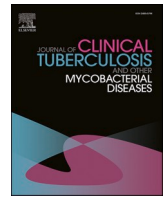




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In-hospital mortality of pulmonary tuberculosis with acute respiratory failure and related clinical risk factors

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ABSTRACT

Background/objective: Data on acute respiratory failure (ARF) in pulmonary tuberculosis (PTB) patients is limited. This study aims to investigate in-hospital mortality, its clinical risk factors and the accuracy of the existing scoring system in predicting in-hospital mortality.

Methods: An observational prospective cohort study involving PTB patients with ARF in tertiary hospital, between January 2017 and December 2018, was conducted. The in-hospital mortality was predicted using the National Early Warning Score 2 (NEWS2), quick Sequential Organ Failure Assessment (qSOFA) and CRB-65. Regression models were run to analyze the clinical risk factors for in-hospital Mortality. Sensitivity and specificity of scoring systems were calculated using a Wilson score interval.

Results: A total of 111 subjects were included. Most of subjects were hypoxemic type respiratory failure (68.5%), advanced lesions (62.2%), new cases (70.3%) and pneumonia co-infection (72.1%) patients. Invasive mechanical ventilation was utilized for 29.73% of cases. There were 53 (47.75%) in-hospital mortality cases and its risk factors were intensive phase treatment (3.34 OR; CI95% 1.27–8.78), P/F ratio < 100 (OR 4.30; CI 95% 1.75–10.59) and renal insufficiency (4.09 OR; CI95% 1.46–11.49). The sensitivity and specificity of NEWS2 ≥ 6 , qSOFA ≥ 2 and CRB-65 ≥ 2 were 62.26% and 67.24%; 60.38% and 72.41%; 41.51% and 84.48% respectively.

Conclusions: Most of PTB with ARF were new cases, advanced lesion and hypoxemic type respiratory failure. Intensive phase treatment, severe hypoxemia and renal insufficiency are independent predictors of in-hospital mortality in PTB patients with ARF. NEWS2, qSOFA and CRB-65 scores were poor to predict the in-hospital mortality.

1. Introduction

Pulmonary tuberculosis (PTB) is still a major public health problem despite well-established prevention and therapeutic guideline and advanced anti-tuberculosis drugs. It is one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS) caused by the bacillus *Mycobacterium tuberculosis*. Indonesia, according to the World Health Organization (WHO), is considered one of the high-burden countries for tuberculosis (TB), TB-HIV and MDR-TB, with an estimated total TB incidence of 316/100,000 and 69% increased of people newly diagnosed in the last three years [1].

Tuberculosis is preventable and curable disease but has substantial mortality of 34 per 100,000 population [1]. In-hospital mortality of PTB patients range 2–17% and dramatically increased to 40–60% in patients

who developed acute respiratory failure [2–8]. Acute respiratory failure caused by PTB is rare but PTB with complicated comorbidities and sepsis can lead to ARF and death. A variety of risk factors of PTB patients with ARF have been associated with in-hospital mortality, including male gender, elderly, consolidation on chest x-ray, secondary infection, low albumin and sepsis [7,9–11]. Underlying HIV infection were risk factors to develop severe disease but not to mortality [9]. Several predictive scoring systems such as National Early Warning Score 2 (NEWS2), quick Sequential Organ Failure Assessment (qSOFA) and CRB-65, also commonly used to identify in-hospital mortality but their accuracy in particular PTB patients with ARF were unknown [12,13]. Identifying clinical factors and predicting mortality at admission may help clinician to optimize the treatment and lower the mortality. The present study was, therefore, conducted to: 1) investigate the clinical characteristics of Indonesian PTB patients with ARF; 2) determine the mortality rate and

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predictors of in-hospital Mortality; and 3) evaluate the NEWS2, qSOFA and CRB-65 scoring system on predicting in-hospital Mortality.

2. Methods

2.1. Study population

An observational prospective cohort study involving PTB patients with ARF in National referral for respiratory diseases, Persahabatan Hospital, Jakarta was conducted. Pulmonary tuberculosis adult (≥ 18 years old) patients with ARF admitted to emergency department (ED) from January 2017 to December 2018 were consecutively included in the study. Patients with pregnancy and trauma cases were excluded. Pulmonary tuberculosis cases were defined as bacteriologically confirmed TB and clinically diagnosed TB cases. A bacteriologically confirmed TB case was one from whom a biological specimen was positive by smear microscopy, culture or WHO-approved rapid diagnostics such as Xpert MTB/RIF. While a clinically diagnosed TB case was one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment [14]. Patients who were already diagnosed as clinically PTB before admission but based on clinical judgement were not diagnosed as PTB at the end of observation were excluded from the analysis.

