Effectiveness of systemic corticosteroids in hospitalized pulmonary tuberculosis with acute respiratory failure: a retrospective cohort study

ORIGINAL ARTICLE

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ABSTRACT

OBJECTIVE

To evaluate the effectiveness of systemic corticosteroids in hospitalised patients with pulmonary tuberculosis (TB) with acute respiratory failure (ARF).

METHODS

A retrospective cohort study was conducted by reviewing all medical records of hospitalized patients with pulmonary TB with ARF from January 2014 through December 2016 in Khon Kaen Hospital, Thailand. The exposure of our interest was the systemic corticosteroids regardless of doses and durations. Our primary outcome was 90-day all-cause mortality after admission and our secondary outcomes were cardiac arrest, shock, duration of hospital stay and duration of mechanical ventilator use.

RESULTS

There were 481 pulmonary TB with ARF patients during the study period; 167 were treated with systemic corticosteroids and 314 were not. We found that 90-day all-cause mortality was not significantly different between the two groups (adjusted hazard ratio, 0.80; 95% confidence interval (CI), 0.62 to 1.03). For secondary outcome, we found that cardiac arrest (relative risk (RR), 0.99; 95% CI, 0.84 to 1.17), shock (RR, 1.15; 95% CI, 0.99 to 1.33) and duration of hospital stay (mean difference, 2.41; 95% CI, -0.14 to 4.96) were not significantly different between the two groups. However, the systemic corticosteroids were associated with significantly increased duration of mechanical ventilator use (mean difference, 2.42; 95% CI, 0.48 to 4.36).

CONCLUSION

The 90-day all-cause mortality was not significantly different between with and without systemic corticosteroids in patients with pulmonary TB with ARF.

INTRODUCTION

Tuberculosis (TB) is one of the major causes of death worldwide, it caused 1.3 million deaths in 2016.[1] Its mortality rate is 3 to 8%, and the rate can increase to 59 to 66% when the disease presents together with acute respiratory failure (ARF).[2–5] Generally, treatment of ARF comprises management of the underlying causes, oxygen supplement[6] and supportive modality including systemic corticosteroids.[7] However, the benefit of systemic corticosteroids in those with TB and ARF is still unclear.

In a previous systematic review and meta-analysis in 2012, it stated that corticosteroids were not effective in reducing mortality in 187 patients who diagnosed TB with HIV-infected that had CD4+ T cell counts at least 200 cells/μL.[8] However, the conclusion of this review was solely based on one retrospective cohort study in TB with HIV-infected in 2005 without stating the condition of ARF in the included patients.[9] Nonetheless, a later retrospective cohort study in 2016 from South Korea with 124 pulmonary TB patients with ARF admitted in the intensive care unit (ICU), it found that corticosteroids were associated with lower 90-day mortality rate.[10] The limitation of this study was small numbers of the patient with pulmonary TB in the ICU and doses and durations of corticosteroids were not analyzed in the study. Due to the controversy mentioned above, thus, the main objective of the present study was to examine the effectiveness of systemic corticosteroids in pulmonary TB with ARF on the 90-day all-cause mortality.

METHODS

STUDY DESIGN AND ETHICAL APPROVAL

The present study was a retrospective cohort evaluating the relationship between systemic corticosteroids and 90-day all-cause mortality in pulmonary TB patients with ARF at Khon Kaen Hospital, Thailand. We reviewed data from medical records of hospitalized patients who diagnosed pulmonary TB with ARF. All patient data were concealed and collected in a closed system. This study was approved by the Khon Kaen Hospital Institutional Review Board (IRB) for ensuring that it was ethically acceptable (KE 60146).

PATIENTS

We identified pulmonary TB patients with ARF who admitted from 2014 through 2016 in Khon Kaen Hospital. Patients were divided into three groups; (i) confirmed pulmonary TB diagnosed by positive for culture *Mycobacterium tuberculosis*, acid-fast bacilli (AFB) or polymerase chain reaction (PCR) for TB[11,12] (ii) probable pulmonary TB for those with negative for culture and other tests but exhibiting clinical symptoms and radiographic features, and (iii) possible cases for those without the criteria mentioned above but somehow having diagnosis by the international classification of disease, 10th revision (ICD-10) for pulmonary TB (codes A15). ARF in our study was defined in those with ventilator or two or more following criteria; (i) respiratory rate at rest >35 per minute or active respiratory accessory muscle use; (ii) arterial oxygen partial pressure (PaO_2) <68 mmHg while ventilator setting fractional inspired oxygen (FiO_2)

