The factors predicting mortality in pulmonary tuberculosis with acute respiratory failure

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ABSTRACT

Background: Acute respiratory failure might complicate pulmonary tuberculosis (TB), leading to a high mortality rate. The inadequate number of respiratory intensive-care unit (RICU) for TB patients might contribute to the mortality rate. However, other factors should be considered as predictors of mortality. This study aimed to analyse the predictors of mortality in hospitalized pulmonary TB patients with acute respiratory failure.

Methods: This prospective cohort study was implemented in a tertiary hospital in Surabaya, East Java, Indonesia. Demographic data, acid-fast bacilli (AFB) sputum smear, radiographic conclusion, biochemical analysis of blood, and clinical outcomes from active pulmonary TB patients who had acute respiratory failure were collected. A chi-square test was run to analyse the relationship between variables. The statistically significant variables were then evaluated with multivariate logistic regression analysis. Odds ratio (OR) and their 95% confidence intervals (CI) indicated factors that predicted mortality.

Results: 35 patients had acute respiratory failure among the 234 pulmonary TB patients who were being hospitalized in the pulmonary ward from July 2019 to September 2019. The average age of patients was 50.2 ± 15.1 years-old, 45.7% had Diabetes Mellitus, albumin level were 3.07 ± 0.56 g/dL, median procalcitonin 0.73 ng/mL, median Body Mass Index (BMI) 20.7 kg/m^2 , 54.3% with $\text{PaO}_2/\text{FiO}_2$ ratio 200–300 mmHg, mortality rate 42.9%. Multivariate logistic regression analysis illustrated lower albumin level ($<3 \text{ g/dL}$) (OR 12.254 (CI 95% [1.924–78.062]; $p = 0.008$) and Diabetes Mellitus (OR 8.448, CI 95% [1.350–52.872]; $p = 0.023$) were the independent predictor factors correlated to mortality.

Conclusions: Pulmonary TB cases that were aggravated with acute respiratory failure showed a high mortality rate. Lower albumin levels and Diabetes Mellitus were significantly related to in-hospital mortality.

1. Introduction

Tuberculosis (TB) remains a global health problem with high morbidity and mortality rate.¹ The high mortality rate of this disease was caused by many factors and complications such as hemoptysis, septic shock, and respiratory failure. Several studies reported the mortality rate in pulmonary TB patient who went through acute respiratory failure were as high as 65.6–74.0%.^{2,3}

The availability of the intensive-care unit (ICU) for TB patients is one important factor that can contribute to lower mortality rate, especially for pulmonary TB cases with acute respiratory failure, multiorgan failure, decreased consciousness, etc.⁴ In some developing countries, the availability of respiratory intensive-care unit (RICU) needed in treating pulmonary TB patients who need mechanical ventilation support was

limited. The inadequate number of RICU will eventually increase the mortality rate of the patients. Understanding the independent factors related to mortality in pulmonary TB patients who had acute respiratory failure will improve management and treatment.⁵ Some studies in several countries showed that old age, positive acid-fast bacilli (AFB) smear of sputum, severity of chest radiograph, presence of pneumonia, Diabetes Mellitus (DM), low albumin level, sepsis, and multiorgan failure were the mortality predictor factors in pulmonary TB with acute respiratory failure.^{6,7}

This study aimed to analyse factors that predict mortality in active pulmonary TB patients with respiratory failure.

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2. Methods

2.1. Population and design study

This prospective cohort study was implemented in the pulmonary ward of Dr. Soetomo Academic Hospital, a tertiary hospital in Surabaya, East Java, Indonesia between July to September 2019. Data were collected with consent from active pulmonary TB patients (≥ 18 years old) with acute respiratory failure, who were hospitalized in the pulmonary ward (not in the ICU nor treated with mechanical ventilator). This study received approval from Dr. Soetomo Academic Hospital Ethics Committee (1391/KEPK/VIII/2019). Diagnosis of active pulmonary tuberculosis was based on respiratory symptoms, chest x-ray, and AFB sputum.⁸ Respiratory failure refers to blood gas analysis with $\text{PaO}_2 \leq 60$ mmHg and/or $\text{PaCO}_2 > 45$ mmHg without supplementary oxygen or $\text{PaO}_2/\text{FiO}_2$ ratio < 300 mmHg with supplementary oxygen.⁹ Patients who were diagnosed with pulmonary malignancies, chronic kidney disease, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), acute heart failure, and chronic liver disease were excluded. The independent variables were age, AFB sputum smear results, thorax radiographic findings, concomitant pneumonia, sepsis, hypoalbuminemia, and DM. The dependent variable was mortality rate. Follow-up was carried out until two weeks after participating patients were discharged from the hospital.

