BLOOD CD4 AND CD8 COUNT AS PREDICTORS OF 30 DAYS MORTALITY IN SEVERE PNEUMONIA PATIENTS AT THE DR. CIPTO MANGUNKUSUMO NATIONAL GENERAL HOSPITAL JAKARTA

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ABSTRACT

Background: Severe pneumonia is a major health problem in Indonesia and also in the world. The immune system is known to play important role in the pathogenesis of pneumonia, but few studies have assessed the relationship between blood CD4 and CD8 count and mortality from severe pneumonia in negative HIV population.

Methods: This study was a prospective cohort study conducted at Cipto Mangunkusumo General Hospital from June to August 2020. The outputs were 30-days survival rate and optimal cut-off value for blood CD4 and CD8 count to predict 30-days mortality and mortality risk. Data analysis used Kaplan-Meier survival, ROC curves and multivariate Cox regression.

Results: Of the 126 subjects, there was one subject who was lost to follow up. The 30-days mortality rate was 26.4%. The optimal cut-off value for blood CD4 count was 406 cells/μL (AUC 0,651, P=0,01, 95%CI 0,541-0,760, sensitivity 64%, specificity 61%), blood CD8 count was 263 cells/μL (AUC 0,639, P=0,018, 95% CI 0,534-0,744, sensitivity 62%, specificity 58%). CD4 blood count < 406 cells/μL had a crude HR of 2,696 (P=0,008, 95%CI 1.298-5.603), blood CD8 count < 263 cells/μL had a crude HR of 2,133 (P=0,042, 95%CI 1,035-4,392) and adjusted HR of 2,721 (P=0,005, 95%CI 1,343-5,512). If sepsis and pulmonary tuberculosis were added to the blood CD4 and CD8 count, the AUC value was 0,752 (P=0,000, 95%CI 0,662-0,842).

Conclusion: Blood CD4 and CD8 count had poor accuracy in predicting 30-days mortality in patients with severe pneumonia. Groups with lower blood CD4 and CD8 count had a higher risk of 30-days mortality.

Keywords: severe pneumonia, CD4 count, CD8 count, 30 days mortality

ABSTRAK

Latar Belakang: Pneumonia berat masih menjadi masalah kesehatan utama di Indonesia dan dunia. Sistem imun diketahui memiliki peranan penting dalam patogenesis pneumonia, namun tidak banyak studi yang menilai hubungan antara kadar CD4 dan CD8 darah dengan mortalitas akibat pneumonia berat pada pasien dengan status HIV negatif.

Tujuan: Mengetahui data hubungan dan nilai potong kadar CD4 dan CD8 darah dengan angka mortalitas 30 hari pada pasien pneumonia berat di RSCM.

Metode: Penelitian ini berdesain kohort prospektif yang dilakukan di ruang rawat intensif RSCM dalam periode Juni-Agustus 2020. Keluaran berupa kesintasan 30 hari dan nilai titik potong optimal kadar CD4 dan CD8 darah untuk memprediksi mortalitas 30 hari dan risiko kematian. Analisis data menggunakan analisis kesintasan Kaplan-Meier, kurva ROC, dan multivariat regresi Cox.

Hasil: Dari 126 subjek, terdapat 1 subjek yang loss to follow up. Mortalitas 30 hari didapatkan 26,4%. Nilai titik potong optimal kadar CD4 darah 406 sel/μL (AUC 0,651, p=0,01, IK95% 0,541-0,760, sensitivitas 64%, spesifisitas 61%) dan kadar CD8 darah 263 sel/μL (AUC 0,639, p=0,018, IK95% 0,534-0,744, sensitivitas 62%, spesifisitas 58%). Kadar CD4 darah < 406 sel/μL memiliki crude HR 2,696 (IK 95% 1,298-5,603) dan kadar CD8 darah < 263 sel/μL memiliki crude HR 2,133 (IK 95% 1,035-4,392) dengan adjusted HR 2,721 (IK 95% 1,343-5,512). Bila sepsis dan tuberkulosis paru ditambahkan dengan kadar CD4 darah dan CD8 darah, didapatkan nilai AUC 0,752 (p=0,000, IK 95% CI 0,662-0,842).