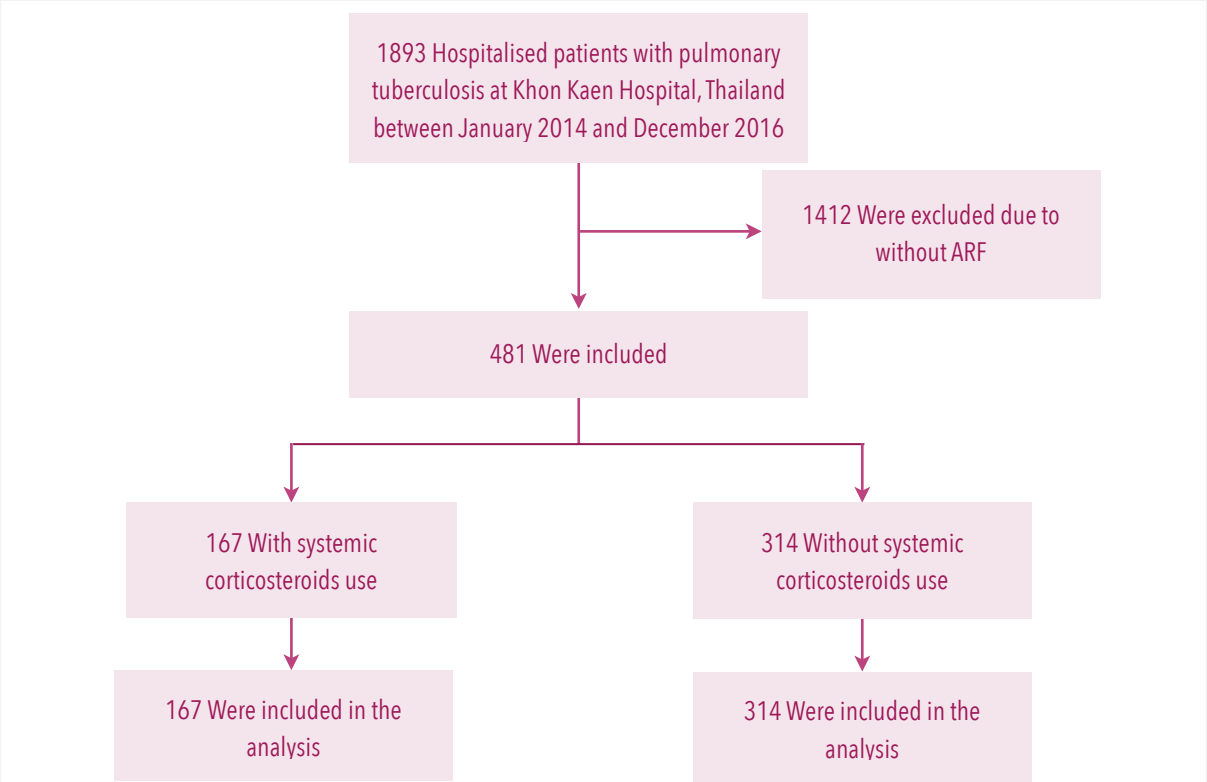


Figure 1. The patients flow in the analysis

0.4, or the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2:FiO_2) <250 while ventilator setting FiO_2 0.5, and (iii) hypercapnia (arterial carbon dioxide partial pressure [$PaCO_2$] >50 mmHg) with respiratory acidosis (pH<7.33)[13] or diagnosed by ICD-10 (code J91).

EXPOSURE

Systemic corticosteroids use was our interested exposure. Type, dosage and duration of use were also collected.

OUTCOMES

The primary outcome was 90-day all-cause mortality after admission and secondary outcomes were cardiac arrest, shock, duration of hospital stay and duration of mechanical ventilator use

DATA COLLECTION

We verified and extracted data from medical records of hospitalized patients who were diagnosed with pulmonary TB with ARF. Patient characteristics were collected in relation to sex, age, body mass index (BMI), coexisting conditions (pulmonary diseases including chronic obstructive pulmonary disease, bronchiectasis and asthma,[18,19] diabetes mellitus,[20,21] hypertension,[19,22] chronic kidney diseases,[18,19,23,24] human immunodeficiency virus (HIV) infected,[22,25,26] cardiovascular disease,[27] cancer,[24,26,28] acute respiratory distress syndrome (ARDS)[10,14] and

Table 1. Characteristics of patients.

