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Original Research Article

Relationship between neutrophil to lymphocytes ratio, red cell distribution width, procalcitonin, neutrophil to albumin ratio, and bun to albumin ratio with mortality of severe cap patients with septic shock

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ABSTRACT

Background: Septic shock is one of severe community-acquired pneumonia (CAP) complication with high mortality. Various laboratory parameters had been associated with poor outcome including neutrophil-to-lymphocyte ratio (NLR), red cell distribution width (RDW), procalcitonin, neutrophil to albumin ratio (NAR), and bun to albumin ratio (BAR). This study aimed to know the relationship between inflammatory markers with mortality of severe CAP patients with septic shock.
Methods: This study is an observational analytic study using a cohort retrospective design conducted in Prof. I.G.N.G. Ngoerah General Hospital over a 3 years' period (January 2020 to July 2023). The relative risk (RR) values showed relative risk of each parameter to mortality.
Results: Of total 73 subjects, mortality was found in 68.5%. Male predominance was found (65.8%). Comorbid disease was reported in 69 subjects (94.5%), most found was cardiovascular disease (63%). Majority of the subjects did not have history of prior antibiotics use (86.3%). In multivariate analysis, it was found that NLR with cutoff ≥16.5 (p value 0.044; 95% CI 1.039-14.011; RR 3.816), procalcitonin ≥1.82 (p value 0.029; 95% CI 1.148-13.560; RR 3.945), and BAR ≥8.13 (p value 0.003; 95% CI 1.961-21.912; RR 7.399) are associated with mortality. There was no relationship between RDW ≥14.65 (p value 0.159; 95% CI 0.658-12.877) and NAR ≥4.5 (p value 0.436; 95% CI 0.429-7.106) with mortality in this study.
Conclusions: Mortality of severe CAP patients with septic shock in this study is high. Higher NLR, procalcitonin, and BAR values have a significant relationship with mortality of severe CAP patients with septic shock.

Keywords: Community acquired pneumonia, Septic shock, Mortality

INTRODUCTION

Community-acquired pneumonia (CAP) contribute significantly to global health burden with various clinical spectrum. Septic shock is one of harmful complication of severe CAP with high mortality. The prevalence of CAP in United States of America (USA) was 4.2 million with 128,000 emergency visit in 2017.[1] Based on Riskesdas 2018, pneumonia account to one million cases per year in Indonesia, showing an increase of 0.4% compared to

2013.[2] Sepsis and septic shock kills one of three and one of six patients, respectively. Study in Egypt demonstrated that pneumonia contributes to 62% of all sepsis cause.[3]

Various laboratory parameters had been associated with mortality of severe CAP patients with septic shock. Neutrophil to lymphocyte (NLR) ratio in CAP with cutoff >10 predicts mortality better than C-reactive protein, white blood cell counts, neutrophil counts, lymphocyte levels, pneumonia severity index (PSI), and CURB-65 alone.[4] Recent studies also shows an association between increased RDW and prognosis of several diseases including CAP. This parameter is routinely checked and accessible. Increased RDW is associated with high mortality and morbidity in CAP patients at all ages.[5] Procalcitonin was reported as the most accurate marker in pneumonia with sepsis for prognostic assessment (sensitivity 84.7%, specificity 94.1%).[6] Novel parameters such as neutrophil to albumin ratio (NAR) was identified to be associated with all causes of mortality in critically ill patients treated for sepsis and septic shock. Pneumonia caused by COVID-19 shows that high NAR values have a higher likelihood of mortality.[7] However, NAR value in severe CAP patients with septic shock has not yet been reported. Other study reported a high BUN-to albumin ratio (BAR) is an independent risk factor for mortality in severe CAP patients.[8]

This study aimed to know the relationship between inflammatory markers with mortality of severe CAP patients with septic shock.

METHODS

This study is an observational analytic study using a cohort retrospective design conducted in Prof I.G.N.G. Ngoerah General Hospital over a 3 years period (January 2020 to July 2023).

Inclusion criteria

Patients with age above 18 years, and diagnosed as severe CAP with septic shock were included.