Kesimpulan: Kadar CD4 dan CD8 darah memiliki akurasi yang lemah dalam memprediksi mortalitas 30 hari pasien pneumonia berat. Kadar CD4 darah < 406 sel/μL dan kadar CD8 darah < 263 sel/μL memiliki risiko mortalitas 30 hari yang lebih tinggi.

Kata kunci: pneumonia berat, kadar CD4, kadar CD8, mortalitas 30 hari

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INTRODUCTION

Pneumonia is a global health burden in the world and Indonesia with high morbidity and mortality.[1-7] Pneumonia is the leading cause of death from infectious diseases and the number eight cause of death in the United States.[3] Data showed severe pneumonia had 40% of mortality rate in Cipto Mangunkusumo National Hospital.[6,7]

Immunological responses plays important role in severe pneumonia patophysiology through the activation of specific immune system such as CD4 and CD8.[8] This immunological role has proven to predict mortality in severe pneumonia with positive HIV patients, but not enough evidence supports CD4 and CD8 role in negative HIV population.[6,9]

MATERIALS AND METHODS

This was a prospective cohort study with 30 days mortality as an endpoint conducted from June to August 2020 in Cipto Mangunkusumo National General Hospital Jakarta (RSCM). All adults patients aged 18 years old and above, negative HIV status and diagnosed as severe pneumonia who required intensive care by attending physician were included in this study. Pneumonia diagnosis was based on the clinical criteria from the Infectious Diseases Society of America. Written informed consent was obtained from those who fulfilled the criteria in accordance with the Declaration of Helsinki. Patients with respiratory distresses caused by other than pneumonia, advanced cancer and refused to participate in this study were excluded. Baseline demographic, clinical characteristic, blood CD4 and CD8 count were obtained in the first 24 hours of diagnosis using laser flow-cytometry technique done by the Clinical Pathology Laboratory. All eligible subjects then were being followed up for the next 30 days after admission to assess their mortality status.

The optimal blood CD4 and CD8 count cut off were determined by the Receiver Operating Characteristic (ROC) curves, then the subjects were assigned into two groups based on cut off value. Both groups were analyzed using survival analysis with Statistical Package for the Social Sciences (SPSS) version 22. Numerical variables with normal distribution were displayed in the form of mean and SD. Numerical data with abnormal distribution were presented in median and minimum–maximum values. All predicted confounding variables were analyzed bivariately using the Chi-square analysis with the variables met a *P*-value < 0,25 then progressed to the multivariate Cox analysis. This study had received ethical approval by the Ethics Committee of the Faculty of Medicine Universitas Indonesia (No. KET-457/UN2.F1/ ETIK/PPM.00.02/2020).

RESULTS

Of the 126 patients who participated in this study, there was one subject who was lost to follow up, so 125 patients then were analyzed. The youngest subject was 18 years old, the oldest was 94 years old and the largest age group was the 41-60 years old age category with a percentage of 44,8%. In this study, it was found that patients with severe pneumonia also presented with acute renal failure, followed by type 2 diabetes mellitus and pulmonary tuberculosis. We also found 15 subjects were positive to Coronavirus disease (COVID-19). The other characteristics can be found in table 1.

In this study, in general, the 30-days mortality rate for patients with severe pneumonia was 26,4%. The Kaplan-Meier survival curve can be seen in Figure 1. From this analysis, the 5-days survival rate was 89,6% and the 15-days survival rate was 78,4%.

