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Risiko Kematian pada Pasien Tuberkulosis Paru Berulang dengan Malnutrisi: Laporan Kasus dan Tinjauan Literatur Komprehensif

Risk of Mortality in Recurrent Pulmonary Tuberculosis Patient with Malnutrition: Case Report and Comprehensive Literature Review

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Abstrak

Tuberkulosis (TB) dan malnutrisi masih menjadi beban kesehatan masayarakat yang menantang di dunia. Kedua kondisi klinis tersebut dapat terjadi bersamaan dan menciptakan vicious cycle yang memperburuk infeksi TB atau status gizi.Laporan kasus ini bertujuan untuk mengkaji hubungan status gizi rendah (malnutrisi) penderita dengan kematian akibat TB paru. Perempuan usia 31 tahun datang ke poliklinik paru rumah sakit tersier di Jakarta untuk bulan ketiga kontrol pengobatan obat anti TB (OAT) sensitif obat. Tiga bulan sebelumnya, pasien menjalani rapid diagnostic test (RDT) untuk mengetahui resistensi OAT. Kesimpulan pemeriksaan antropometri pasien adalah sangat kurus dengan indeks massa tubuh (IMT) 15,6 kg/m^2. Sebelum terdiagnosis TB paru, pasien selalu kesulitan menaikkan berat badan. Selama perjalanan penyakit, BB pasien turun 5 kg per bulan. Pasien dinyatakan selesai pengobatan setelah 6 bulan menjalani terapi, tanpa ada perbaikan status gizi. Follow-up 1 tahun, pasien mengalami relaps TB paru dengan IMT 13,2 kg/m^2. Pasien meninggal 2 bulan setelah diagnosis TB relaps.. Perbaikan keluhan klinis dan konversi pemeriksaan bakteriologis merupakan indikasi keberhasilan terapi, termasuk peningkatan status gizi. Pencarian literatur komprehensif dilakukan di database jurnal PubMed, Cochrane, dan Scopus, dilanjutkan dengan analisis sesuai flowchart PRISMA 2020, untuk studi kohort prognostik kasus kematian pasien TB paru dengan malnutrisi. Terdapat hubungan IMT dengan risiko kematian pasien TB. Pengukuran antropometri khususnya IMT perlu dilakukan pada setiap pemeriksaan fisik kasus TB paru.

***Kata Kunci**: Indeks Massa Tubuh; Malnutrisi; Mortalitas; Tuberkulosis*

Abstract

Tuberculosis (TB) and malnutrition are still major public health problems in the world. These two clinical conditions can occur simultaneously and create a vicious cycle that worsens TB infection or nutritional status. This case report aims to examine the relationship between low nutritional status (malnutrition) of patients and death due to pulmonary TB. A 31 year old woman came to the pulmonary clinic of a tertiary hospital in Jakarta for her third month of drug-sensitive anti-TB drug (OAT) treatment control. Three months earlier, the patient underwent a rapid diagnostic test (RDT) to determine OAT resistance. The conclusion of her anthropometric examination was body mass index (BMI) of 15.6 kg/m^2. Before being diagnosed with pulmonary TB, she always had difficulty gaining weight. During the course of disease, her weight decreased by 5 kg per month. After undergoing treatment for 6 months, the patient was declared complete after 6 months of therapy, without any improvement in nutritional status. At 1 year follow-up,

the patient experienced a relapse of pulmonary TB with a BMI of 13.2 kg/m^2. She died 2 months after diagnosis of relapse TB. Improvement in clinical complaints and conversion to bacteriological examination are indications of successful therapy, including improvement in nutritional status. To analyze the relationship between malnutrition and pulmonary TB and death, the authors conducted a comprehensive literature search in the journal databases PubMed, Cochrane, and Scopus, followed by analysis according to the PRISMA 2020 flowchart, for a prognostic cohort study of cases of death in pulmonary TB patients with malnutrition. There is a relationship between BMI and the risk of death in TB patients. Anthropometric measurements, especially BMI, need to be carried out during every physical examination of pulmonary TB cases.