ARF diagnosis based on pulse oximetry test or arterial blood gas analysis. Acute hypoxemic respiratory failure was defined as arterial oxygen pressure (PaO₂) < 60 mmHg, pulse oxygen saturation (SpO₂) < 91% and the ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F) < 300. Acute hypercapnic respiratory failure was defined as arterial carbon dioxide (PaCO₂) > 50 cmH₂O with pH < 7.35 or increase of 10 mmHg PaCO₂ from baseline.

2.2. Measures and definitions

In-hospital mortality was defined as death occurring during the 30 day hospital stay. Patients were observed until 30 days or discarded or death. The severity of disease were assessed by clinical scoring systems, P/F ratio and chest x-ray, which were recorded at the admission. Related organ insufficiency were evaluated within 48 h admission. Cardiac insufficiency was defined as a non-ischemic acute cardiac dysfunction [15]. Renal insufficiency was defined as an increase in serum creatinine to ≥ 2 times baseline or urine output < 0.5 ml/kg/h for ≥ 12 h [16]. Liver insufficiency was defined by at least two of the following items: an increase bilirubin of greater than 2.5 mg/dL (> 43 μ mol/L), serum alanine transaminase concentration of more than twice the upper limit, and prothrombin time of greater than 1.5 times the control value [17].

Clinical scores examined were NEWS2, qSOFA and CRB-65. The NEWS2 is based on a simple aggregate scoring system of six physiological parameters; level of consciousness or new confusion, respiratory rate, oxygen saturation, systolic blood pressure, pulse rate and body temperature. A NEWS2 score of 5 or more is the key trigger threshold for clinical deterioration, urgent clinical review and action [18].

qSOFA score was used to assess organ dysfunction and to help identify patients with suspected infection that are at high risk for poor outcome. Three clinical variables: altered mental status, systolic blood pressure ≤ 100 mmHg, and respiratory rate of ≥ 22 /min; are scored with one point each. A qSOFA score of ≥ 2 points indicates organ dysfunction [13]. CRB-65 is a clinical score that is used to predict the severity of community-acquired pneumonias. One point each is given for the clinical variables new confusion, respiratory rate ≥ 30 /min, pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg. In addition, age ≥ 65 years is scored with one point. A score of two or more indicates a need for hospitalization and in-patient management [19].

P/F ratio < 100 was categorized as severe hypoxemia, while P/F 100–200 and 200–300 was categorized moderate and severe hypoxemia

respectively. The severity of lung lesion was evaluated qualitatively scored for each lung quadrant using the Northern score (0–20), with a higher score reflecting more severe radiological change and then categorized into three group: minimal 0–33.3%; moderate 33.3–66.7% and severe > 66.7% [20].

2.3. Statistical analysis

Chi-squared and Fisher's exact tests were used to compare the proportion in categorical variables. Categorical values were presented as numbers or percentage while continuous values were presented as mean with standard deviation or median with range for continuous variables. The independent risk factors for in-hospital mortality were evaluated using a stepwise forward multiple logistic regression model. A p-value of 0.05 was considered to be statistically significant. Sensitivity, specificity, positive predictive value and negative predictive value were calculated using a Wilson score interval.

2.4. Ethical considerations

This study has granted an ethical approval by the Institutional Review Board (IRB) of Persahabatan Hospital (Ethical Clearance No.01/KEPK-RSUPP/01/2017).

3. Results

3.1. Clinical characteristics

During two years, there were 126 PTB patients with ARF admitted to ED and 114 patients were included in the study. There were three patients excluded at the end of observation because they were not PTB based on clinical judgement. Patients flow diagram is shown in Fig. 1. Clinical characteristics are listed in table 1. The patients were dominated by middle-aged adults, with median age was 44 years old (range 18–83) years old. The elderly group were minority (17.2%). The gender ratio was 3:2 (male: female).

Pulmonary TB and pneumonia co-infection was occurred in 80 patients (72.1%). Bronchiectasis and hypertension were the frequent underlying diseases, while diabetic mellitus was found in 24 patients (21.6%) and HIV was found in 16 patients (14.4%). Patients, clinically recognized as renal, cardiac and liver insufficiency, were 26.1%, 7.2% and 7.2% respectively.