Table 1. Characteristics of research subjects (original)

Characteristics	Total (n=125)	Death (n=33)	Survivors (n=92)
Gender, n (%)			
Male	72 (57,6)	19 (57,6)	53 (57,6)
Female	53 (42,4)	14 (42,4)	39 (42,4)
Age median (min-max)	54 (18-94)	55 (22-79)	53.5 (18-94)
Age categories, n (%)			
18-40 years old	29 (23,2)	7 (21,2)	22 (23,9)
41-60 years old	56 (44,8)	15 (45,5)	41 (44,6)
>60 years old	40 (32)	11 (33,3)	29 (31,5)
Breathing rate (times/minute), mean (SD)	31 (2,5)	32.4 (3,0)	30,5 (2,1)
MAP (mmHg), mean (SD)	86,62 (11,4)	82.3 (11,8)	88,2 (10,9)
PO2/FiO2 ratio, median (min-max)	156,8 (71,4-298,7)	137,8 (71,4-253,3)	169,3 (82,8-298,7)
Invasive mechanical ventilation, n (%)	17 (13,6)	11 (33,3)	6 (6,5)
Comorbidities, n (%)			
Sepsis	22 (17,6)	11 (33,3)	11 (11)
Type 2 DM	49 (39,2)	11 (33,3)	38 (41,3)
Acute Kidney Injury	63 (50,4)	18 (54,5)	45 (48,9)
Pulmonary TB	29 (23,2)	5 (15,2)	24 (26,1)
Liver insufficiency	15 (12)	6 (18,2)	9 (9,8)
Malignancy	19 (15,2)	11 (33,3)	8 (8,7)
Autoimmune diseases	7 (5,6)	1 (3)	6 (6,5)
Blood CD4 count (cells/µL), median (min-max)	435 (113-1.679)	307 (124-952)	464,5 (113-1.679)
Blood CD8 count (cells/µL), median (min-max)	295 (50-1.738)	222 (50-714)	317 (58-1.738)
Positive PCR SARS CoV2 swab, n (%)	15 (12)	5 (15,2)	10 (10,9)

Abbreviations: SD=standard deviation; MAP=Mean Arterial Pressure; DM=Diabetes Melitus; TB=Tuberculosis; PCR SARS CoV2=Polymerase Chain Reaction Severe Acute Respiratory Syndrome Coronavirus 2.

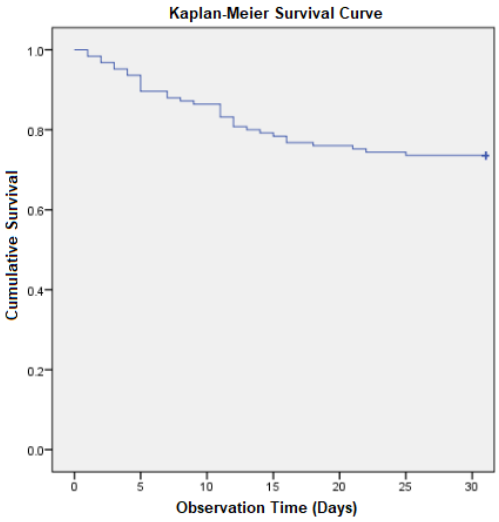

Figure 1. Analysis of cumulative survival in patients with severe pneumonia at RSCM using the Kaplan Meier method (original)

To determine the cutoff points for blood CD4 and CD8 counts which can predict mortality, a Receiver Operating Characteristic (ROC) curve was created (Figure 2). From the ROC curve, an AUC ± SE value of 0,651 ± 0,056 (*P*=0,01, 95% CI 0,541-0,760) was obtained and it was determined that the optimal blood CD4 count was 406 cells/µL (sensitivity 64%, specificity 61%) using the graph in Figure 3.

The blood CD8 count showed an AUC ± SE value of 0,639 ± 0,054 (P=0,018, 95% CI 0,534-0,744) and the optimal blood CD8 count was 263 cells/µL (sensitivity 62%, specificity 58%).