Exclusion criteria

Patients with incomplete medical record data; other etiology of shock than septic shock is found; patients with hematological disorders, immunodeficiency, and/or pregnancy; patients with confirmed COVID-19; patients with pulmonary mycosis; underlying diseases that can cause alteration of albumin level including liver cirrhosis, malnutrition, chronic kidney failure on hemodialysis, and burns; patients who refuse resuscitation; more than one known source of infection; and patients on corticosteroid treatment equivalent to or more than prednisolone 1 mg/kg/day for more than one month were excluded.

Univariate analysis presents data in the form of frequency, mean, standard deviation, median, and interquartile range (IQR). ROC analysis is determined from the best intersection point based on coordinates of the curve furthest from the diagonal line. Bivariate analysis was carried out using chi square test. Multivariate analysis using a logistic regression test. The RR values showed relative risk of each parameter to mortality. The entire analysis process was carried out using statistical software statistical package for the social sciences (SPSS) version 26.0.

RESULTS

Of the 1857 subjects hospitalized with sepsis during the study period, 359 subjects were diagnosed with severe CAP with septic shock. A total of 286 subjects were excluded from the study based on exclusion criteria, resulting a total of 73 subjects. Characteristics of the subjects in this study is presented in Table 1. Laboratory parameters value is shown in Table 2. Based on Table 1, mortality rate in our study was 68.5%. Male predominance was found. Comorbid disease was reported in 69 subjects (94.5%) and majority of the subjects did not have history of prior antibiotics use (86.3%).

Table 1: Characteristics of the study subjects (n= 73).

Characteristics	Description, N (%)
Age (years)	
Range	21–93
Mean±SD	62.84±17.19
<60	29 (39.7)
≥60	44 (60.3)
Sex	
Male	48 (65.8)
Female	25 (34.2)
Comorbidities	
Without comorbidity	4 (5.5)
With comorbidities	69 (94.5)
Cardiovascular	46 (63)
COPD	12 (16.4)
CKD	26 (35.6)
DM	17 (23.3)
Cerebrovascular	20 (27.4)
History of antibiotics use	
No	63 (86.3)
Yes	10 (13.7)
Mortality	
Yes	50 (68.5)
No	23 (31.5)

Laboratory parameters in this study demonstrated various range value in Table 2. Data presented as median (interquartile range/IQR). Procalcitonin had the widest range.

Bivariate analysis in Table 3 demonstrated significant relationship between NLR ≥16.5 with mortality in this study. Other parameters that demonstrated significant

relationship with mortality in this study were procalcitonin ≥1.82 ng/ml (Table 5) and BAR ≥8.13 (Table 7). Our study did not find significant relationship between RDW ≥14.65% (Table 4) and NAR ≥4.5 (Table 6).

Multivariate analysis in this study was presented in Table 8. Similar to bivariate results, three parameters demonstrated significant relationship with mortality in this study (NLR, procalcitonin, and BAR). Of these, highest relative risk was found in BAR parameter (RR 7.399).

Table 2: Laboratory parameters of study subjects.

Parameter	Unit	Minimum	Maximum	Median (IQR)
NLR		1.89	98.78	15.39 (9.43–23.45)
RDW	%	10.5	61.87	14.6 (13.38–16.45)
Procalcitonin	ng/ml	0.04	504.09	2.51 (0.51–14.94)
NAR		1.15	14.76	4.55 (3.02–7.17)
BAR		1.88	51.5	10.5 (5.89–19.35)

Table 3: NLR relationship with study subjects' mortality.

NLR	Mortality, N (%)		RR (95% CI)	P value
	Yes	No		
≥16.5	28 (84.8)	5 (15.2)	1.543 (1.126–2.114)	0.006
<16.5	22 (55.0)	18 (45.0)		

CI=Confidence interval.

Table 4: RDW relationship with study subjects' mortality.

RDW (%)	Mortality, N (%)		RR (95% CI)	P value
	Yes	No		
≥14.65	26 (76.5)	8 (23.5)	1.243 (0.911–1.695)	0.171
<14.65	24 (61.5)	15 (38.5)		

CI=Confidence interval.

Table 5: Procalcitonin relationship with study subjects' mortality.

Procalcitonin (ng/ml)	Mortality, N (%)		RR (95% CI)	P value
	Yes	No		
≥1.82	33 (82.5)	7 (17.5)	1.601 (1.117–2.296)	0.005
<1.82	17 (51.5)	16 (48.5)		

CI=Confidence interval.

Table 6: NAR relationship with study subjects' mortality.