2.2. Statistical analysis

Demographic data and patients' characteristics were descriptively presented in frequency and percentage for categorical data. Average standard intersection was used for continuous data. Mortality predictor factors were analyzed using Chi-square continue with multivariate logistic regression to obtain the mortality predictor factor model. The result was presented in Odds Ratio (OR) with a significant p-value of < 0.05 and a confidence interval (CI) of 95%.

3. Results

3.1. Patients characteristics

During the 3 months observation period, 234 tuberculosis patients were hospitalized in the pulmonary ward, of which 35 had acute respiratory failure. Of the 35 patients, 27 (77.1%) were male and 8 (22.9%) were female. Mean age was 52 years old. Mean hospitalization duration was 10.0 ± 5.83 days, 16 (45.7%) patients had DM as a comorbid disease. 23 (65.7%) patients had concomitant pneumonia which was categorized as community-acquired pneumonia (CAP). From physical examination, Body Mass Index (BMI) median was 20.76 kg/m^2 . Based on the laboratory result, mean albumin level was $3.07 \pm 0.56 \text{ g/dL}$. Median of procalcitonin level was 0.73 ng/mL . 19 (54.3%) patients had a $\text{PaO}_2/\text{FiO}_2$ ratio range between 200–300 mmHg. Microbiology examination showed 25 (71.4%) patients had positive AFB smear of sputum and 10 (28.6%) patients had negative results. Radiology examination demonstrated fibroinfiltrate with consolidation (65.7%) and cavity lesion (65.7%) as the common findings in the study subjects. The median chest X-Ray score in this study was 6, while the majority of the patients (60%) had a lower median total score (≤ 6). The median of the Sequential Organ Failure Assessment (SOFA) score was 3. The demographic data, radiology, microbiology, and laboratory results are presented in Table 1.

3.2. Mortality distribution

Among 35 patients with active pulmonary TB and acute respiratory failure, a total of 15 (42.9%) patients died and 20 (57.1%) patients survived (Table 2).

Table 1

Demographic data and characteristic of patients.

Characteristics	Results (n = 35)
Age (in years), mean (SD)	50.2 $\pm$ 15.19
Gender, n (%)	
Male	27 (77.1)
Female	8 (22.9)
Diabetes Mellitus, n (%)	
Yes	16 (45.7)
No	19 (54.3)
Pneumonia, n (%)	
CAP	23 (65.7)
HAP	0 (0)
Non-Pneumonia	12 (34.3)
BMI, kg/m^2 , median	20.76 (8.01–25.39)
Procalcitonin, ng/mL , median	0.73 (0.04–72.07)
< 0.05 , n (%)	9 (25.7)
$> 0.05 - < 0.5$, n (%)	5 (14.3)
$\geq 0.5 - < 2.0$, n (%)	5 (14.3)
$\geq 2.0 - < 10.0$, n (%)	9 (25.7)
≥ 10.0 , n (%)	7 (20)
Albumin, g/dL , mean $\pm$ SD	3.07 $\pm$ 0.56
$\text{PaO}_2/\text{FiO}_2$ ratio, mmHg, n (%)	
200–300	19 (54.3)
100–200	8 (22.8)
< 100	8 (22.8)
AFB, n (%)	
Negative	10 (28.6)
Positive	25 (71.4)
1+/2+/3+	6 (17.1)/12 (34.3)/7 (20)
Radiologic Findings, n (%)	
Fibroinfiltrate	9 (25.7)
Fibroinfiltrate + consolidation	23 (65.7)
Milliary	3 (8.6)
Cavity lesion	23 (65.7)
No cavity	12 (34.3)
Affected Area $< 50\%$	13 (37.1)
Affected Area $\geq 50\%$	22 (62.9)
Chest X-Ray Score, median	6 (2–9)
> 6 , n (%)	14 (40)
≤ 6 , n (%)	21 (60)
SOFA Score, median	3 (0–11)
Duration of hospitalization (days), mean $\pm$ SD	10.0 $\pm$ 5.83
Median	10 (2–23)