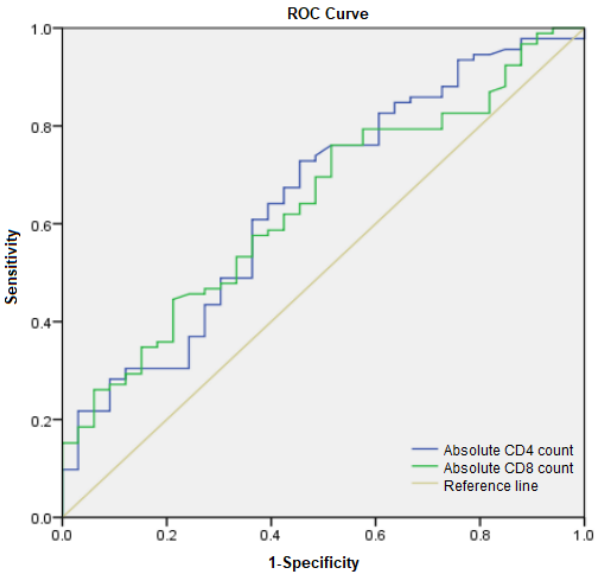

Figure 2. ROC curve comparison of blood CD4 count (AUC 0.651, P=0.01, 95% CI 0.541-0.760) and blood CD8 (AUC 0.639, P=0.018, 95% CI 0.534-0.744) to the 30-days mortality of patients with severe pneumonia (original)

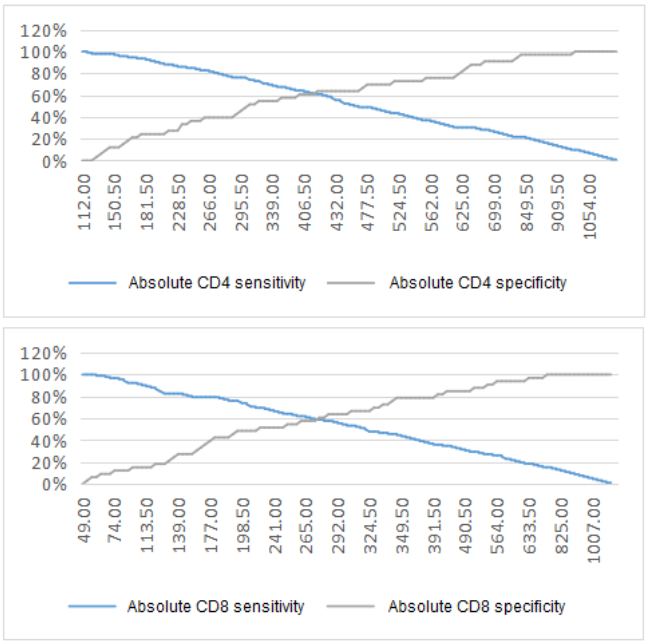

Figure 3. Graph to help determine optimal cut-off values for blood CD4 count (top) and blood CD8 count (bottom) in predicting 30-day mortality (original)

From the cutoff point values for blood CD4 and blood CD8 count obtained above, we divided the subjects into two groups, group with low blood CD4 count (<406 cells/µL, n=53, 42,4%) and group with high blood CD4 counts (≥ 406 cells/µL, n=72, 57,6%). For blood CD8 count, we also divided subjects into two groups, group with low blood CD8 count (< 263 cells/µL, n=54, 43,2%) and high blood CD8 count (≥ 263 cells/µL, n=71, 56,8%).

The survival rate of patients in high blood CD4 count group was 81,9% with a mean survival rate of 27 days (95% CI 25-29). In group with low blood CD4 count, the survival rate was 62,3% with a mean survival rate of 23 days (95% CI 20-26). While the overall survival rate of all CD4 groups was 25 days (95% CI 24-27). By using cox regression survival analysis, the crude HR was 2,696 (p=0,008, 95% CI 1,298-5,603).