Characteristics	Systemic Corticosteroid (N = 167)	Non Systemic Corticosteroid (N = 314)	P Value
Age-yr			0.83
Median	59.0	58.0	
Interquartile range	41.0-71.0	45.0-71.0	
Male-no. (%)	118 (70.7)	225 (71.7)	0.82
Body mass index-kg/m^2 *	19.23.4	19.04.0	0.87
Coexisting conditions-no. (%)			
Pulmonary disease †	25 (15.0)	30 (9.6)	0.08
Diabetes mellitus	21 (12.6)	68 (21.7)	0.02
Hypertension	24 (14.4)	64 (20.4)	0.11
Chronic kidney disease	11 (6.6)	27 (8.6)	0.44
HIV infected	31 (18.6)	31 (9.9)	0.01
Cardiovascular disease	8 (4.8)	23 (7.3)	0.28
Cancer	8 (4.8)	4 (1.3)	0.03
Acute respiratory distress syndrome	12 (7.2)	7 (2.2)	0.01
Adrenal insufficiency	13 (7.8)	1 (0.3)	<0.001
History of TB treatment-no. (%)	62 (37.1)	112 (35.7)	0.75
Positive AFB smear-no./ total no. (%)	53/88 (60.2)	96/180 (53.3)	0.29
Positive for TB culture-no./ total no. (%)	4/28 (14.4)	3/45 (6.7)	0.42
Positive for PCR for TB-no./ total no. (%)	0/9	2/12 (16.7)	0.49
Sputum gram stain positive-no./ total no. (%)	27/74 (36.5)	61/125 (48.8)	0.09
Anti-TB drug in 24 hr after admission-no. (%)	92 (55.1)	194 (61.8)	0.16
PaO_2/FiO_2 ratio ‡			0.42
Median	740.7	787.1	
Interquartile range	336.6-1153.3	427.3-1152.6	
Hypercapnia-no./ total no. (%)§	9/125 (7.2)	27/231 (11.7)	0.18
Mechanical ventilation use -no./ total no. (%)	154 (92.2)	275 (87.6)	0.12

* 148 patients in steroid group and 265 patients in non steroid group had missing data.
† 42 patients in steroid group and 83 patients in non steroid group had missing data.

Table 2. Primary and secondary outcomes.

Outcome	Systemic Corticosteroid (N = 167)	Non Systemic Corticosteroid (N = 314)	Relative Risk (95% CI)	Means Difference (95% CI)
Primary				
90-day all-cause mortality-no. (%)	117 (70.1)	224 (71.3)	0.98 (0.87-1.11)	
Secondary				
Cardiac arrest-no. (%)	92 (55.1)	175 (55.7)	0.99 (0.84-1.17)	
Shock-no. (%)	110 (37.9)	180 (62.1)		
Duration of hospital stay-days			1.15 (0.99-1.33)	
Median	7.0	5.0		2.41 (-0.14 to 4.96)
Interquartile range	4.0-12.0	3.0-9.0		
Duration on mechanical ventilator-days*				2.42 (0.48 to 4.36)
Median	5.0	3.0		
Interquartile range	3.0-9.0	1.8-6.0		

* 154 patients in steroid group and 275 patients in non steroid group received mechanical ventilation.

adrenal insufficiency (AI)[10], history of TB treatment[29] also time to start anti-TB drugs after admission, mechanical ventilation use[18] with duration and cardiac arrest. Laboratory results e.g., sputum AFB, sputum culture for TB, PCR for TB, sputum gram stain and liver function test including albumin[18-20,26] were collected from a database of laboratory, Khon Kaen Hospital, Thailand.

STATISTICAL ANALYSIS

We divided patients into two groups; with and without systemic corticosteroids use. For variable analysis, we used descriptive statistics to summarize characteristic variables in each group; numbers and percentages for presenting categorical variables mean with standard deviation (SD) for normally distributed continuous variables and median with interquartile range (IQR) for non-normally distributed continuous variables. For inferential statistics, we used either Pearson's chi-squared or Fisher's exact test for categorical variables and t-test or Mann-Whitney U test for distributed continuous variables comparison. Relative risk (RR) was applied for comparing event rates of the primary and secondary outcomes. Moreover, the Kaplan-Meier survival plot was performed for comparing 90-day all-cause mortality among patients with and without systemic corticosteroids. In addition, crude and adjusted odds ratios (COR and AOR) which were used for factors that might affect our primary outcome were calculated from the binary logistic regression analysis. Crude and adjusted hazard ratios (CHR and AHR) were calculated by Cox proportional hazard regression analysis. P or 95% confidence intervals (CI) were demonstrated

Table 3. Factor determined 90-day mortality.

