

Body Mass Index As A Predictor Of Negative Sputum Conversion In Underweight Patients With Newly Diagnosed Pulmonary Tuberculosis: Evidence Based Case Report

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Abstract

Introduction: Tuberculosis infection remains a global problem especially in developing countries. In 2013, approximately 9 million of people were diagnosed with tuberculosis and 1.5 million died from tuberculosis. The association between tuberculosis and malnutrition is well established that tuberculosis can cause malnutrition and an individual with malnutrition is susceptible to tuberculosis. Therefore, low body mass index (BMI) as seen in patients with tuberculosis is often present at the time of diagnosis.

Aim: to assess the role of body mass index in predicting the negative sputum conversion in patients with tuberculosis

Methods: Searching was carried out using the database of Pubmed, Cochrane Central Register of Clinical Trials and Science Direct on 20th March 2015. The search strategy included following keywords and combinations “body mass index AND pulmonary tuberculosis AND sputum conversion”. Three articles was included in the critical appraisal.

Results: A study conducted by Putri FA et al revealed severely low BMI (BMI < 16 kg/m²) is significantly associated with longer negative sputum conversion (HR 0.56, 95%CI 0.38–0.81 and lower probability of conversion before 4 months (aRR 0.67, 95%CI 0.56–0.93). A study by Kenangalem E et al showed that in patients with pulmonary tuberculosis, the time to predict the accomplishment in negative conversion of sputum culture by lower body mass index is not significant with p value of 0.91 and hazard ratio of 0.99 (95%CI 0.85-1.16). A study by Hesselting AC et al revealed low body mass index (BMI <18 kg/m²) is not significantly associated with sputum culture conversion after 2 months of treatment but it significantly predicted a tuberculosis recurrence within 24 months after the completion of treatment.

Conclusion: Based on the critical appraisal of three studies, the predictor factor of sputum conversion in patients with pulmonary tuberculosis by body mass index is not significant and needs further study.

Keywords: tuberculosis, body mass index, sputum conversion

ABSTRAK

Introduksi: Infeksi tuberkulosis merupakan permasalahan global terutama pada negara berkembang. Pada tahun 2013, setidaknya 9 juta populasi dunia menderita tuberkulosis dan 1,5 juta populasi meninggal karena tuberkulosis. Asosiasi antara tuberkulosis dan malnutrisi diantaranya adalah tuberkulosis dapat menyebabkan malnutrisi dan individu yang malnutrisi rentan pada tuberkulosis. Oleh karena itu indeks massa tubuh (IMT) rutin diukur saat awal diagnosis dibuat.

Tujuan: untuk menelaah fungsi dari indeks massa tubuh dalam memprediksi konversi negatif dahak pada pasien dengan tuberkulosis

Metode: Pencarian literatur dilakukan menggunakan Pubmed, Cochrane Central Register of Clinical Trials dan Science Direct pada 20 Maret 2015. Strategi pencarian menggunakan kombinasi kata kunci “body mass index AND pulmonary tuberculosis AND sputum conversion”. Tiga artikel dipilih untuk telaah kritis jurnal.

Hasil: Hasil studi yang dilakukan Putri FA et al menunjukkan IMT yang sangat rendah (IMT < 16 kg/m²) secara signifikan berhubungan dengan konversi sputum yang lebih panjang (HR

0.56, 95%CI 0.38–0.81) dan kemungkinan lebih kecil untuk konversi sebelum 4 bulan (aRR 0.67, 95%CI 0.56–0.93). Studi oleh Kenangalem E et al menunjukkan pada pasien dengan tuberkulosis, waktu prediksi dalam pencapaian konversi negatif dengan indeks massa tubuh tidak signifikan dengan nilai p 0.91 dan rasio hazard of 0.99 (95%CI 0.85-1.16). Studi yang dilaksanakan oleh Hesselting AC et al mengemukakan indeks massa tubuh rendah (IMT < 18 kg/m²) tidak secara signifikan dalam konversi sputum setelah terapi selama 2 bulan namun secara signifikan memprediksi kekambuhan tuberkulosis dalam 24 bulan setelah selesai berobat.