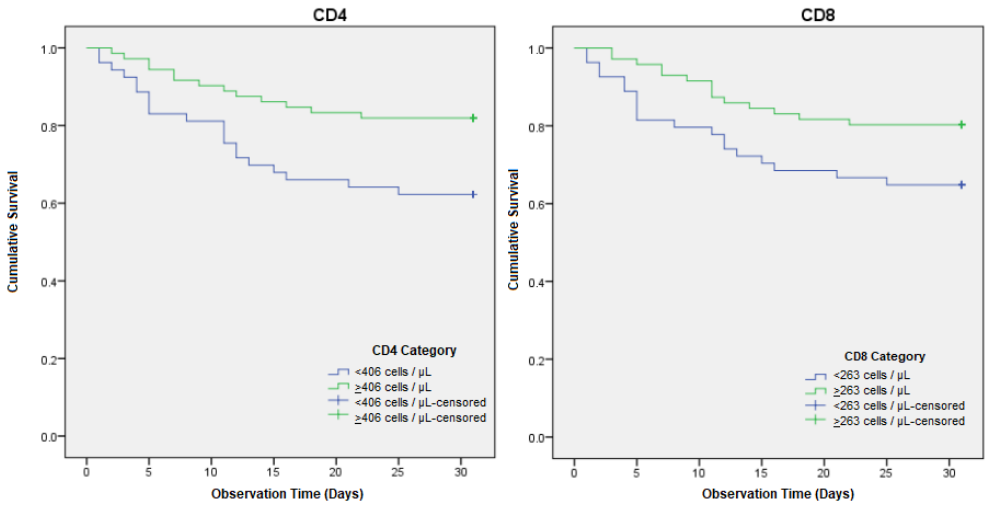

Figure 4. Kaplan-Meier survival curve between blood CD4 count (left) and blood CD8 count groups (right) (original)

Meanwhile, for the blood CD8 count, the survival rate of patients in high blood CD8 count was 80,3% with a mean survival rate of 27 days (95% CI 25-29). In group with a low blood CD8 count, the survival rate was 64,8% with a mean survival rate of 23 days (95% CI 20-26). While the overall survival rate of all CD8 groups was 25 days (24-27). By using cox regression survival analysis, crude HR was 2,133 (*P*=0,042, 95% CI 1,035-4,392). The Kaplan-Meier survival curves can be found in Figure 4.

Confounding variables were analyzed bivariately using the chi-square test as shown in table 2.

Table 2. Bi-variate analysis on independent variables (original)

Variables	Survivors		*P* value
	No (n,%)	Yes (n,%)	
Age category			
< 60 years old	22 (66,7)	61 (66,3)	0,97
≥ 60 years old	11 (33,3)	31 (33,7)	
Sepsis			
Yes	11 (33,3)	11 (12)	0,006
No	22 (66,7)	81 (88)	
Pulmonary tuberculosis			
Yes	5 (15,2)	24 (26,1)	0,202
No	28 (84,8)	68 (73,9)	
Type 2 diabetes mellitus	11 (33,3)	38 (41,3)	0,421
Yes	22 (66,7)	54 (58,7)	
No			

From the table above, it can be seen that apart from the main independent variables of blood CD4 and blood CD8 count, only sepsis and pulmonary tuberculosis had a *P* value of < 0,25, so we included these variables into further analysis using multivariate cox regression. The results are listed in table 3. The changes in crude HR is less than 10%, it was then

concluded that sepsis and pulmonary tuberculosis were not confounding variables in this study. The cumulative survival curve after controlling confounders can be seen in Figure 5.

