



# Associated Risk Factors for Depression in MDR-TB Patients Receiving Cycloserine Therapy at dr. Soebandi Regional Hospital

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## Abstract

**Background:** The most common psychological disorder in cycloserine treatment is depression. The purpose of this study was to identify the risk factors associated with depression in MDR-TB patients receiving cycloserine therapy at dr. Soebandi Regional Hospital. Data were obtained from medical records and the Depression Anxiety Stress Scales (DASS-42) questionnaire from 89 MDR-TB patients at dr. Soebandi Regional Hospital in 2022-2024.

**Methods:** Data analysis was performed using the Lambda and Somers' tests, followed by multivariate analysis using ordinal logistic regression.

**Results:** Out of a sample of 89 patients, 27 (30.3%) experienced depression, with the majority experiencing moderate-level depression (18%). The bivariate test results showed that the variables that significantly influenced the level of depression were gender ( $P=0.011$ ), education ( $P=0.000$ ), occupation ( $P=0.037$ ), BMI ( $P=0.000$ ), and comorbidities ( $P=0.029$ ). Multivariate tests showed that three variables had a significant effect ( $P<0.05$ ) on the level of depression: gender ( $P=0.047$ ), occupation ( $P=0.001$ ), and comorbidities ( $P=0.011$ ). The top two dominant risk factors affecting the level of depression are occupation ( $OR=17.12$ ) and comorbidities ( $OR=9.14$ ).

**Conclusion:** Occupation and comorbidities are the risk factors that most influence the level of depression in MDR-TB patients receiving cycloserine.

**Keywords:** antibiotics, resistant, risk of depression, tuberculosis

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**Submitted:** December 23<sup>rd</sup>, 2024

**Accepted:** July 17<sup>th</sup>, 2025

**Published:** July 31<sup>st</sup>, 2025

**J Respirol Indones. 2025**

**Vol. 45 No. 3: 184–93**

<https://doi.org/10.36497/jri.v45i3.883>

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## INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB), caused by resistance of *Mycobacterium tuberculosis* to isoniazid and rifampicin, is a global health problem, with 450,000 cases and 191,000 deaths by 2021.<sup>1</sup> MDR-TB cases in Indonesia in 2022 amounted to 12,531, whereas East Java Province contributed the highest number of cases, with 1,595.<sup>2</sup>

Clinical treatment of MDR-TB is more complicated than sensitive TB due to the use of first- and second-line drugs, requires at least five drugs, and takes 18 to 24 months of treatment. Drug tolerance and side effects are problems experienced by patients due to the use of multiple medications in MDR-TB therapy.<sup>3</sup> These can have both economic and psychological impacts due to the length of

treatment, hindering patients' activities.

Compared to other second-line drugs, such as kanamycin, ethionamide, levofloxacin, pyrazinamide, and ethambutol, cycloserine has higher neurological and psychological side effects.<sup>4</sup> Symptoms usually appear within the first two weeks of therapy and disappear if the drug is discontinued.<sup>5</sup> Neurological effects include headaches and seizures, while psychological effects include depression, anxiety, and suicidal ideation.

Supriyanto et al in 2017 observed that cycloserine dosage can directly affect the central nervous system and cause psychological disorders.<sup>5</sup> The research results of Pang et al in 2022 showed that 9.28 percent of MDR-TB patients in China experienced psychological disorders during

cycloserine treatment, with moderate severity.<sup>6</sup> The most common psychological disorder in cycloserine treatment was depression, which amounted to 4.22%.

Research conducted by Tornheim et al in 2022 in a private hospital in Mumbai, India, found that the incidence of depression in cycloserine treatment was 102.6 per 1000 people per year.<sup>7</sup> Various factors can increase a person's risk of developing depression, including age, gender, education, occupation, body mass index (BMI), comorbidities, and length of treatment.<sup>8</sup>

The epidemiology of depressive side effects in cycloserine treatment is quite large, and the impact is very significant, so this research needs to be done. Research on risk factors for depressive side effects of cycloserine in MDR-TB patients, including age, gender, education, occupation, BMI, comorbidities, and length of treatment, has never been conducted.