Kesimpulan: Berdasarkan telaah kritis jurnal pada tiga studi, faktor prediksi konversi sputum pada pasien tuberkulosis dengan menggunakan indeks massa tubuh tidak signifikan dan membutuhkan studi lebih lanjut.

Kata kunci: tuberkulosis, indeksmassatubuh, konversidahak

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CLINICAL QUESTION

Based on the illustration above, the clinical question is formulated as follow:

“Can body mass index predict the negative sputum conversion in underweight patients with newly diagnosed pulmonary tuberculosis?”

CASE ILLUSTRATION

A 21-year-old woman presented with productive cough since 1½ months ago. She also complained of having low-grade fever, breathing difficulty, night sweats, weight loss of 6 kg and loss of appetite. Her physical examination was unremarkable except for increased respiratory rate, chest retraction, crackles on both lungs and decreased vesicular breathing sounds in the parasternal line from 3rd to 5th intercostal space. A sputum examination showed positive results (+3) and her chest x-ray revealed consolidation on the 3rd to 5th intercostal space in the parasternal line and infiltrates on both lungs. After 2 months of treatment with anti-tuberculosis drugs, her sputum results were negative.

INTRODUCTION

Tuberculosis infection remains a global problem especially in developing countries. In 2013, approximately 9 million of people were diagnosed with tuberculosis and 1.5 million died from tuberculosis.¹ Tuberculosis remains a big burden in Indonesia as according to World Health Organization (WHO), the country ranks fourth amongst countries with most cases of tuberculosis with estimated 450,000 new per annum.²

According to a study by Mallacan DC et al, the association between tuberculosis and malnutrition is well established that tuberculosis can cause malnutrition and an individual with malnutrition is susceptible to tuberculosis.³ Therefore, low body mass index (BMI) as seen in patients with tuberculosis is often present at the time of diagnosis.⁴ A study by Zachariah et al revealed that there is an increased of premature death in patients with tuberculosis and BMI less than 17 kg/m².⁵

The diagnosis of pulmonary tuberculosis is carried out based on the established guidelines by assessing the sputum results.⁶ Therefore, the aim of the report is to assess the role of body mass index in predicting the negative sputum conversion in patients with tuberculosis.

Table . Components of Clinical Question, Type of Question and Type of Study

Population	Underweight patients with newly diagnosed pulmonary tuberculosis
Intervention	Body mass index
Comparison	-
Outcome	Negative sputum conversion
Type of Question	Prognosis
Type of Study	Systematic review of cohort study, cohort study

METHOD

Search Strategy

Searching was carried out using the database of Pubmed, Cochrane Central Register of Clinical Trials and Science Direct on 20th March 2015. The search strategy included following keywords and combinations “body mass index AND pulmonary tuberculosis AND sputum conversion”.

Table 1. Search Strategy

Database	Search Strategy	Finding	Selected
Pubmed	Body mass index AND pulmonary tuberculosis AND sputum conversion	10	3
Cochrane	Body mass index AND pulmonary tuberculosis AND sputum conversion	5	0
Science Direct	Body mass index AND pulmonary tuberculosis AND sputum conversion	54	1

Inclusion Criteria of the Studies

The inclusion criteria of the studies are studies regarding nutritional status as the prediction of negative sputum conversion in underweight patients with newly diagnosed pulmonary tuberculosis, publication in the last 10 years, full-text availability, language in English, cohort study or control arm of randomized trial, and systematic review.

Exclusion Criteria of the Studies

A study was excluded in this review if it was an expert opinion and/or studies older than 10 years.