SD; standard deviation, CAP; community-acquired pneumonia, HAP; hospital-acquired pneumonia, BMI; body mass index, AFB; acid-fast bacilli, SOFA; Sequential Organ Failure Assessment.

Table 2

The mortality rate of patients.

Variable	Results (n = 35)
Mortality, n (%)	
Yes	15 (42.9)
No	20 (57.1)

3.3. The factors that predict mortality in pulmonary TB patients with acute respiratory failure

Mortality predictor factor analysis was done in two steps. The first step was bivariate analysis. Because the data is categorical, Chi-square test was used. Then predictor factors with p-value < 0.25 were evaluated using multivariate logistic regression analysis. Variables with p-value < 0.05 is statistically significant. Odds ratio (OR) and their 95% CIs indicated factors that predicted mortality.

Table 3 showed the result of Chi-square test. Variables of the non-survivor group were positive AFB smear result, pneumonia classification, hypoalbuminemia (albumin level $< 3 \text{ g/dL}$), SOFA score, and presence of DM.

Result of multivariate logistic regression analysis showed that hypoalbuminemia (OR, 12.254; 95% CI, 1.924–78.062) and DM (OR, of 8.448; 95% CI, 1.350–52.872) were significantly related to mortality

Table 3
Bivariate analysis of predictor factors and mortality.

Variable	n (%)	Mortality Rate		p-value	OR (CI 95%)
		Non-survivor (n = 15)	Survivor (n = 20)		
Age					
>60 y/o	12 (34.3)	4	8	0.411	0.545 (0.128–2.331)
<60 y/o	23 (65.7)	11	12		
DM status					
DM	16 (45.7)	11	5	0.005	8.250 (1.790–38.014)
Non-DM	19 (54.3)	4	15		
AFB					
Positive	25 (71.4)	14	11	0.022	11.455 (1.254–104.601)
Negative	10 (28.6)	1	9		
Hypoalbuminemia					
Yes	17 (48.6)	12	5	0.001	12.000 (2.374–60.648)
No	18 (51.4)	3	15		
Pneumonia					
CAP	23 (65.7)	12	11	0.123	3.273 (0.700–15.291)
Non-CAP	12 (37.1)	3	9		
SOFA score					
>2	22 (62.9)	13	9	0.012	7.944 (1.409–44.804)
≤2	13 (37.1)	2	11		
Chest X-Ray score					
>6	14 (40)	14	0	<0.001	
≤6	21 (60)	1	20		

OR; Odds ratio, CI; Confidence Interval, DM; Diabetes Mellitus, CAP; Community-Acquired Pneumonia, AFB; acid-fast bacilli, SOFA; Sequential Organ Failure Assessment.

increase in active pulmonary TB patients who had acute respiratory failure (Table 4). Kaplan-Meier survival curves showed that in hypoalbuminemia, the survival tends to decrease between 5–15 days with 0% survival rate. A higher mortality rate was seen in hypoalbuminemia than non-hypoalbuminemia patients ($p = 0.001$, log-rank test). A similar outcome was seen in the analysis of the presence of DM, the survival decreased between 5–15 days with 30% survival rate. A higher mortality rate was seen in patients with DM than non-DM patients ($p = 0.015$, log-rank test) (Fig. 1).

4. Discussion

The overall mortality rate in this study was 42.9%. Some studies reported similar results (37% and 44.4%).^{10,11} Other previous study demonstrated contrasting result, the mortality rate in TB patients who had acute respiratory failure were higher (ranging from 65.6% to 74.0%)^{2,3} compared to this study (42.9%). Several factors might affect these different results, such as patients' initial condition when first

Table 4
Multivariate analysis of predictor factors with mortality.