The importance of this study is that MDR-TB patients with risk factors that affect the level of depression can be referred for prior consultation with a psychiatrist before cycloserine treatment. Psychiatrists are expected to provide preventive therapy against the side effects of depression with the use of cycloserine. MDR-TB patients receiving cycloserine should be monitored regularly for depressive side effects so that they can be recognized and treated early.<sup>9</sup>

## METHODS

This study used an analytic research design with an observational study. The design used in this study was a cross-sectional study. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Jember, Number: 2105/UN25.1.10.2/KE/2024. This study was conducted at dr. Soebandi Regional Hospital, Jember Regency, from April to May 2024.

The population in this study were all MDR-TB patients at dr. Soebandi Regional Hospital during the period April 30, 2022–April 30, 2024, who were still on treatment, namely a total of 115 people. This study used a non-probability sampling technique with an accidental sampling method, which involved subjects

in the hospital at the time of the study. The sample size in this study was calculated using the formula according to Slovin, and 89 samples were obtained.

Inclusion criteria for this study included patients diagnosed with MDR-TB based on WHO criteria and currently undergoing treatment at dr. Soebandi Regional Hospital, aged 18 years and over, currently undergoing treatment using cycloserine for two weeks or more, willing to provide information and participate in this study, and having complete medical records related to MDR-TB treatment. Exclusion criteria included patients who reported a history of psychological disorders at the first hospital visit, patients diagnosed with psychological disorders during initial screening using the Depression Anxiety Stress Scales (DASS), and MDR-TB patients who died, could not be contacted, or withdrew from the study.

The independent variables of this study are risk factors for cycloserine side effects, including age, gender, education, occupation, BMI, comorbidities, and length of treatment. The dependent variable in the study was the level of depression. This study used primary and secondary data for data collection. Primary data included age, gender, education, occupation, and depression levels obtained from questionnaires. Secondary data, namely BMI, comorbidities, and length of treatment, were obtained from patient medical records.

Primary data were collected through interviews using the DASS-42 questionnaire in patients who met the inclusion criteria. Research subjects must fill out an identity and informed consent form before data collection. Data analysis used in this study was the lambda statistical test, Somers, and ordinal logistic regression.

## RESULTS

From the research which was carried out for one month, from April 16, 2024, to May 31, 2024, at dr. Soebandi Regional Hospital, data were obtained for 89 MDR-TB patients who received cycloserine treatment and met the inclusion criteria. The frequency distribution of the characteristics of the study subjects is presented in Table 1.

Table 1. Frequency distribution of subject characteristics

Characteristic	n	%
Age		
≤30 years	35	39.3
>30 years	54	60.7
Gender		
Male	58	65.2
Female	31	34.8
Education		
No education	-	0
Elementary school	49	55.1
High school	34	38.2
University/College	6	6.7
Occupation		
Did not work	47	52.8
Work	42	47.2
BMI		
Underweight	39	43.8
Normal	37	41.6
Overweight	13	14.6
Obesity class I	-	0
Obesity class II	-	0
Comorbid		
No comorbidities	50	56.2
Comorbidities	39	43.8
Length of treatment		
Intensive phase	36	40.4
Advanced phase	53	59.6

The proportion of patients who experienced psychological disorders after receiving cycloserine therapy at dr. Soebandi Regional Hospital is presented in Table 2.