There are three articles chosen for this review (Figure 1), which are:

1. Hesselink AC, Walzl G, Enarson DA, Carroll NM, Duncan K, Lukey PT, Lombard C, P. R. Donald PR, Lawrence KA, Gie RP, van Helden PD, Beyers N. Baseline sputum time

to detection predicts month two culture conversion and relapse in non-HIV-infected patients. *Int J Tuberc Lung Dis.* 2010;14(5):560–570

2. Putri FA, Burhan E, Nawas A, Soepandi PZ, Sutoyo DK, Agustin H, Isbaniah F, Dowdy DW. Body mass index predictive of sputum culture conversion among MDR-TB patients in Indonesia. *Int J Tuberc Lung Dis.* 2014;18(5):564–570
3. Kenangalem E, Waramori G, Pontororing GJ, Sandjaja, Tjitra E, Maguire G, Kelly PM, Anstey NM, Ralph AP. Tuberculosis outcomes in Papua, Indonesia: the relationship with different body mass index characteristics between Papuan and Non-Papuan ethnic groups. *PLoS ONE.* 2013;8(9):1-9

Article Selection

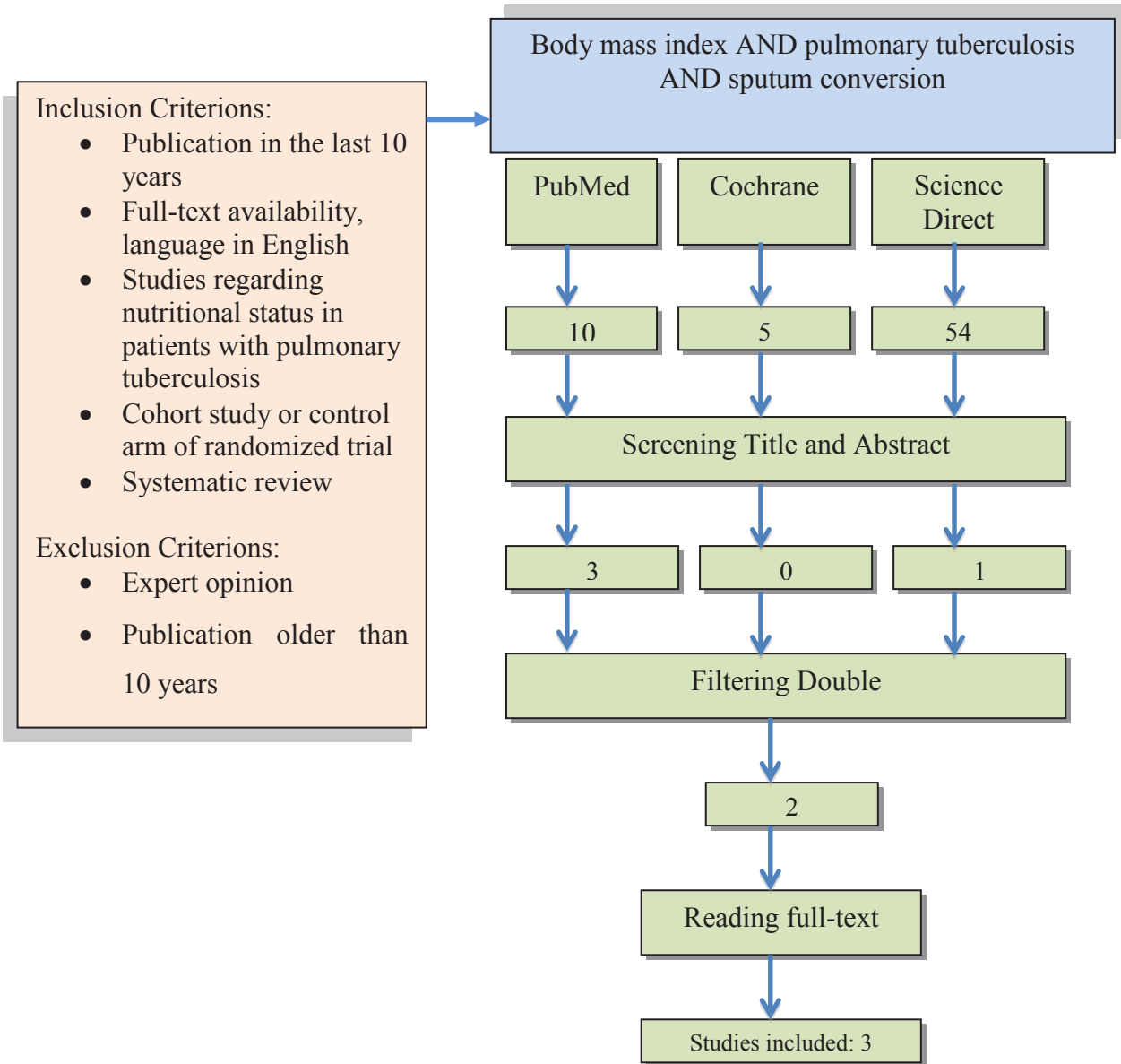


Figure 1. Literature Searching

RESULTS

The initial literature search from PubMed, Cochrane and Science Direct by using search strategy yielded 10 studies, 5 studies and 54 studies, respectively. After further selection based on the title and abstracts using inclusion and exclusion criteria, 65 studies were excluded hence four studies were filtered (Figure 1). Furthermore, a study was excluded due to the filtering double; therefore three studies were included in this review. Critical appraisal of the chosen studies was summarized on Table 2. Critical appraisal is assessed using three components, which are validity, importance and applicability.

Table 2. Summary of the Chosen Articles

Author (year of publication)	Study design	Study Objective	Method	Result	Level of Evidence*
Hesseling AC, et al. 2010	Prospective cohort study	The aim of the study is to evaluate whether 2-month bacteriological conversion and TB relapse can be predicted by baseline treatment time to detection (TTD).	Two hundred sixty three patients were recruited from 5 primary healthcare TB clinics within the public health system aged 20–65 years between 15 May 1999 and 15 July 2002. There were two primary study outcomes, which are sputum conversion after 2 months and bacteriological relapse and recurrence following anti-tuberculosis treatment for 24 months after treatment completion.	There is no significant association between body mass index (BMI) ≥ 18 kg/m ² and sputum culture conversion after 2 months of treatment but lower BMI shows higher probability of tuberculosis recurrence 24 months following treatment completion.	3