Variable	p-value	Odds Ratio	Confidence Interval (CI)	
			Lower	Upper
Presence of Diabetes Mellitus	0.023	8.448	1.350	52.872
Hypoalbuminemia	0.008	12.254	1.924	78.062

admitted to the hospital, comorbid and other concomitant diseases, early PaO₂/FiO₂ ratio, and medication before hospitalization.^{1,10,12}

This prospective study displayed the characteristic of 35 patients with active pulmonary TB and acute respiratory failure as the complications from July to September 2019. All patients were treated at the low-care ward due to the inadequate number of respiratory intensive-care unit (RICU).

Pulmonary TB is exceedingly endemic in Indonesia with a high burden of morbidity and mortality.¹³ Pulmonary TB patients with acute respiratory failure which required mechanical ventilation and intensive-care treatment often come late to the healthcare facilities. A higher mortality rate was seen at times when the intensive-care facilities were limited. Understanding the independent factors that predict mortality in these patients can be beneficial for early detection, appropriate management, and further complications prevention.

In this study, lower albumin serum level and the presence of DM were the independent factors that predict mortality in active pulmonary TB patients with acute respiratory failure. A retrospective study conducted in Thailand found that lower serum albumin level (2.89 ± 0.06 g/dL) was one of the variables found in the non-survivor group.¹⁴ Another retrospective study in France showed that albumin level <2.0 g/dL was a significant mortality predictor in TB patients with acute respiratory failure admitted to ICU.¹⁵ Prospective study in Brazil regarding the association between serum albumin level and in-hospital tuberculosis mortality found that a low level of albumin serum (≤ 2.7 g/dL) correlated with mortality in tuberculosis patients who were treated in hospital.¹⁶

Albumin is one of the plasma protein which is incorporated by the liver and undergoes a catabolic process by multiple organs with balanced production and degradation rates. Albumin is vital in maintaining fluid balance and transporting function and has antioxidant, anticoagulant, and anti-inflammation effects. There is a change of Albumin physiologic function under certain conditions, especially in a condition where oxidative stress occurs, such as sepsis.¹⁷ Hypoalbuminemia is defined as albumin serum level <3.0 g/dL.^{18,19} Hypoalbuminemia is commonly seen in critically ill conditions such as bleeding, increase of capillary permeability, and malnutrition. In critically ill patients, hypoalbuminemia and worse clinical outcome, such as more complications and lower survival rate, is correlated.¹⁷

Hyperglycemia is often found in uncontrolled DM patients. Hyperglycemia is known to induce impaired host defences, leading to susceptibility and infection, and is related to poor outcome in critically ill patients.²⁰ This study revealed that the mortality rate was higher in pulmonary TB with acute respiratory failure patients who had DM (73.3%), compared to non-DM patients (26.7%) in. Study of Deng et al. also reported that more non-survivor (30.0%) than survivor (8.89%) was found in TB with acute respiratory distress syndrome (ARDS) patients who had DM.²¹

The interaction between TB and DM will likely result in treatment failure or longer duration will be required. Meanwhile, TB also complicates blood sugar levels control. Malnutrition in TB patients induces hormonal production which resulted in higher level of blood sugar.²² The association between DM and mortality in TB patients has been mentioned in many studies. Pulmonary TB patients with DM as comorbid disease have a higher mortality risk, so more concern is needed in the treatment and management of TB.²³

This study had some limitations due to the small sample size and was conducted in one single-centre hospital. Therefore, the results cannot be generalized to a different region or other healthcare facilities. A multi-centre study is needed to obtain a larger sample size to acquire more and better predictor variables.

5. Conclusion

Active pulmonary tuberculosis with acute respiratory failure was associated with a high mortality rate. Low serum albumin (<3.0 g/dL)

Fig. 1. a) Kaplan-Meier survival curves for patients with hypoalbuminemia, $p = 0.001$; b) for patients with DM $p = 0.015$.

and Diabetes Mellitus were significant predictor factors for mortality in this prospective study. Prompt and early diagnosis followed by aggressive appropriate treatments may contribute to lower mortality rate.

Declaration of competing interest

There was no conflict of interest in this study. No funding was received for this study.

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