NAR	Mortality, N (%)		RR (95% CI)	P value
	Yes	No		
≥4.5	29 (78.4)	8 (21.6)	1.344 (0.972–1.857)	0.065
<4.5	21 (58.3)	15 (41.7)		

CI=Confidence interval.

Table 7: BAR relationship with study subjects' mortality.

BAR	Mortality, N (%)		RR (95% CI)	P value
	Yes	No		
≥8.13	39 (83.0)	8 (17.0)	1.961 (1.229–3.129)	<0.001
<8.13	11 (42.3)	15 (57.7)		

CI=Confidence interval.

Table 8: Multivariate analysis results with stepwise logistic regression (backward elimination) the relationship between study variable and mortality.

Variable	Coef	Wald	P value	RR	95% CI	Ch-2LR
NLR	1.339	4.074	0.044	3.816	1.039-14.011	0.036
RDW[a]	1.037	1.861	0.173	2.822	0.636-12.527	0.160
Procalcitonin[b]	1.372	4.746	0.029	3.945	1.148-13.560	0.025
NAR	0.411	0.366	0.545	1.508	0.398-5.705	0.545
BAR	2.001	8.729	0.003	7.399	1.961-21.912	0.002
Age	0.967	1.524	0.217	2.630	0.567-12.209	0.198
Sex	-1.140	2.304	0.129	0.320	0.073-1.394	0.111
Antibiotic history	-0.821	3.504	0.061	0.440	0.186-1.039	0.063
Comorbidity	-0.438	0.474	0.491	0.645	0.185-2.247	0.489

Coef=Coefficient, Ch-2LR=changed in -2 likelihood ratio, a=RDW value in %, b=procalcitonin value in ng/ml, bold letters showed parameter with significant p value.

DISCUSSION

CAP had negative impact on various sectors leading to complication that increase mortality rates. Epidemiological data support our results which indicate the incidence of CAP patients with septic shock is higher in older individual. Study by Guel, et al in severe CAP patients with septic shock reported similar average age 63 years.[9] Male predominance (65.8%) was found in this study (Table 1). This result is consistent with study by Avci et al that found CAP mostly affects male (61.9%).[10] Older age and male sex tend to have more comorbidities. Poor performance status and the aging process itself also reduce individual's ability to recover from critical illness as well as being susceptible to the development of ALI, severe pneumonia, and *S. pneumoniae*-induced mortality secondary to decreased NOD, LRR and pyrin domain-containing protein 3 (NLRP3), a component of pattern recognition receptor. Male hormones may play role in immune response suppression, whereas female hormones showed a natural protective effect in women.[11]

Our study found that 63% subjects had cardiovascular disease and majority of the subjects have comorbid disease (94.5%) as shown in Table 1. Cardiovascular disease also most commonly found comorbidity (75.3%) in CAP patients with sepsis by other study.[12] Different study reported that hypertension and DM were most commonly observed in sepsis patients. Comorbidity was thought to influence the host defense mechanisms, therefore patient is more susceptible to serious infections. Heart disease influence patient outcomes through various mechanisms such as relative ischemia, upregulation of the sympathetic system, systemic inflammation, and direct damage to the cardiovascular system.[13]

Majority of the subjects in this study had no previous history of antibiotic use within the last 90 days (n=63, 86.3%). History of intravenous (IV) antibiotic administration in the last 90 days is a risk factor for drug-resistant pathogens. There is a strong and significant correlation between antibiotic resistance and the development of sepsis in CAP patients. Adherence with guidelines and early administration of antibiotics are protective factors against 30-day mortality in severe CAP patients with sepsis.[15] This should be taken into consideration when selecting initial antibiotic therapy for severe CAP patients with septic shock.

Mortality of severe CAP patients with septic shock in our study was 68.5%. Higher mortality of CAP patients with septic shock admitted to intensive care unit (ICU) without adequate infection control was reported to be 84.4% by previous study.[16] This result may be affected by patient's initial condition when admitted to hospital, antibiotic resistance, adequacy of management, and pathogen factors.

Characteristics of laboratory parameter in this study (Table 2) was consistent with various other studies. Similar range and/or median for NLR, RDW, procalcitonin, NAR, and BAR has been reported in pneumonia and sepsis patients.[17-21] Factors such as time of sampling, type of equipment and reagents used should be considered for these laboratory results.