Factor	Odds Ratio (95% confidence interval)		Hazard Ratio (95% confidence interval)	
	Crude analysis	Adjusted analysis	Crude analysis	Adjusted analysis
Systemic corticosteroid use	0.94 (0.62-1.42)	0.76 (0.46-1.27)	0.89 (0.71-1.11)	0.80 (0.62-1.03)
Age-yr	1.01 (1.00-1.03)	1.02 (1.01-1.04)	1.01 (1.00-1.02)	1.01 (1.01-1.02)
Miliary tuberculosis	1.03 (0.32-3.33)	0.69 (0.19-2.43)	1.00 (0.53-1.87)	0.79 (0.40-1.55)
Coexisting conditions				
Pulmonary disease	0.58 (0.32-1.03)	0.81 (0.39-1.68)	0.72 (0.50-1.02)	0.80 (0.53-1.19)
Diabetes mellitus	1.14 (0.68-1.91)	1.28 (0.66-2.46)	1.08 (0.82-1.41)	1.08 (0.79-1.49)
Hypertension	1.04 (0.63-1.74)	1.12 (0.58-2.16)	1.04 (0.79-1.37)	1.09 (0.79-1.51)
Acute respiratory distress syndrome	1.56 (0.51-4.80)	1.53 (0.42-5.61)	1.12 (0.66-1.87)	1.14 (0.64-2.03)
Adrenal insufficiency	1.02 (0.32-3.33)	0.97 (0.27-3.54)	1.05 (0.56-1.98)	1.08 (0.56-2.09)
Human immunodeficiency virus infected	1.83 (0.94-3.56)	3.32 (1.40-7.90)	1.20 (0.89-1.61)	1.36 (0.95-1.96)
History of tuberculosis treatment	1.12 (0.74-1.70)	1.12 (0.69-1.82)	1.15 (0.92-1.43)	1.18 (0.92-1.52)
Albumin-mg	0.40 (0.29-0.56)	0.40 (0.28-0.57)	0.64 (0.54-0.76)	0.63 (0.52-0.75)
Anti-tuberculosis drugs in 24 hr after admission	1.05 (0.71-1.57)	1.21(0.75-1.94)	1.13 (0.91-1.40)	1.23 (0.96-1.57)

together with all inferential statistical analysis tests. For subgroup analysis, we converted corticosteroid dose to dexamethasone equivalent dose.

RESULTS

CHARACTERISTIC OF PATIENTS

A total of 1,893 hospitalized patients with pulmonary TB were diagnosed from January 2014 through December 2016. We excluded 1,412 patients due to pulmonary TB without ARF. All of 481 pulmonary TB with ARF who diagnosed by three criteria groups; 152 confirmed pulmonary TB, 274 probable pulmonary TB and 55 possible pulmonary TB were included in the analysis. Of these, 167 (34.7%) were received systemic corticosteroids (52.1% were received dexamethasone 47.9% were received others) and 314 (65.3%) were not received systemic corticosteroids (Figure. 1). Most of them were male with a median age of 59 years. Nearly 90% were on a ventilator. Generally, the characteristics of the

patients between the two groups were similar (Table 1). However, comparing between the former and the latter group, proportion of those with diabetes, the former group tended to have lower proportion of those with diabetes (12.6% vs. 21.7%, P=0.02), higher proportion of patients with HIV infection (18.6% vs. 9.9%, P=0.02), cancer (4.8% vs. 1.3%, P=0.03), ARDS (7.2% vs. 2.2%, P=0.01), adrenal insufficiency (7.8% vs. 0.3%, P<0.001), and history of tuberculosis treatment in confirmed pulmonary TB group (31.5% vs. 17.3%, P=0.05).

STUDY OUTCOMES

All of 481 pulmonary TB patients with ARF, the 90-day all-cause mortality was not significantly different between with and without systemic corticosteroid use (RR, 0.98; 95% CI, 0.87 to 1.11) (Table 2). Then, we divided patient into 3 groups for confirmed pulmonary TB, probable pulmonary TB, and possible pulmonary TB, It showed that systemic corticosteroids were not associated with 90-day all-cause mortality in the all groups (RR, 1.03; 95% CI, 0.82 to 1.30), (RR, 1.00; 95% CI, 0.86 to 1.16), (RR, 0.76; 95% CI, 0.47 to 1.21) (Table 2.1). The secondary outcomes showed that cardiac arrest (RR, 0.99; 95% CI, 0.84 to 1.17), shock (RR, 1.15; 95% CI, 0.99 to 1.33), duration of hospital stay (means difference, 2.41; 95% CI, -0.14 to 4.96) were not significantly different between with and without systemic corticosteroids use. On the other hand, duration of mechanical ventilator use was significantly increased in patients who received systemic corticosteroids (means difference, 2.42; 95% CI, 0.48 to 4.36) (Table 2) (Table 2).