***Keywords**: Body Mass Index; Malnutrition; Mortality; Tuberculosis*

Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb). Although it primarily affects the respiratory system (pulmonary TB), Mtb can also be detected in the liver, gastrointestinal (GI) system, lymphoreticular system, skin, central nervous system, musculoskeletal system, and central reticular system. Based on the data by World Health Organization (WHO) in 2019, TB is one of the top 10 leading causes of death worldwide and ranked first on mortality rate of infectious diseases. Indonesia ranked second on world TB cases after India, with an increase of cases up to 69% from 2015 to 2019. It is estimated that in Indonesia alone, the number of people infected with TB reaches 845,000 with a death rate of 19,000 in HIV positive patients and 92,000 in HIV negative patients. (Adigun & Singh, 2020; Irawati et al., 2020; World Health Organization, 2020)

It has been demonstrated that there is a bidirectional relationship between malnutrition and TB, with malnutrition worsening a patient's response to treatment. (Chakaya et al., 2021; Musuenge et al., 2020) TB patients typically have worse nutritional condition than the general population. Patients with TB have a reduction in appetite, nutritional malabsorption, including both vitamin and macronutrient deficiencies, as well as metabolic alterations that may result in wasting and emaciation. Wasting is associated with a low Body Mass Index (BMI), which is <18.5 kg/m^2.(Lönnroth et al., 2010; Musuenge et al., 2020) Malnutrition induces secondary immunological insufficiency, which raises a patient's vulnerability to infections. As a result, malnourished patients have a 3 times higher chance of contracting TB infection than healthy people. Additionally, TB patients who were malnourished experienced slower healing periods and greater fatality rates. (Lönnroth et al., 2010; Musuenge et al., 2020)

Low BMI can impair the immune system, thereby increasing the incidence of TB and worsening TB treatment outcomes because nutritional deficiencies are associated with malabsorption of anti-TB drugs. Therefore, giving proper nutritional supplements or support can increase BMI, improve TB treatment outcomes, and reduce mortality rates.(Samuel et al., 2016) It is supported by study from Indonesia which states that BMI in TB patients who were given Channa striata supplements increased faster than the BMI of the population who were not given supplements.(Ma'rufi et al., 2020; Zhang et al., 2017) Higher BMI is generally related with a lower risk of tuberculosis, but there is an exception for BMI 28.0 kg/m^2, since large quantities of adipose tissue in obese people might negatively impact immunological function and reduce lung defense against bacterial infection, as well as raising risk of diabetes.(Kim et al., 2018; Lönnroth et al., 2010) Although various studies showed association between mortality and BMI, the evidence regarding this association is limited and inconsistent, because there is study which shows no association between BMI and TB mortality.(Samuel et al., 2016)

In this evidence-based case report, authors present a case of drug-sensitive adult pulmonary TB patient with history of relaps, and severe malnutrition. Authors aim to assess the relationship between BMI and mortality in adult pulmonary TB patients through available literature.

Patient	:	Adult pulmonary TB patients
Prognostic	:	Low BMI, underweight, malnutrition
Control	:	N/A
Outcome	:	Mortality

Case Report

A 31-years old woman came to the pulmonary clinic in tertiary hospital in Jakarta for her third month control of TB drug-sensitive (DS) on anti-TB drug treatment. She initially came with chief complaints of chronic coughing and was already bacteriologically diagnosed with TB. She still has symptoms of coughing and weight loss even though the primary one has now subsided. She didn't have any negative effects from the drugs, such as blurred vision, color blindness, or other issues. The patient was HIV negative and had no history of other systemic diseases. Five years ago, the patient was diagnosed with lung TB and underwent complete TB therapy. She showed clinical improvement and was determined cured through bacteriological testing by a specialist in pulmonology. During the five years, the patient had no known contact with any TB positive patients.

On physical examination, the patient was stable with normal findings. Her BMI was 15,6 kg/cm3 (severely underweight). Prior to being diagnosed with TBC, the patient has always had difficulties gaining weight, but ever since the diagnosis, the patient had undergone weight loss with around 5 kg of weight loss in a month. Other physical examinations showed no abnormalities, except for rales on the right apex of the lungs. On diagnostic work-up, the patient's sputum was found TB negative on her 2nd month of medication, which indicated successful conversion. The chest x-ray showed some remaining infiltrate on the right and left lungs (**Figure 1**). The patient was planned to be given Rifampicin 450 mg, Isoniazid 2 x 100 mg, and Ethambutol 750 mg every day, as well as monitoring for her nutritional status.