Analysis in this study demonstrated NLR value ≥16.5 was associated with a 3.81-fold increased risk of mortality (Table 8). Previous study also found similar results. The highest sensitivity and specificity of NLR in predicting poor CAP outcomes is when using a cutoff 11.2 and 13.4, respectively.[4] On the contrary, other study reported that NLR value <12 increases the risk of mortality in CAP patients with septic shock.[9] Infection and stress-related conditions leads to B cell and T cell apoptosis decreases, resulting in lymphopenia. Simultaneously, there is a rapid increase in neutrophil levels due to mobilization from the bone marrow to the blood. Release of activated inflammatory cytokines can cause tissue damage and organ dysfunction.[22]

The predictive role of RDW related to mortality in CAP patients with sepsis remain unclear in the literature. Underlying mechanism that causes an increase in RDW in severe CAP patients with septic shock is thought to be related to disruption of erythropoiesis due to an inflammation.[3,20] Our study did not find a significant

relationship between RDW value ≥14.65% and mortality (Table 4). A study at Dr. Sardjito Hospital in Indonesia that included HAP patients found there was no significant relationship between increased RDW and mortality.[5] This has similar result with our study. Contrary to this, other study reported that every 1% increase in RDW was equivalent to a 15% increase in the 30-day mortality rate of elderly patients with severe sepsis and septic shock in the first year. Time from blood collection to analysis was determined uniformly (three hours) in their study, thus it can affect the result.[13] Another report demonstrated that RDW increase (cutoff 15.45) significantly associated with 30-day mortality of CAP. This study also determined a uniform sampling time, i.e. four hours after admission.[17] RDW is a nonspecific inflammatory marker, elevated in conditions such as heart failure, stroke, peripheral arterial disease, and chronic lung disease.[13] Recent study found that RDW >15 affects red blood cell deformability.[23] Inflammation and oxidative stress stimulate premature erythrocyte production. Inefficient erythropoiesis lead to structural and functional changes of erythrocytes, with volume variations and increased RDW.[22] It is recommended that RDW measurement is repeated during hospitalization. Suggestion was made to evaluate other inflammatory indicators such as CRP and gamma-glutamyl transferase along with RDW to provide better information of inflammatory status.[17]

Procalcitonin has been widely used to help differentiate bacterial infections from non-infectious conditions, predict severity, mortality, and monitor patients, especially CAP and sepsis. Our study found statistically significant relationship between procalcitonin and mortality with 3.94-fold higher likelihood of mortality (Table 8). Consistent with our study, procalcitonin was reported as the most accurate marker in prognostic assessment of CAP patients with sepsis. Procalcitonin cutoff ≥2 ng/ml demonstrate significant relationship with sepsis patients who died.[24] Different result found that procalcitonin ≥2 ng/ml did not have significant relationship with mortality in septic pneumonia patients (total 43 subjects).[25] Bacterial infection induce procalcitonin production due to release of endotoxin from bacterial cell wall. Alveolar macrophages phagocytose bacteria and produce proinflammatory cytokines, which initiate innate immune system response against bacterial pathogen. This results in the production of IL-1β, TNF-α, and IL-6 which subsequently induce procalcitonin production. During sepsis, an increase in calcitonin-1 (CALC-1) gene expression prompt the release of procalcitonin. Persistent increase for a relatively long period was associated with severity and mortality.[26] Several factors could contribute to lower cutoff of procalcitonin in this study (≥1.82 ng/ml) than other studies (≥2 ng/ml). History of previous antibiotic use before admitted at the study location is an important factor. Other possible reasons were high doses of biotin supplements consumption and polypharmacy.[27,28]

This study did not found statistically significant relationship between NAR ≥4.5 and mortality. To the best of our knowledge, this is the first study that evaluate the relationship between NAR in severe CAP patients with septic shock. Previous studies reported that NAR is a better predictor mortality than albumin or neutrophil count alone. Similarly, critical COVID-19 patients with NAR value 41.3 was not statistically significant in predicting mortality.[7] Whereas, increased NAR associated with increased risk of all-cause mortality at 30, 90 and 365 days in severe sepsis or septic shock.[29] In retrospective study of critical COVID-19, NAR value 267.2 is significantly associated with mortality. Laboratory parameters also analyzed within 30 minutes of diagnosis.[30] Increased albumin leakage is a feature of sepsis. Low albumin level was associated with severe systemic inflammation and multi-organ failure. Severe infectious conditions were associated with increased vascular permeability and capillary leakage resulting in loss of albumin from intravascular, it can also occur due to reduced synthesis and increased catabolism of albumin.[31] Pharmacological therapies commonly administered to severe CAP patients with septic shock may also influence results. Immunomodulatory effects of vasopressor can be a double-edged sword in sepsis because host may be susceptible to infection through reduced defense mechanisms as a consequence of neutrophil paralysis, but also prevent worsening of tissue injury by neutrophil activation. Fluids used in resuscitation of septic shock also had heterogeneous effects on the interaction of neutrophils with endothelial cells. Albumin reduces sepsis-associated neutrophil adhesion and aggregation in varying degrees.[32]