Table 3. Adjusted Hazard Ratio for blood CD4 count value <406 cells/µL to 30-days mortality on gradually adding variables (original)

Variables	Adjusted HR (95% CI)	*P* value	Crude HR changes
Blood CD4 count <406 cells/µL	2,696 (95% CI 1,298-5,603)	0,008	-
+ Blood CD8 count < 263 cells/µL	2,501 (95% CI 1,060-5,903)	0,036	7,23%
+ Sepsis	2,535 (95% CI 1,257-5,111)	0,009	1,34%
+ Pulmonary tuberculosis	2,721 (95% CI 1,343-5,512)	0,005	6,84%

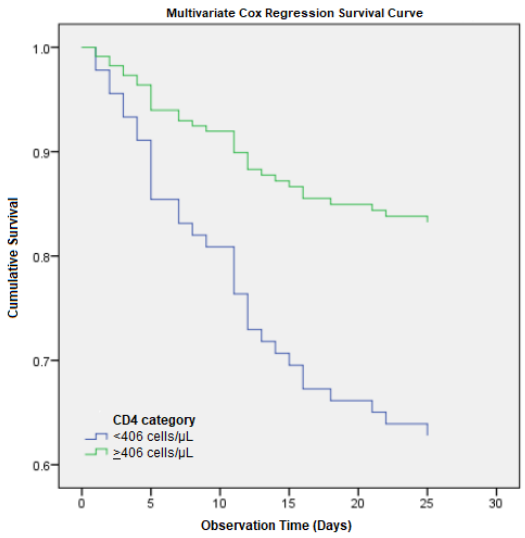

Figure 5. Multivariate Cox regression cumulative survival curve (after controlling for confounding variables) (original)

In addition to the research results, the calculations for AUC ± SE for sepsis was 0,607 ± 0,061 (*P*=0,069, 95% CI 0,488-0,726) and AUC ± SE for pulmonary TB was 0,555 ± 0,057 (*P*=0,353, 95% CI 0,444-0,666). Then, if the blood CD4 count and blood CD8 count were combined to predict the 30-days mortality of severe pneumonia, the AUC ± SE value was 0,659 ± 0,054 (*P*=0,007, 95% CI 0,554-0,764). Furthermore, if the variables of sepsis and pulmonary tuberculosis were added to the blood CD4 and CD8 count to predict 30-days mortality, the AUC ± SE value was 0,752 ± 0,046 (*P*=0,000, 95% CI 0,662-0,842) as seen in Figure 6.

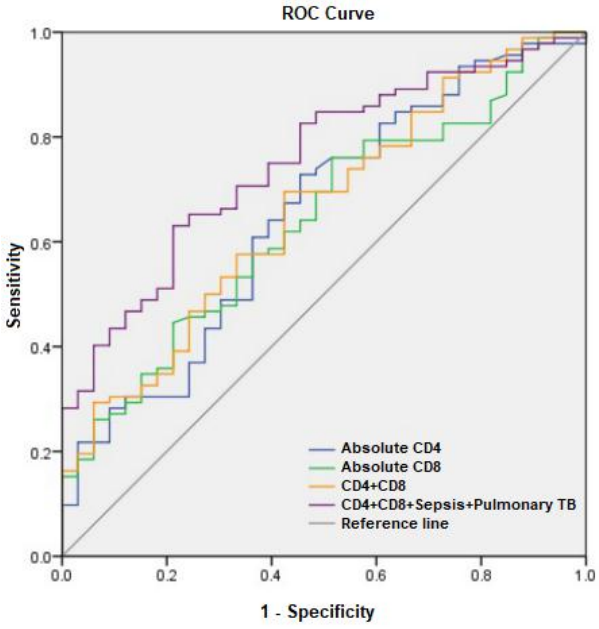

Figure 6. ROC curve comparison of blood CD4 count (AUC ± SE = 0,651 ± 0,056, *P*=0,01, 95% CI 0,541-0,760), blood CD8 (AUC ± SE = 0,651 ± 0,056, *P*=0,01, 95% CI 0,541-0,760), blood CD4 + blood CD8 (AUC ± SE = 0,659 ± 0,054, *P*=0,007, 95% CI 0,554-0,764), blood CD4 + blood CD8 + Sepsis + Pulmonary tuberculosis (AUC ± SE = 0,752 ± 0,046, *P*=0,000, 95% CI 0,662-0,842) against 30-day mortality in patients with severe pneumonia (original)

DISCUSSION

The subjects sex proportion investigated in this study was not so much distinct with another similar studies about severe pneumonia.[6,7,10-12] The median age of the subjects was also not so differ from previous studies in Indonesia,[5-7] but this age was much younger if compared with studies from developed countries like the United States and Singapore.[10,12] It was thought that some factors in our subjects may affect this difference such as lower life expectancy especially in the elderly population, level of education, health awareness, and the utilization of pneumonia vaccine.