Diagnosis was bacteriologically confirmed in 89 patients (80.2%) and clinically diagnosed in 22 patients (19.8%). Most of patients were new cases, 78 patients (70.3%). Relapse case were found in 15 patients (13.5%), loss to follow-up case were found in 15 patients (13.5%) and failure case were found in 3 patients (2.7%). Drug susceptibility testing (DST) of *Mycobacterium tuberculosis* data were available for bacterial isolates from 76 patients; isolates from 65 patients (85.7%) showed no drug resistance and isolates from 11 patients (14.5%) exhibited multi-drug resistance (MDR). There were 35 patients (46.1%) with no DST data since no sample to be examined.

Majority of chest x-ray lesion in PTB patients with ARF was advanced abnormality (62.16%). Mean value of P/F ratio was 132.44 (56.40–295.34). The severity of hypoxemia was moderate-severe (P/F ratio 100–200) in majority of patients (40.5%). The proportion of hypoxemic type respiratory failure were higher than hypercapnic type (68.5% vs 31.5%).

All patients were received national standard anti-tuberculosis drugs. A total 74 patients (66.67%) got ARF during intensive phase of anti-tuberculosis treatment. Intensive-phase drugs bacteria consist of Rifampicin (R), Isoniazid (H), Pyrazinamide (Z) and Ethambutol (E), were given to 56 patients, additional intramuscular Streptomycin (S) were given to six patients and twenty two patients were given only RH. There were nine patients received only E and streptomycin (S) due to liver insufficiency. Patients with multidrug resistance (MDR) were

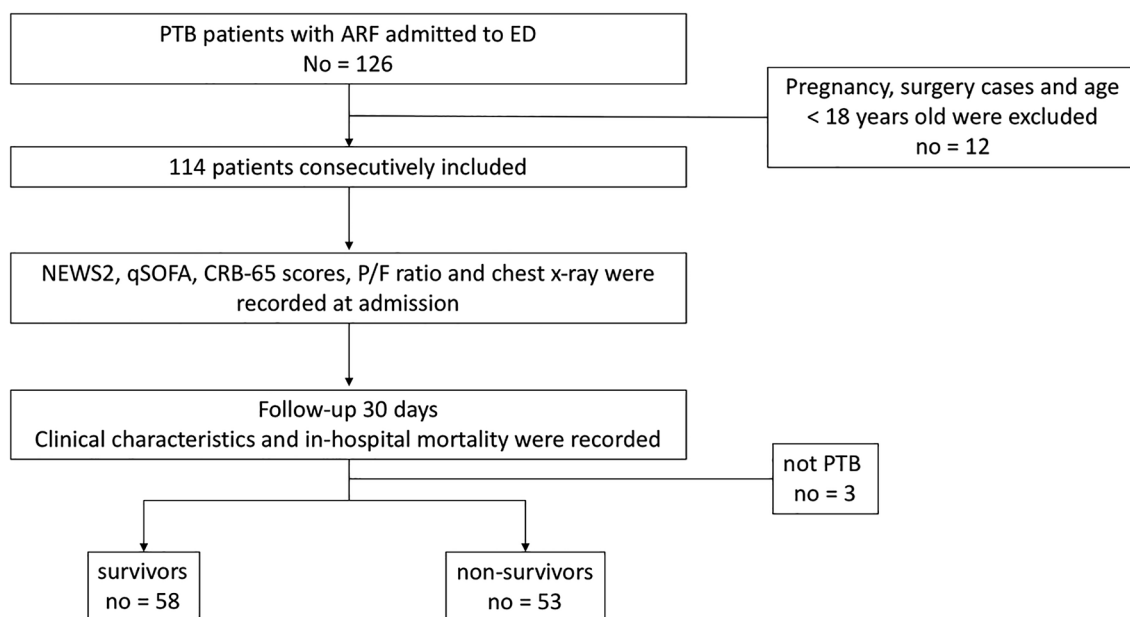


Fig. 1. Patients flow diagram.

received individual regimen combination of Z, E, kanamycin injection, Levofloxacin (Lfx), Moxifloxacin (Mfx), Cycloserine (Cs), Ethionamide (Eto), Para-amino salicylic acid (PAS) and Linezolid (Lzd). Steroid as adjuvant therapy were given to 53 patients (47.7%). A total of 78 patients (70.3%) only received supplemental oxygen therapy including high-flow nasal, without ventilatory support while the rest received invasive mechanical ventilation. There was no non-invasive ventilation utility.