BUN and albumin are important biochemical parameters. BAR ≥8.13 had statistically significant relationship with mortality (RR 7.39). CAP patients with BAR ≥10.2 require ICU care and statistically significant high mortality in one study.[33] BAR value of ≥9.6 is an independent risk factor for predicting short-term mortality and one-year mortality in septic shock patients.[34] Slightly different result were reported by other study found that BAR ≥4.15 only predict the need for ICU care in CAP, but not significant in predicting mortality. Subjects in their study had a relatively milder degree of CAP based on severity score at initial admission. Elevated BUN describes protein catabolism indicating renal hypoperfusion. Dehydration that is commonly found in CAP occurs due to increased excretion of BUN from the kidneys. BUN level is considered as predictive marker that reflects the cumulative effects of hemodynamic damage in critical illness.[8]

Multivariate analysis of this study demonstrated three independent variables including NLR ≥16.5, procalcitonin ≥1.82 ng/ml, and BAR ≥8.13 had statistically significant relationship with mortality. Multivariate analysis demonstrate that NLR was an independent risk factor for mortality at 28 days in sepsis.[35] It has been reported that simultaneous lymphopenia and increased neutrophils indicates increased immunological failure in severe CAP patients with septic shock compared with lymphopenia alone.[9] Prognostic value of NLR related to mortality in

CAP patients also showed significant relationship in multivariate analysis after adjustment for age, gender and comorbid.[36] Indeed, procalcitonin value >1.1 ng/ml at baseline independently predict mortality in elderly CAP patients.[37] Clinical implications of procalcitonin are primarily to guide the decision to discontinue antibiotic. Moreover, in some clinical scenarios, procalcitonin assist in antibiotic prescription.[38] High mortality rate in severe CAP patients with septic shock as obtained in this study may have an impact on high treatment costs and prolong hospitalization. Accurate evaluation of prognosis will help making clinical decisions to reduce its burden. Similar multivariate analysis in CAP patients were reported found BAR value at the time of initial hospital admission was an independent risk factor capable of predicting the need for intensive care (cutoff 9.84) and 30 days mortality (cutoff 10.2).[34] After adjusting for age, gender, APACHE II score, and lactate level, BAR value remained associated with mortality in septic shock patients in ICU.[21] BAR evaluates complex relationship between nutritional status, hydration, liver reserve, and kidney condition, especially in critical patients. Therefore, BAR is more useful for assessing disease severity than using BUN or albumin alone.[39]

In general, the results obtained in this study show that mortality can be reflected through inflammatory markers include NLR, procalcitonin, and BAR. Highest risk of mortality are patients with BAR ≥8.13 (RR 7.399) compared to other parameters studied in this study. Implications of this study are early detection of poor outcomes in patients with severe CAP with septic shock as well as for consideration in patient management strategies.

This study has several strengths. First, this is the first study to analyze the relationship of several laboratory parameters in severe CAP patients with septic shock. Second, results of this study may provide information and suggestion related to factors that influence mortality of severe CAP patients with septic shock. Lastly, this study measures laboratory parameters that are commonly evaluated in severe CAP patients with septic shock so it will be easy to apply to assess the risk of mortality.

Limitations

This study also has several limitations. This study is conducted in one center, which can be overcome by conducting research in several centers. The use of secondary data, raise a possibility of information bias. This study also did not evaluate the etiology and overall management of the subjects.

CONCLUSION

Mortality of severe CAP patients with septic shock in this study was found in 50 subjects (68.5%). Higher NLR, procalcitonin, and BAR values have a statistically significant relationship with mortality of severe CAP patients with septic shock.

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