Putri FA, et al. 2014	Retrospective cohort study	The aim of the study is to assess the association between body mass index (BMI) and sputum culture conversion for patients with multidrug resistant Tuberculosis (MDR-TB).	Two hundred twenty MDR-TB patients were confirmed using sputum culture in liquid medium and line-probe assay. Patients were treated with the standard regimen except if they were resistant to the standard regimen. The outcomes of the study were time to culture conversion (primary) and probability of culture conversion within 4 months (secondary).	This study revealed that MDR-TB patients with severely underweight nutritional status (BMI ≤ 16 kg/m ²) had longer time to initial conversion and a lower probability for negative sputum conversion within 4 months. Other predictors for longer sputum culture conversion were female sex, resistance to injected drugs and high baseline smear grade.	3
Kenangalem E, et al. 2013	Control arm of randomized clinical trial	The objective of the study was to evaluate predictors of negative sputum conversion to pulmonary tuberculosis treatment	One hundred and eighty six patients (83 Papuan, 103 non-Papuan Indonesians) were confirmed with pulmonary tuberculosis. Patients were recruited from June 2008 to November 2009 and followed up for 6 months. In this study, the treatment outcomes were 1- and 2-month sputum culture and time to microscopy conversion. Clinical measures in this study were body weight, body mass index, chest radiograph, pulmonary function including forced expiratory volume in 1 second (FEV ₁) and hemoglobin level.	Negative sputum culture conversion in previously positive sputum culture was achieved by 62% (93/151) of participants at 1 month and 78% (94/120) of participants at 2 months. There is no significant result in the probability of sputum smear conversion by body mass index. However, a significant association is found between body weight and sputum conversion.	3

*OCEBM Levels of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

Validity

Validity of the studies was assessed. A study by PutriFA et al was a retrospective cohort study therefore they did not perform follow up. Blinded assessment of the outcome was not stated in studies by Putri FA et al and Kenangalem E et al (Table 3).