3.2. Risk factor of in-hospital mortality

There were 53 patients (47.75%) in-hospital mortality cases. Several clinical factors were identified to have risk of in-hospital Mortality (table 2). Patients who were on intensive phase treatment had three times in-hospital mortality risks compared to patients on continuation phase treatment (OR 3.34; CI95% 1.27–8.78; p-value 0.014). Severe hypoxemia had higher risk to death than mild-moderate hypoxemia (OR 4.30; CI 95% 1.75–10.59; p-value 0.001). Patients with renal insufficiency were four times more likely (OR 4.09; CI 95% 1.46–11.49; p-value 0.007) to have mortality during hospital stay.

3.3. Performance of clinical scoring systems to predict in-hospital mortality

We tried to assess the performance of clinical risk scores at emergency department admission to predict in-hospital mortality in PTB patients with ARF (Table 3). NEWS2 had 62.62% sensitivity and 67.24% specificity; qSOFA had 60.38% sensitivity and 72.41% specificity; CRB-65 had 41.51% sensitivity and 84.48% specificity. All the scoring scores had weak sensitivity and only CRB-65 had moderate specificity.

4. Discussion

This cohort study identified several clinical characteristics including organ insufficiency to be the risk factors for in-hospital mortality PTB patients with ARF in Indonesian tertiary referral hospital. Using primary data, we found a high in-hospital mortality rate despite standardized anti-tuberculosis drugs administration and respiratory support. In particular, intensive-phase treatment patients, severe hypoxemia and renal insufficiency were significantly associated with death during

hospital stay in PTB patients with ARF. Additionally, PTB patients with ARF admitted to ED mostly at middle age, secondary pneumonia infection, new cases and severe condition with moderate P/F ratio, advanced lesion and high NEWS2, qSOFA and CRB-65. However common these clinical scoring systems were indicated to be poor in predicting in-hospital mortality.

The in-hospital mortality rate in the present study was 47.75% (53 out of 111), which is consistent to those previously reported (26–59%) though mechanical ventilated patients was markedly greater than 90% [6,9,22–24]. These variety rate were associated with clinical characteristics baseline, progressivity and respiratory support. In our centre, the availability of invasive mechanical ventilation sometimes were limited while non-invasive ventilation were not commonly be used. Mortality rate in the PTB requiring invasive mechanical ventilation also reported to be higher than in the pneumonia community. A more extensive lung lesion in PTB were indicated to be independent risk of mortality even the severity scoring were lower [8,24]. Most of PTB patients in this study had advanced lung destruction even though it was not shown to be risk of mortality.

Acute respiratory failure directly triggered by PTB is a rare occurrence [21]. Pulmonary TB has been considered as one of the leading pneumonia causes in Indonesia but acute tuberculous pneumonia is a rare clinical form of pulmonary TB [25]. This study shows high proportion of pneumonia coinfection in PTB patients with ARF which is aligned with the results of previous studies [9,26]. On the contrary, pneumonia-induced ARF patients that show signs and symptoms of PTB supported by multiple lesions on the chest radiographs can be assessed as clinical PTB and thus treatment of tuberculosis can be initiated [14,27]. Most of PTB patients with ARF in this study were new cases, diagnosed as clinical PTB and started treatment upon admission. Therefore the proportion of intensive-phase treatment were high and associated with risk of in-hospital mortality. The death of TB patients on their intensive phase of TB treatment are defined as early deaths [3,28]. We found that patients in this group with ARF had three times in-hospital mortality risks compared to patients on their continuation phase treatment. Min J et al stated that patients with shortness of breathing and bilateral lung lesions were found more in early death TB group although they had relatively fewer or even unreported comorbid [28]. Advanced disease state in this study could be seen from the lesions of chest x-ray that are relatively severe.

Table 1
Clinical characteristics of lung tuberculosis with acute respiratory failure.