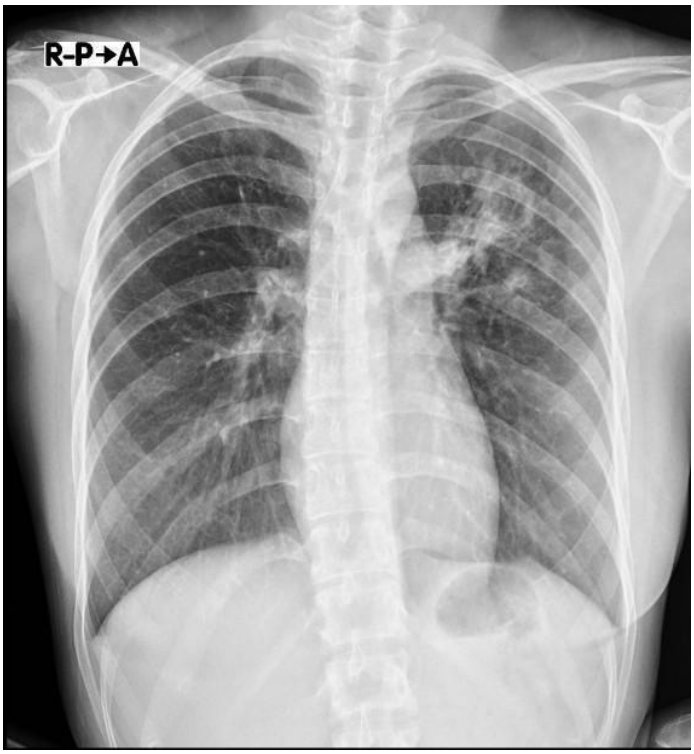

Figure 1. Patient's Chest X-ray

The improvement of clinical complaints and the conversion of bacteriological testing were indications of successful therapy, but she still had difficulties gaining weight. It is also important to note that the patient's underweight condition since the first TB diagnosis 5 years prior has become a concern for relapse. At 1 year follow-up, the patient experienced a relapse of pulmonary TB with a BMI of 13.2 kg/m2. The patient died 2 months after diagnosis of relapse TB

Discussion

TB is an infectious disease causing the highest number of infection-related mortality in the world. Indonesia has become one of the countries with the highest number of TB cases in the world. Mortality caused by TB could be due to the bacterial infection, emerging complications, or worsening comorbidities triggered by the infection. By enforcing the combination of antibiotics and the directly observed therapy system (DOTS), the worldwide mortality rate of TB is decreasing. However, TB is a chronic infection with a variety of comorbidities, hence, requiring comprehensive care (Adhikari, 2022).

Malnutrition and TB are two prevalent problems in developing countries. Both problems tend to interact, causing them to become a global burden. Individuals with malnutrition are more susceptible to TB, while TB patients often lose their appetite, which makes them prone to malnutrition. The catabolic metabolism in chronic infection also increases the basal energy expenditure. Aside from the susceptibility to infection, malnutrition in TB patient tend to correlate with unfavorable outcome of treatment and an increase in mortality (Feleke et al., 2019; Kant et al., 2015; Lönnroth et al., 2010; Musuenge et al., 2020).

Five cohort studies explored the association between BMI and mortality rate in adult patients with lung TB (Supplementary File A). To maximize the possibility of the validity and quality of the literature, researchers used the PRISMA guide for literature search **(Figure 2)** (Page et al., 2021). Critical appraisal was carried out independently by 3 authors (MIDR, AMKS, BILS) using the English version of the Oxford Center for Evidence-based Medicine Prognosis study tool (Supplementary File B). Differences in views on the review process were resolved through discussions involving pulmonologists (FI) and nutrition experts (LIO). The characteristics of each study are shown in Table 1 (Bhargava et al., 2013; Seid & Ayele, 2020; Yen et al., 2016, 2017; Zhang et al., 2017).