Table 2. The proportion of MDR-TB patients who experienced psychological disorders after receiving cycloserine therapy

Disorders	Level of severity				
	Not depression/ Not anxiety/ Not stress	Mild	Moderate	Severe	Very severe
Depression	62 (69.7%)	5 (5.6%)	16 (18.0%)	4 (4.5%)	2 (2.2%)
Anxiety	55 (61.8%)	5 (5.6%)	14 (15.7%)	12 (13.5%)	3 (3.4%)
Stress	60 (67.4%)	5 (5.6%)	15 (16.9%)	6 (6.7%)	3 (3.4%)

The results of bivariate analysis using the Somers and Lambda test of the effect of risk factors on the level of depression in this study sample are shown in Table 3. The variables that significantly affect the level of depression are gender ( $P=0.014$ ), education ( $P=0.014$ ), occupation ( $P=0.000$ ), BMI ( $P=0.001$ ), and comorbidities ( $P=0.027$ ).

Table 3. Bivariate analysis

Risk factors	Level of depression					P
	Not depression	Mild	Moderate	Severe	Very severe	
Age						
≤30 years	23 (25.8%)	3 (3.4%)	9 (10.1%)	0 (0.0%)	0 (0.0%)	0.801
>30 years	39 (43.8%)	2 (2.2%)	8 (9.0%)	4 (4.5%)	2 (2.2%)	
Gender						
Male	43 (48.3%)	3 (3.4%)	12 (13.5%)	0 (0.0%)	0 (0.0%)	0.011*
Female	19 (21.3%)	2 (2.2%)	4 (4.5%)	4 (4.5%)	2 (2.2%)	
Education						
Elementary school	25 (28.1%)	4 (4.5%)	14 (15.7%)	4 (4.5%)	2 (2.2%)	0.0001*
High school	32 (36.0%)	1 (1.1%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	
University/College	5 (5.6%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	
Occupation						
Did not work	23 (25.8%)	5 (5.6%)	13 (14.6%)	4 (4.5%)	2 (2.2%)	0.037*
Work	39 (43.8%)	0 (0.0%)	3 (3.4%)	0 (0.0%)	0 (0.0%)	
BMI						
Underweight	17 (19.1%)	5 (5.6%)	12 (13.5%)	4 (4.5%)	1 (1.1%)	0.0001*
Normal	33 (37.1%)	0 (0.0%)	4 (4.5%)	0 (0.0%)	0 (0.0%)	
Overweight	12 (13.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	
Comorbid						
No comorbidities	39 (43.8%)	4 (4.5%)	7 (7.9%)	0 (0.0%)	0 (0.0%)	0.029*
Comorbidities	23 (25.8%)	1 (1.1%)	9 (10.1%)	4 (4.5%)	2 (2.2%)	
Length of Treatment						
Intensive phase	23 (25.8%)	2 (2.2%)	7 (7.9%)	4 (4.5%)	0 (0.0%)	0.284
Advanced phase	39 (43.8%)	3 (3.4%)	9 (10.1%)	0 (0.0%)	2 (2.2%)	

Note: \*significant <0.05

Table 4. Multivariate analysis

Variable	Coeff.	P	OR
Gender	-1.259	0.047	3.52
Education			
Elementary school	0.954	0.539	-
High school	-0.803	0.652	-
Occupation	2.840	0.001	17.12
BMI			
Underweight	1.092	0.337	-
Normal	-1.810	0.156	-
Comorbid	-2.213	0.011	9.14

The results of the ordinal regression in the multivariate analysis are written in Table 4. The three variables that significantly influenced the level of depression were gender ( $P=0.047$ ), occupation ( $P=0.001$ ), and comorbidities ( $P=0.011$ ), with the dominant risk factors being occupation and comorbidities.

## DISCUSSION

The results showed that male patients were more susceptible to MDR-TB infection due to work environment and public exposure, workload, unhealthy lifestyle, and frequent work-related activities.<sup>10,11</sup> Most MDR-TB patients were >30 years old. This result aligns with research by Miftakhul in 2019, which stated that the highest age range for MDR-TB is 30–45 years and >45 years. The lifestyle at the age of >30 years is more intense and involves greater social interaction, making it vulnerable to MDR-TB infection.<sup>12</sup>