Characteristics	Total n (%)	Non-survivors n (%)	Survivors n (%)	p-value
Age in year				0.117
< 40	47 (42.3)	19 (40.4)	28 (59.6)	
40-64	45 (40.5)	21 (46.7)	24 (3.3)	
≥ 65	19 (17.2)	13 (68.4)	6 (31.6)	
Gender				0.997
Female	44 (39.6)	21 (47.7)	23 (52.3)	
Male	67 (60.4)	32 (47.8)	35 (52.2)	
Smokers	62 (55.8)	30 (48.4)	32 (51.6)	0.879
Comorbid				
Diabetic mellitus	24 (12.6)	11 (45.8)	13 (54.2)	0.832
Hypertension	32 (26.1)	7 (26.7)	3 (30.0)	0.119
COPD	32 (28.8)	7 (21.5)	3 (9.4)	0.140
Pneumonia	10 (9.0)	44 (55.0)	36 (45.0)	0.014*
Bronchiectasis	80 (72.1)	15 (38.5)	24 (61.5)	0.149
Cardiac insufficiency	8 (7.2)	5 (62.5)	3 (37.5)	0.386
Renal insufficiency	29 (26.1)	18 (62.1)	11 (37.9)	0.010*
Liver insufficiency	9 (7.2)	6 (66.7)	3 (33.3)	0.236
HIV	16 (14.4)	7 (43.8)	9 (56.2)	0.729
Meningitis	10 (9.0)	7 (70.0)	3 (30.0)	0.140
Tuberculosis case				0.234
Bacteriologically confirmed	89 (80.2)	40 (44.9)	49 (55.1)	
Clinically diagnosed	22 (19.8)	13 (59.1)	9 (40.9)	
History of previous TB treatment				0.321
New	78 (70.3)	40 (51.3)	38 (48.7)	
Relapse	15 (13.5)	4 (26.7)	11 (73.3)	
Failure	3 (2.7)	2 (66.7)	1 (33.3)	
Loss to follow-up	15 (13.5)	7 (46.7)	8 (53.3)	
Drug susceptibility bacteria				0.037
Sensitive	65 (58.5)	29 (44.6)	36 (55.4)	
Multidrug resistance	11 (10.0)	2 (18.2)	9 (81.8)	
Not known	35 (31.5)	22 (62.9)	13 (37.1)	
Chest x-ray lesion				0.489
Minimal	5 (4.5)	2 (40.0)	3 (60.0)	
Moderate	37 (33.3)	15 (40.5)	22 (59.5)	
Advanced	69 (62.2)	36 (52.2)	33 (47.8)	
Type of respiratory failure				0.179
Hypoxemic	76 (68.5)	33 (43.4)	43 (56.6)	
Hypercapnic	35 (31.5)	20 (57.1)	15 (42.9)	
P/F ratio				<0.001*
< 100	39 (35.1)	28 (71.8)	11 (28.2)	
100-200	45 (40.5)	19 (42.2)	26 (57.8)	
200-300	27 (24.3)	6 (22.2)	21 (77.8)	
	74			0.022*

Table 1 (continued)

Characteristics	Total n (%)	Non-survivors n (%)	Survivors n (%)	p-value
Treatment phase	(66.7)			
intensive phase	37 (33.3)	41 (55.4)	33 (44.6)	
continuation phase		12 (32.4)	25 (67.6)	
Anti-tuberculosis regimen				0.151
RHZE	56 (50.5)	30 (53.6)	26 (46.4)	
RH	22 (19.8)	7 (31.8)	15 (68.2)	
MDR regimen	13 (11.7)	3 (23.1)	10 (76.9)	
ES	6 (5.4)	6 (66.7)	3 (33.3)	
RHZES	9 (8.1)	4 (66.7)	2 (33.3)	
Others	5 (4.5)	3 (60.0)	2 (40.0)	
Steroid Use	53 (47.7)	28 (52.8)	25 (47.2)	0.509
Respiratory Support				0.178
Supplemental oxygen therapy	78 (70.3)	34 (43.6)	44 (56.4)	
Invasive mechanical ventilation	33 (29.7)	19 (57.6)	14 (42.4)	

^) category was combined in statistic test.

*) significant with p-value < 0.05.

Table 2
Risk factors of in-hospital mortality.

Variable	Bivariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Pneumonia	2.98 (1.22-7.29)	0.016		
Intensive phase treatment	2.58 (1.13-5.98)	0.024	3.34 (1.27-8.78)	0.014
P/F ratio < 100	4.78 (2.04-11.23)	0.000	4.30 (1.75-10.59)	0.001
Renal Insufficiency	3.15 (1.31-7.56)	0.010	4.09 (1.46-11.49)	0.007

Table 3
Performance of clinical risk scores at admission to predict in-hospital mortality in PTB patients with ARF.