This case report included five cohort studies which met the clinical question. All studies showed underweight as a risk factor for increasing mortality in TB patients. Study by Bhargava et al showed TB patients with a BMI of <18.5 kg/m2 had a higher mortality risk compared to those with normal BMI (aOR 1.9 (CI 1.3-2.6) for male and aOR 2.4 (CI 1.4-3.9) for female). Similar results were shown in other studies with aOR 1.66 (CI 1.21-2.30)) and aHR 1.86 (CI 1.51-2.29). Study by Lai et al analyzed the mortality caused by TB according to time of death and found an increase in risk of early TB death in underweight patients (aOR 2.22 (CI 1.45-3.40)), but no significant relationship with late TB death (aOR 1.14 (0.72-1.81). Similar results were shown by Seid et al in which three per fourth of all deaths in TB patients happened within the 2 months intensive treatment phase. (Bhargava et al., 2013; Seid & Ayele, 2020; Yen et al., 2016, 2017; Zhang et al., 2017)The study by Zachariah et al showed moderate malnutrition (BMI <17.0 kg/m2) had a higher risk of death compared to normal BMI (aOR 1.8 (CI 1.0-3.5)) (Zachariah et al., 2002).

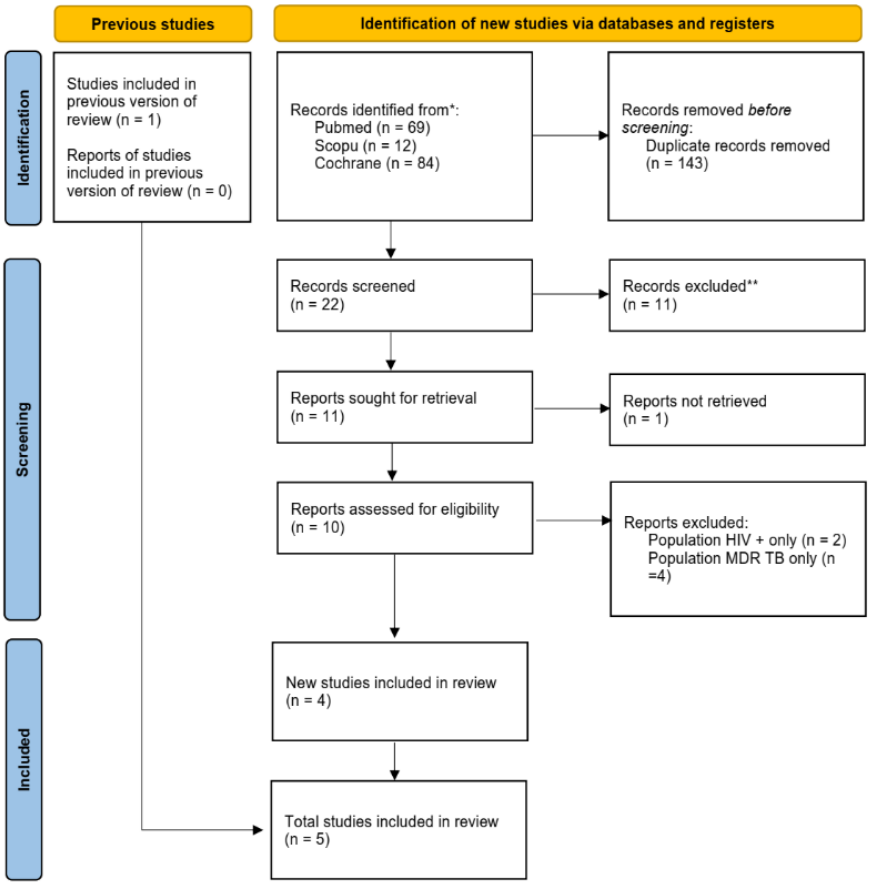

Figure 2. Literature Search Flow

Tabel 1. Characteristics of Cohort Studies

Study	Design	No. Subject	Duration of Study	Definition of TB Death	Number of Deaths n (%)
Bhargava A 2013(Bhargava et al., 2013)	Retrospective cohort study	1179	5 years	WHO criteria	60 (5%)
Yen F 2016(Yen et al., 2016)	Retrospective cohort study	1608	1 year	TB principal recorded cause	63 (3,3%)
Yen F 2017(Yen et al., 2017)	Retrospective cohort study	2410	2 years	TB principal recorded cause	389 (16,1%)
Lai H 2017(Lai et al., 2017)	Retrospective cohort study	1557	1 year	TB principal recorded cause	247 (15,8%)
Seid G 2020(Seid & Ayele, 2020)	Retrospective cohort study	284	8 months	WHO criteria	17 (6,0%)