The majority of the samples in this study had only graduated from elementary school. This result is in accordance with the research of Prasetya et al in 2022, which showed that the characteristics of MDR-TB patients are mostly low education. Low education is associated with low knowledge absorption. Low absorption of knowledge about MDR-TB greatly influences patient non-compliance behavior and results in patients paying less attention to their health and nutrition, including in the prevention and treatment of MDR-TB.<sup>13</sup>

This study shows that most MDR-TB patients are not working. These results are in accordance with research by Kasron et al in 2019, which showed that most MDR-TB patients did not work. Unemployment

can lead to a lack of patient access to health services due to limited costs, such as transportation costs and additional medicines, even though the government currently covers treatment costs.<sup>14</sup> Patients who are not working tend to develop side effects of MDR-TB treatment because they do not seek regular follow-up. This is based on their opinion that going to health facilities requires money for transportation, while the available funds are prioritized to meet daily needs rather than treatment.<sup>15</sup>

The majority of the samples in this study had an underweight BMI. The research by Cahyani et al in 2021 found that the nutritional status of MDR-TB patients was mostly underweight. Poor nutritional status can cause physical weakness and reduced endurance, thus increasing sensitivity to infection.<sup>16</sup>

This study found that MDR-TB patients mostly underwent treatment in the advanced phase, in accordance with the research of Rahayu et al in 2023, which also observed that most MDR-TB patients were undergoing treatment in the advanced phase. In the advanced phase, MDR-TB patients can adapt to the disturbances that occur due to the side effects of MDR-TB drugs, thereby increasing treatment adherence.<sup>17</sup>

The results showed that most MDR-TB patients did not have comorbidities. This is similar to research by Kasron et al in 2019, which pointed out that most MDR-TB patients did not have comorbidities. MDR-TB cases are common in patients of young age, while comorbidities are more common in patients of older age.<sup>14</sup>

This study revealed that patients with MDR-TB undergoing cycloserine therapy experienced not only depression but also other psychological disturbances such as anxiety and stress at varying levels of severity. While the majority of patients did not exhibit symptoms, a significant proportion experienced moderate to very severe conditions, particularly in the domains of anxiety and stress. These findings highlight the importance of regular mental health monitoring and the provision of psychological support during treatment, considering the potential neuropsychiatric side effects of long-term cycloserine

use.

Of the 89 samples, 30.3% of patients experienced depression, with 18% experiencing moderate depression, 5.6% experiencing mild depression, 4.5% experiencing severe depression, and 2.2% experiencing very severe depression, characterized by sadness, loss of interest, feeling worthless, and difficulty starting activities. Moderate depression affects the thinking process, communication, and social activities in patients.<sup>18</sup>

That result is consistent with previous research that 9.28 percent of MDR-TB patients in China experienced moderately severe psychological disorders during cycloserine treatment, with depression being the most common.<sup>6</sup> The ability of cycloserine to cross the blood-brain barrier and the interaction of cycloserine with NMDA receptors lead to the onset of psychotic symptoms.<sup>5</sup>

This study did not find any effect of age on the level of depression. In line with the research of Ariyanto et al in 2020, age was not related to depression. Ages under 30 years and over 30 years have the same risk of developing depression. Individuals under 30 years of age are found to have the most symptoms of psychological trauma, with the most common complaints being feelings of constant alertness and feeling alone or isolated.<sup>19</sup> Depression in the age range above 30 years arises due to illness and weakened conditions, coupled with stressful events that can trigger depression.<sup>20</sup>

This study shows that gender affects the level of depression, and it was found that both patients with very severe depression were female. These results are similar to research by Ambaw in 2020, which stated that gender was associated with depression in MDR-TB patients. Depression is more often diagnosed and found in women because they are more often examined. Women are more likely to experience depression due to hormonal differences with men, childbirth, and menopause. Women have the hormones estrogen and progesterone, which men do not have. Increased and decreased levels of both hormones can affect parts of the nervous system related to mood and can affect the occurrence of

depression.<sup>21,22</sup>

The hormone estrogen plays an important role in reproduction and the development of sexual characteristics. Changes in estrogen levels, such as a decrease during menopause and an increase during pregnancy, can increase the occurrence of depression. Progesterone is more involved in regulating the menstrual cycle and pregnancy. Changes in progesterone levels can affect mood, especially before and during menstruation and after childbirth.<sup>21</sup>

