system in an addictive state. In addition, smoking also produces free radicals, namely an increase in reactive oxidative species (ROS) associated with depression.[10]

For HIV status in this study the majority were HIV negative (84.7%). In this study, after a multivariate analysis of HIV positive versus negative HIV, it was found that there was an association between HIV status and depression scores in pulmonary TB patients (r = 0.27, p <0.001), which means that HIV was positively associated with depression scores in pulmonary TB patients. This is in line with a study by Kehbila et al. In 2016 in Cameroon, where this study found an association between HIV status and depression scores in pulmonary TB patients (p <0.001).[3] Long-term infection in immune system cells causes the release of toxic viral proteins and increased release of proinflammatory cytokines, especially tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), interleukin 1 (IL-1), and interleukin 6 (IL- 6). Proinflammatory cytokines cause a decrease in tryptophan, thereby affecting the serotoninergic neurotransmitters in the brain, leading to depression.[11]

For diabetes mellitus status in this study, the majority of diabetes mellitus was negative (73%). In this study, after a multivariate analysis of positive DM compared to negative DM, it was found that there was a relationship between DM status and depression scores in pulmonary TB patients (r = 0.22, p <0.001), which means that DM was positively associated with depression scores in pulmonary TB patients. This is in line with a study by Koyanagi et al. In 2017 in Spain, where this study found an association between DM status and depression scores in pulmonary TB patients (p <0.001).[7] Glucose accumulation in the extracellular space because DM can bypass the blood brain barrier, and affects certain brain areas involved in mood and memory regulation. Oxidative stress plays an important role in the development of DM because of the high production of free radicals, cell damage, and disruption of antioxidant defense enzymes such as superoxide dismutase and catalase. Depression is also characterized by activating oxygen and nitrogen species pathways, which cause damage to lipids, proteins and DNA.[12]

For the length of TB treatment in this study, the median (minimum-maximum) value was 4 (2 - 8). After multivariate analysis, there was an association between TB treatment duration and depression scores in pulmonary TB patients (r = -0.21, p <0.001), which means that the increased duration of TB treatment was associated with lower depression scores in pulmonary TB patients. This is in line with the study by Dasa et al. In 2019 in Ethiopia, where in this study there was an association between length of TB treatment and depression scores in pulmonary TB patients (p = 0.003). There has been an adaptation to the disease as the length of TB treatment increases and symptom reduction with the help of health professionals in pulmonary TB patients.[6] The strength of this study is that based on the knowledge of researchers assessed from several literature reviews, studies with similar methods and measuring instruments have never been conducted in Indonesia using the HADS-D measurement tool to screen for depression symptoms that occur in pulmonary TB patients. The limitation of this study is that it is only possible to do cross-sectional due to limited resources.

VI. Conclusion

That there are several factors that are associated with depression scores in pulmonary tuberculosis patients, namely age, total cigarette consumption, length of TB treatment, gender, employment status, HIV status and DM status.

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AUTHORS

First Author – Risni Nanda, Departement of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara

Second Author – Bahagia Loebis, Departement of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara
Third Author – Vita Camellia, Departement of Psychiatry, Faculty of Medicine, Universitas Sumatera Utara

Corresponding E-mail: risninandapsy@gmail.com