Nutritional status of TB patients is not only determined by body mass index, but can also be measured by other parameters such as upper arm circumference, albumin level in the blood, and nutritional risk score (NRS). Systematic review by Waitt et al showed a number of parameters to predict risk of mortality. If bacterial resistance was taken into consideration, multidrug resistant (MDR) and extensively drug resistant (XDR) TB patients with malnutrition (BMI <18.5 kg/m2) are associated with higher risk of mortality (HR = 2.33 (CI;1.19-3.47)) (Alemu et al., 2021).

In our case, the patient is making good clinical progress and is benefiting from the treatment. However, the patient has been malnourished ever since before receiving her initial diagnosis five years ago, supporting the theory that malnutrition increases one's vulnerability to TB infection. The patient had more difficulty gaining weight after the diagnosis. She did not gain weight even after finishing her TB treatment for a year; this continued till the patient passed away. This confirmed the hypothesis that TB infection increases the risk of death by causing or worsening malnutrition in patients. It is extremely important to address the patient's undernutrition in order to reduce morbidity and death.

Conclusion

This evidence-based case report concluded that there is strong evidence association between undernutrition and higher risk of

mortality in adult pulmonary TB patients. The evaluation of BMI in the pulmonary TB patients should be conducted regularly to assess the patients' nutritional status and to evaluate treatment response. In patients with undernutrition to severe malnutrition, special nutritional intervention is required, especially during the intensive phase of treatment to overcome the comorbidity of TB patients. Collaborative care between specialties should be considered, including consultations and care by clinical nutrition specialists.

Conflict of interest

The authors declare that there is no competing interest regarding the manuscript.

Ethical Declaration and Consent

The patient, family and doctor responsible for the patient have agreed to permission to use clinical data as publication material, while maintaining patient confidentiality.

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Supplementary File A

Literature Searching

Database	Keywords	Findings
Pubmed	(((((((malnutrition[MeSH Terms]) OR (malnourished[MeSH Terms])) OR (undernourished[MeSH Terms])) OR (body mass index[MeSH Terms])) OR (BMI[Title/Abstract]))) AND (((tuberculosis[MeSH Terms]) OR (tuberculosis[Title/Abstract])) OR (TB[Title/Abstract]))) AND (((mortality[MeSH Terms]) OR (death[MeSH Terms])) OR (survival rate[MeSH Terms]))	69
Cochrane	(malnourished OR malnutrition OR undenourish OR body mass index OR nutritional status):ti,ab,kw AND (tuberculosis OR TB):ti,ab,kw AND (mortality OR death OR survival rate):ti,ab,kw	84
Scopus	TITLE (malnourished OR undernourish OR malnutrition OR "body mass index" OR bmi OR "nutritional status") AND (TITLE (tuberculosis OR tb) AND TITLE (mortality OR death OR "survival rate"))	12

Supplementary File B

Critical Appraisal – Cohort Study*

Studies	Appraised Aspect**							
	Validity				Importance		Applicability	
	Defined, representative sample	Patient follow-up	Objective outcome	Adjustment for important factor	Likely outcome	Precise prognostic estimation	Patients of the study were similar	This evidence will make a clinically important impact
Bhargava A 2013	✓	✓	✓	✓	✗	✓	✓	✓
Yen F 2016	✓	✓	✓	✗	✓	✓	✓	✓
Yen F 2017	✓	✓	✓	✓	✗	✗	✓	✓
Lai H 2017	✓	✓	✓	✓	✗	✓	✓	✓
Seid G 2020	✓	✓	✓	✗	✗	✗	✓	✓

*Oxford Centre for Evidence-based Medicine, Prognosis Study, English ver.
**The results of this critical appraisal are results that have been approved by all authors