These hormonal changes can affect the balance of chemicals in the brain, such as serotonin, which can affect mood and the risk of depression. Hormonal changes that only occur in women can increase the risk of depression compared to men.<sup>21</sup> Women may also experience a lack of support from their husbands, which may increase the risk of further depression.<sup>23</sup> Psychoeducational interventions can be provided to women who experience depression due to hormonal changes. These interventions can help increase confidence, reduce stigma, and improve adherence to MDR-TB treatment.<sup>24</sup>

Education of MDR-TB patients had a significant effect on the level of depression. Patients with primary education had a higher level of depression than patients with secondary and higher education. This is in accordance with previous research, which stated that the final education level was associated with depressive status in TB patients.<sup>25</sup> Low education can be related to a lack of knowledge that can potentially trigger depression because it is known that knowledge can affect a person's mental health.<sup>26</sup>

Low education greatly affects the occurrence of depression due to a lack of understanding in dealing with problems. Individuals with higher education have broader knowledge to control themselves and overcome their difficulties. Rational responses in dealing with problems in individuals with higher education are better than in individuals with lower education, so that the incidence of depression can be minimized.<sup>27</sup> Health education is needed to reduce symptoms of depression in MDR-TB patients.<sup>28</sup>



This study observed that occupational status had a significant effect on the level of depression. In accordance with the research of Soladia et al in 2019, which obtained a relationship between work and depression levels. Patients who do not work have higher levels of depression than patients who work.<sup>29,30</sup>

Multidrug-resistant tuberculosis can endanger the mental health of patients and can worsen in housewives due to the accumulation of household chores, the absence of a husband's involvement in caring for children and doing homework, and limited access to socializing with other adults. Students are at higher risk for mental health problems due to pressure from teachers or lecturers, parents, and factors such as academic demands, responsibilities, study workload, tight schedules, lack of rest, conflicts with friends, and stigma towards TB.<sup>29,30</sup>

High levels of stress, TB symptoms, and treatment side effects experienced by students affect daily life and mental health conditions. Unemployed and retired people may experience depression due to loss of social contact and status or stress related to loss of income. Depressive events can arise as a result of financial difficulties experienced by unemployed patients.<sup>29,30</sup> Unemployed individuals require support from social networks to reduce the risk of experiencing depression.<sup>31</sup>

The results of testing the effect of BMI on the level of depression showed a significant effect. Patients with underweight BMI had the highest level of depression compared to patients with normal BMI, overweight, obesity class I, and obesity class II. Previous research also revealed that BMI had a correlation with the depressive status of MDR-TB patients. Patients with underweight BMI were more at risk of depression than patients with normal BMI.<sup>32</sup> Another study conducted by Pang et al in 2022 pointed out that underweight was a risk factor for the incidence of psychiatric disorders in patients receiving cycloserine treatment.<sup>6</sup>

Patients with underweight BMI were the most numerous, and one of the patients with severe depression had an underweight BMI. Underweight

conditions can potentially cause physiological depression, especially when certain nutrients are lacking that can disrupt the body's metabolic balance, including carbohydrates, protein, fat, and vitamins. Insufficient intake of complex carbohydrates results in decreased insulin levels, which can trigger depression due to decreased serotonin production.<sup>33</sup>

This study found that one patient with an overweight BMI had a very severe level of depression. Research conducted by Badillo et al in 2022 showed that men and women with an overweight BMI had a higher prevalence of depression-related symptoms than men and women who had a normal weight. One biological explanation for the relationship between overweight and depression is the regulation of the HPA-axis (hypothalamus-pituitary-adrenal axis).<sup>34</sup>