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
NEWS2 ≥ 6	62.26 (48.81-74.06)	67.24 (54.42, 77.92)	63.46 (49.87, 75.2)	66.1 (53.37-76.86)
qSOFA ≥ 2	60.38 (46.94-72.41)	72.41 (59.8-82.25)	66.67 (52.54-78.32)	66.67 (54.37-77.05)
CRB-65	41.51 (29.26-54.91)	84.48 (73.07-91.62)	70.97 (53.41-83.9)	61.25 (50.29-71.18)

Tuberculous pneumonia should be taken into consideration as one of the differential diagnoses when a patient presents with pneumonia in high incidence of TB and HIV country [27,29]. Acute tuberculous pneumonia is often closely resembled bacterial pneumonia and especially difficult to differentiate from ARF patients with secondary infections, therefore definitive diagnosis might be delayed [30]. Delay in the diagnosis and treatment of tuberculosis patients is still a problem and attributed to both the patient and the health system. Diagnosis delay may lead to treatment delay and a more advanced disease state at presentation, which contributes to late sequelae, risk of respiratory failure and Mortality. Prior study suggested that treatment delay of more than one month was independently predictor of mortality [6,7].

The P/F ratio of this study is comparable with a study of mechanically ventilated TB patients with ARF done by Kim et al, but much lower compared to a study by Muthu et al that evaluated TB patients with

ARDS in the intensive care unit (ICU) and a study by Bhurayanontachai et al that evaluated mechanically ventilated TB patients [9,24,31]. Hypoxemia severity in this study is equal to moderate acute respiratory distress syndrome and severe hypoxemia is significantly independent factor to in-hospital mortality [32]. SRLF Trial Group reported that mortality was higher in hypoxemic than in non-hypoxemic patients (27% vs 12%) and mortality increased with severity of hypoxemia: 21–29% in mild-moderately and 51% in severely hypoxemia [33]. In acute hypoxemic respiratory failure patients and ARDS, inadequate oxygenation and pulmonary dysfunction were suggested the most common primary causes of death [34].

Acute respiratory failure patients with tuberculosis prone to have organ insufficiency due to disease progressivity. The disease severity and the development of new organ dysfunction rather than the presence of ARDS were the risk of in-hospital mortality [31]. We found high incidence of renal insufficiency in PTB patients with ARF and it was significantly associated risk of in-hospital mortality. This renal involvement was part of respiratory failure and sepsis progressivity rather than disseminated TB infection or a localized genitourinary disease. A higher severity of disease and diabetes were associated with occurrence of acute renal insufficiency in ARF and ARDS patients [35]. Prior studies showed incidence of acute kidney injury was higher in the TB patients with ARF and predictor of mortality [22,24]. Acute renal insufficiency is the most frequent complication of the critically ill patient including ARF and often associated with high morbidity and mortality [36].

We tried to use NEWS2, qSOFA and CRB-65 scoring systems to predict in-hospital mortality, as reported by other studies that respective scoring system validities are good to predict in-hospital Mortality in pneumonia cases [37]. Previous cohort study mentioned that NEWS2 was superior to qSOFA for mortality among infected patients at emergency departments. The average NEWS2 score of PTB patients with ARF admitted to our ED were higher than the critical threshold [38]. Despite of patients with NEWS2 score ≥ 6 , qSOFA score ≥ 2 , CRB-65 ≥ 2 had higher risk of in-hospital mortality, the sensitivity and specificity of those scoring systems were considered low to predict in-hospital mortality. Further cohort studies are needed to determine a more accurate scoring system in predicting in-hospital mortality of PTB patients with ARF.

There are several limitations of our study. First, this is a single-centre study so that it may be lacking of generalizability. However, our centre is national referral of respiratory diseases, we accommodated many complicated tuberculosis patients from nationwide including those with ARF. We took primary data, we screened and examined all PTB patients with ARF admitted to ED over 2-year. Second, it might be bias in considering ventilatory support and steroid as in-hospital mortality predictors since there were few indicated patients who were not treated with invasive mechanical ventilation. There were also clinical guideline for additional steroid in disease management. Third, not all patients underwent drug susceptibility test while resistance bacteria might be associated to mortality. Therefore we did not analyse this variable even though there were significantly difference survivor proportion between drug susceptibility bacteria.

5. Conclusion

Most of PTB patients underwent ARF were new cases, advanced lesion and acute hypoxemic type respiratory failure. Risk of in-hospital Mortality was higher in intensive phase treatment, severe hypoxemia, and renal insufficiency. NEWS2, qSOFA and CRB-65 had low sensitivity and specificity in in predicting in-hospital Mortality of PTB patients with ARF.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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