All studies performed adjustment for subgroups with different prognoses.

Table 3. Validity Assessment of the Included Studies

Parameter	Author and Year of Publication		
	Hesseling AC, et al. 2010	Putri FA, et al. 2014	Kenangalem E, et al. 2013
Sample	263 patients with untreated pulmonary tuberculosis	220 patients with confirmed multidrug resistant tuberculosis	186 patients with confirmed pulmonary tuberculosis
Follow up	Yes	No	Yes, 6 months.
Blinded assessment of outcome	Yes, culture examination is evaluated by a molecular biologist blinded to clinical and participant data. Radiological data is evaluated by pulmonologist blinded to patient clinical data	Not stated	Not stated
Adjustment for subgroups with different prognoses (if present)	Yes, outcomes of the study are further subdivided into several groups	Yes, since a very high proportion of underweight patients, they categorized the body mass index as normal or over weight, mild-moderate and severe underweight	Yes, the outcome of treatment was further subdivided into cured, completed, failed, died, defaulted or transferred out or dichotomized as successful and unsuccessful

Importance

The importance of the studies included the assessment of the outcomes and the precision of the prognostic estimates using 95% confidence interval (CI).

Table 4. Importance Assessment of the Included Studies

Author, year	Outcomes of the study	Precision of the prognostic estimates
Hesseling AC, et al. 2010	<p>Body mass index ≥ 18 kg/m² is not significantly associated with sputum culture conversion after 2 months of treatment</p> <p>Based on the multivariate Cox regression analysis, it showed TTD and BMI ≥ 18 kg/m² significantly predicted the tuberculosis recurrence 24 months following treatment completion.</p>	<p>Body mass index ≥ 18 kg/m² showed proportion between individuals with culture conversion 45/94 (47.9) and no culture conversion 75/130 (57.7) [Odd Ratio (95%CI 1.49 (0.87–2.53), p value 0.18)</p>
Putri FA, et al. 2014	<p>81% of the participants achieved negative conversion of sputum culture by the end of 8 months and the median time to culture conversion is 2 months. Time to initial negative sputum conversion is significantly longer and higher risk of failure in sputum conversion within 4 months in patients with BMI < 16 kg/m².</p>	<p>BMI < 16 kg/m² is significantly associated with longer negative sputum conversion (HR 0.56, 95%CI 0.38–0.81) and is also significantly associated with lower probability of conversion before 4 months (aRR 0.67, 95%CI 0.56–0.93) when compared to patients with BMI > 16 kg/m².</p>

Kenangalem E, et al. 2013	The percentage of study participants to achieve negative sputum culture conversion were 62% (93/151) at 1 month and 78% (94/120) at 2 months. The probability of sputum smear conversion by body mass index using Kaplan-Meier survival curve showed non-significant result. A univariate analysis showed significant (p value 0.03) association between body weight and sputum culture conversion with odds ratio of 0.93 (95%CI 0.87-0.99).	The probability of sputum culture conversion by body mass index is not significant with p value of 0.91 and hazard ratio of 0.99 (95%CI 0.85-1.16).
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TTD: treatment time to detection aRR: adjusted risk ratio HR: hazard ratio
 BMI: body mass index CI: confidence interval

Applicability

The study participants were similar to the illustrated patient. The second study recruited the multidrug resistant tuberculosis (MDR-TB) patients. Nevertheless, this study still can make a clinically important impact on the conclusion regarding the care of the patient.