The difference in the subjects characteristic, study inclusion or exclusion criteria and a better management of pneumonia in recent years were thought to be some of the reasons why the mortality rate acquired in this study lower than the previous studies about pneumonia in Indonesia.[5-7] For the last couple of years, there has been a more aggressive approach in managing severe pneumonia such as early mechanical ventilation intervention and a broader options of antibiotics availability in our hospital.

In this study, as a primary outcome, we found that the accuracy of blood CD4 and CD8 count to predict 30 days mortality in severe pneumonia was poor with the optimal cut off value 406 cells/µL for blood CD4 count (sensitivity 64%, specificity 61%, AUC $\pm$ SE = 0,651 $\pm$ 0,056, *P*=0,01, 95% CI 0,541-0,760) and 263 cells/µL for blood CD8 count (sensitivity 62%, specificity 58%, AUC $\pm$ SE = 0,651 $\pm$ 0,056, *P*=0,01, 95% CI 0,541-0,760). Previous study showed blood CD4 count less than 500 cells/µL was associated with more severe outcome and complications.[9] This result could be due to the blood CD4 and CD8 count that were collected having an abnormal distribution or large data variability in all groups. Lower blood CD4 and CD8 count groups encountered higher risk of 30 days mortality (adjusted HR 2,721, *P*=0,005, 95% CI 1,343-5,512). In HIV population, many studies concluded that blood CD4 count less than 200 cells/µL is associated with a higher mortality rate in pneumonia.[13-17]

Since blood CD4 and CD8 count had a weak prediction capability of 30-days mortality in patients with severe pneumonia when used alone, a further analysis was carried out in this study to assess their predictive ability when added with the sepsis and pulmonary tuberculosis variables. From the analysis, it was found that by adding the conditions of sepsis and pulmonary tuberculosis as additional variables to low blood CD4 and CD8 count, the ability to predict 30-days mortality against severe pneumonia improved. This was consistent with studies linking higher pneumonia mortality when accompanied by sepsis and pulmonary tuberculosis.[18-24]

To the best of our knowledge, this is the first study in Indonesia to investigate the use of blood CD4 dan CD8 count in predicting mortality of non HIV severe pneumonia patients. This study has an important role to assess the immunological profile of severe pneumonia patients in Indonesia. Furthermore, the results of this study were expected to be used by clinicians as a basis for consideration in choosing therapy and can be personalized to the state of immunity dysregulation in patients.

This study had several limitations. First, this study did not assess the relationship between the microorganisms causing severe pneumonia and other immunological factors in the host. Second, other immunological factors in host which experience dysfunction in severe pneumonia infection, such as the non-specific or innate immune system (e.g. neutrophils, macrophages, dendritic cells, natural killer cells, and complement) and humoral formed immunoglobulins were not studied in this study. Last, this study only assessed the count of blood CD4 and CD8, but not its functional

capacity. It is thought that these factors could also influence the result of this study, so further studies need to be done.

CONCLUSION

Blood CD4 and CD8 count had poor accuracy in predicting 30-days mortality in severe pneumonia patients with the optimal cutoff point values 406 cells/µL for blood CD4 count and 263 cells/µL for blood CD8 count. Blood CD4 and CD8 count should not be used alone to predict mortality and needed to be added with another conditions such as sepsis and pulmonary tuberculosis to increase their accuracy. The groups with lower blood CD4 and CD8 count had a higher risk of 30-days mortality.

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