FACTORS DETERMINE OUTCOME

The binary logistic regression and the Cox regression analysis of factors determining outcome were summarized in Table 3. It demonstrated the same result as a relative risk that systemic corticosteroids were not associated with 90-day all-cause mortality in pulmonary TB patients with ARF (AHR,0.80; 95% CI, 0.62 to 1.03). Other factors that significantly associated with increased 90-day all-cause mortality were HIV infection (AOR, 3.32; 95% CI, 1.40 to 7.90). On the contrary, albumin was significantly decreased by 90-day all-cause mortality (AHR, 0.63; 95% CI, 0.52 to 0.75). After that, we divided patients into 3 groups of pulmonary TB by the criteria explained above. The result of each group was demonstrated in Table 3.1. In the same way, we found that systemic corticosteroids group was not associated with 90-day all-cause mortality all about 3 groups (AHR, 1.00; 95% CI, 0.61 to 1.65), (AHR, 0.77; 95% CI, 0.56 to 1.07), (AHR, 0.51; 95% CI, 0.21 to 1.22). Other factors associated with increased 90-day all-cause mortality were age in a probable group (AOR, 1.02; 95% CI, 1.01 to 1.03) and HIV infection in a confirmed group (AHR, 2.17; 95% CI, 1.02 to 4.61). On the other hand, albumin in confirmed and probable groups was significantly decreased the 90-day all-cause mortality (AHR, 0.45; 95% CI, 0.30 to 0.67), (AHR, 0.66; 95% CI, 0.52 to 0.83). The relationship between all-cause mortality in 90 days and systemic corticosteroids was also shown in the Kaplan-Meier plot (Figure 2).

SUBGROUP ANALYSIS

The Cox proportional hazard regression model analysis and binary logistic regression, both dose