Obesity affects the HPA-axis dysregulation in the human brain, which can cause mood and thought disturbances that lead to depression. Overweight condition or obesity increases the risk of diabetes mellitus and insulin resistance, which can induce physical and chemical dysfunction in the brain, increasing the risk of depression.<sup>34</sup> Adopting a healthy diet that meets food-based dietary recommendations and nutritional needs is important to prevent, slow the progression of, or manage depressive symptoms and promote optimal mental health.<sup>35</sup>

Comorbidities had a significant effect on the level of depression. Patients with comorbidities had a higher level of depression than patients who did not have comorbidities. The result is in accordance with previous studies conducted by Nahda et al in 2017 and Azam et al in 2020, which stated that comorbidity was one of the factors causing depression. Comorbid diseases and chronic diseases are risk factors for complex mental health problems, characterized by increased burden of mind due to illness, decreased quality of life, high mortality rates, financial issues, and family emotions.<sup>8</sup>

Patients with comorbidities in this study were almost entirely DM, and there was one patient with HIV comorbidity. Diabetes causes various

complications, both microvascular and macrovascular, as well as neuropathy and psychological issues. Hyperglycemia in patients with diabetes mellitus causes metabolic disturbances and a lack of nutritional intake for the brain, triggering depression. This condition is suspected to occur due to the inability of the HPA-axis and neurotransmitter system to regulate the brain.<sup>36</sup>

HIV infection is closely associated with depressive disorders. The cause can be due to the presence of HIV disease, which can affect the psychological condition of the patient, or the effects of HIV agents that have infected the central nervous system. The course of HIV disease occurs progressively, the spread is wide and fast, and the stigma and discrimination from the environment against HIV patients can cause psychological stress. These psychological disorders, if not properly managed, can lead to depression in patients with HIV.<sup>37</sup>

Intervention efforts that can be provided to MDR-TB patients with comorbidities include providing good psychosocial support, including psychological therapy or counseling if needed, to reduce stress and the risk of depression in MDR-TB patients.<sup>38</sup>

The results of this study stated that the length of treatment did not influence the level of depression in MDR-TB patients. The result is supported by the research conducted by Ariyanto et al in 2020, which showed no relationship between the length of treatment and the incidence of depression.<sup>39</sup>

Symptoms of MDR-TB tend to be worse during the intensive phase because patients experience coughing, chest pain, night sweats, and fever, which can affect daily activities. The symptoms experienced by patients can interfere with sleep quality, appetite, and self-esteem, making them more likely to experience depression.<sup>39</sup> Prolonged MDR-TB treatment can also result in social isolation, job loss, socioeconomic effects, and long-term psychological effects on patients that can trigger depression.

The absence of the effect of length of treatment on the level of depression in this study is because patients with a long duration of therapy in the

advanced phase have adapted to the changes that accompany treatment. Patients who are still in the intensive phase realize that they must undergo treatment to get well, so they try not to feel burdened by undergoing treatment. Those reasons cause both intensive-phase and advanced-phase patients to be equally protected from the risk of depression.<sup>40</sup>

Employment and comorbidities are the two main risk factors that affect depression rates. Unemployed patients are 17.12 times more likely to have depression, while patients with comorbidities are 9.14 times more likely. Unemployment can lead to stress, anxiety, and low self-esteem. Comorbidities can lead to poor treatment outcomes, increased mortality, and higher healthcare costs, further contributing to depression.<sup>41,42</sup>

## CONCLUSION

The majority of MDR-TB patients at dr. Soebandi Regional Hospital were >30 years old, male, had primary education, did not work, had underweight BMI, did not have comorbidities (56.2%), and were undergoing advanced phase treatment. The proportion of patients who experienced depression was 27 people (30.3%). Risk factors that influence the level of depression in MDR-TB patients receiving cycloserine therapy are gender, education, occupation, BMI, and comorbidities. The risk factors that most influence the level of depression are occupation and comorbidities.

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