Table 5. Designations of levels of evidence of prognostic research question according to OCEBM Levels of Evidence Working Group*

Level of Evidence	Prognosis
1	Systematic review of inception cohort studies
2	Inception cohort studies
3	Cohort study or control arm of randomized study
4	Case-series or case control studies, or poor quality prognostic cohort study
5	N/A

*OCEBM Levels of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

DISCUSSION

Based on the case illustration, the patient has an active pulmonary tuberculosis and low BMI (BMI = 17.3 kg/m²). Despite one of the chosen article depicts the MDR-TB, the study is still considered to be applicable since it can be utilized to make a clinical judgment regarding the patient's future prognosis.

Studies regarding the prognostic factors that influence the negative sputum conversion have been studied extensively. However, studies regarding body mass index to predict the negative sputum conversion is still limited. A study conducted by Putri FA et al revealed severely low BMI (BMI < 16 kg/m²) is significantly associated with longer negative sputum conversion (HR 0.56, 95%CI 0.38–0.81 and is also significantly associated with lower probability of conversion before 4 months (aRR 0.67, 95%CI 0.56–0.93) when compared to patients with higher BMI (BMI >16 kg/m²).⁷ Therefore, this study predicted a longer time needed to accomplish sputum conversion in as

well as higher likelihood of failure to attain sputum conversion within 4 months following treatment initiation in patients with MDR-TB.

A study by Kenangalem E et al showed that in patients with pulmonary tuberculosis, the time to predict the accomplishment in negative conversion of sputum culture by lower body mass index is not significant with p value of 0.91 and hazard ratio of 0.99 (95%CI 0.85-1.16).⁸ However, a univariate analysis between body weight and sputum culture conversion showed significant (p value < 0.05) association with odds ratio of 0.93 (95%CI 0.87-0.99).⁸ Therefore, this study revealed a significant association between body weight and culture conversion, not as a prediction factor towards negative sputum conversion.

A study by Hesselting AC et al revealed low body mass index (BMI ≈ 18 kg/m²) is not significantly associated with sputum culture conversion after 2 months of treatment but it

significantly predicted a tuberculosis recurrence within 24 months after the completion of treatment.⁹This therefore suggested that low BMI could be used as a predictor of tuberculosis recurrence.

Taken together, these three studies suggested the use of body mass index to predict the outcome of negative sputum culture conversion in patients with pulmonary tuberculosis is not significant and still needs further studies. However, in patients with MDR-TB there severely low BMI is associated with longer period of sputum conversion as well as increased probability of failure within 4 months. Based on previous evidences, body mass index lower than 18.5 kg/m² is known to be associated with higher mortality rate nevertheless the causal relationship is otherwise difficult to associate since tuberculosis is also considered to be the most frequent cause of wasting in patients with pulmonary tuberculosis.^{10,11,12} This therefore addresses a limitation of the study. Based on the illustrated case, the patient had BMI lower than 18.5 and managed to fulfill the course of treatment for 2 months with negative sputum conversion. This however strengthened by the result from a study by Hesseling et al, in which low BMI is not associated with sputum conversion after 2 months of treatment. For future direction, a review of studies regarding the causal relationship between low body mass index and the prognosis of tuberculosis should be addressed with the consideration of other confounding factors. Therefore, a direct causal relationship can be established.

CONCLUSION AND RECOMMENDATION

Based on the critical appraisal of three studies, the predictor factor of sputum conversion in patients with pulmonary tuberculosis by body mass index is not significant and needs further study. Based on the case illustration, the patient showed negative sputum conversion after completing the course of 2 months of treatment with anti-tuberculosis drugs which was supported by an evidence from Hesseling et al. Therefore it is recommended to further evaluate the causal relationship between low body mass index and the prognosis of tuberculosis should be addressed with the consideration of other confounding factors. Therefore, a direct causal relationship as well as a more precise prediction can be established.

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