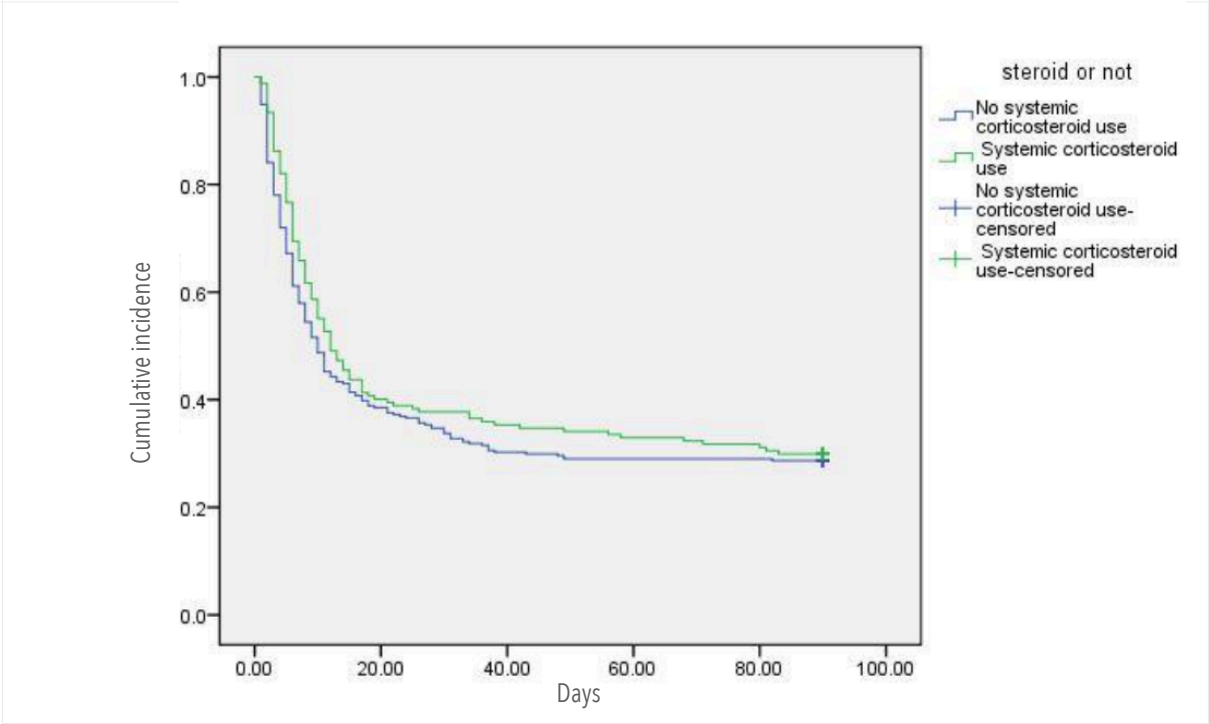


Figure 2. Kaplan-Meier comparing mortality in 90 days versus adjunctive systemic corticosteroid usage.

and duration of systemic corticosteroid use were not significantly associated with 90-day all-cause mortality in pulmonary TB with ARF. The result of the cut-off point about duration and dose which converted any type of systemic corticosteroids to dexamethasone equivalent dose were displayed in Table 3. In the same way, our results of the subgroup analysis in Table 4 explained above also shows no association between with and without systemic corticosteroids group in pulmonary TB with ARF that divided into 3 groups; confirmed, probable and possible pulmonary TB.

DISCUSSION

This retrospective cohort study showed that 90-day all-cause mortality of pulmonary TB with ARF was not significantly different between with and without systemic corticosteroid use. Although, systemic corticosteroid use was not associated with cardiac arrest, shock, and duration of hospital stay.

COMPARISON WITH OTHER STUDIES

In the previous studies conducted between systemic corticosteroid and mortality in TB patients. The retrospective cohort study of 187 TB patients with HIV-infected in Uganda about the benefits of corticosteroids to reducing mortality in TB patients.[9] They are shown that the mortality rate of the patient was 2.1 % while our study was 70.9 %. The probable reason for the difference was we selected only pulmonary TB with ARF that more severe than pulmonary TB with HIV-infected patients. However, they are shown no significant

Table 4. Subgroup analysis.

Group	Odds Ratio (95% CI)	Hazard Ratio (95% CI)
Systemic corticosteroids dose-mg/day*		
<20	0.91 (0.59-1.14)	0.89 (0.70-1.13)
20	1.05 (0.48-2.25)	0.91 (0.60-1.36)
Systemic corticosteroids duration-days		
7	1.01 (0.65-1.56)	0.95 (0.76-1.20)
>7	0.63 (0.26-1.50)	0.61 (0.35-1.04)

* Systemic corticosteroids dose equivalent to dexamethasone dose.[17]

association between systemic corticosteroid and mortality in TB patients same our study. Then, a retrospective cohort study in South Korea presented systemic corticosteroid associated with decreased hospitalize mortality rate in 66 TB with pneumonia patients. However, our study mortality was 70.9 % while their study mortality was 49.2 %. The probable reason was that they include only patients older than 18-year-old and they include all TB pneumonia patients while our study included all aged pulmonary TB patients with ARF. Then, a retrospective cohort study in South Korea found that corticosteroids reduced the 90-day mortality in pulmonary TB with ARF.[10] However, they selected only 124 adult patients who admitted in ICU and excluded patients who had already received anti-TB treatment more than 3 weeks, while we included all of pulmonary TB patients with ARF in this analysis that the biggest population. So we had occasionally included patients with more severity.

STRENGTHS AND LIMITATIONS OF STUDY

To our knowledge, this is the first study to evaluated 90-day all-cause mortality with systemic corticosteroids in a large sample size. Moreover, this study also analyzed systemic corticosteroids in duration and dose. The study had several limitations; first, we used the database from a single referral center. However, medical records were several poor data quality leading to increasing in missing data and unclear evidence of diagnosis pulmonary TB. Besides, we recorded only data from hospitalized patients, thus the duration of systemic corticosteroid use could not truly record because some patients were prescribed oral corticosteroids for home medication. We also did not show information about the adverse effect of systemic corticosteroids. Moreover, the 90-day all-cause mortality outcome was checked from the National Statistical Office of Thailand which can not separate the specific cause of death.

CONCLUSION AND IMPLICATIONS

In conclusion, we found that systemic corticosteroid use was no significant increased 90-day all-cause mortality regarding dose and duration. However, our study has limitations such as missing data and study design as a retrospective study. Thus, further studies are required adequate data and prospective study design to determining better results.

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