Evaluating CRP and Oxygen Requirements as Predictors of Poor Outcomes in COVID-19 Patients with Bacterial Pneumonia

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Abstract

Background: The COVID-19 pandemic has presented significant challenges in the management of bacterial pneumonia co-infections, particularly among elderly populations. These co-infections, most commonly caused by pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, are associated with increased disease severity, higher mortality rate, and poorer outcomes. Data on bacterial co-infections and their impact on patient recovery remain limited, especially in Indonesia. Therefore, this study investigated the associations of age, oxygen supplementation, oxygen saturation, and clinical markers (procalcitonin and CRP) with outcomes in COVID-19 patients with bacterial pneumonia co-infections.

Methods: This cross-sectional predictive study utilized secondary data from medical records of COVID-19 patients with bacterial pneumonia co-infection at the Regional General Hospital of West Nusa Tenggara Province and Universitas Mataram Hospital. Consecutive sampling was used to include patients with confirmed COVID-19 and bacterial pneumonia. Bivariate and multivariate analyses were conducted to assess the association between age, oxygen supplementation, procalcitonin levels, CRP levels, and recovery outcomes.

Results: The study analyzed data from 77 COVID-19 patients with bacterial pneumonia co-infection. Significant predictors of poor outcomes included elevated C-reactive protein (CRP) levels (>75 mg/L) and high oxygen supplementation (>6 L/min). Patients with elevated CRP had a sixfold higher risk of death, and higher oxygen requirements were strongly associated with increased mortality. Lower oxygen saturation was also linked to worse outcomes. Findings highlight CRP levels and oxygen needs as critical factors in predicting mortality. Elevated CRP and higher oxygen supplementation were significantly associated with death, providing insights into the management of co-infected COVID-19 patients.

Conclusion: CRP levels and oxygen requirements are key predictors of poor outcomes in COVID-19 patients with bacterial pneumonia.

Keywords: bacterial co-infection, COVID-19, CRP, outcome status

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INTRODUCTION

The COVID-19 pandemic has ravaged the world for over two years, including Indonesia, where the first case was reported in December 2019. According to the COVID-19 Task Force of the Indonesian Ministry of Health, over 4.4 million positive cases and nearly 145,000 deaths have been recorded in the country.[1] COVID-19 can present with a wide range of clinical manifestations, from asymptomatic cases to severe pneumonia, acute respiratory distress syndrome (ARDS), and even death. The COVID-19 pandemic has highlighted the variability of secondary bacterial co-infections and bacterial pneumonia among patients from differing studies reported worldwide.[2]

Historically, the 1918 influenza pandemic showed that up to 95% of severe cases and deaths were the result of secondary bacterial infections, mainly caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*.[1] Similar findings are emerging from current studies on COVID-19, emphasizing the importance of understanding these co-infections.[3] For example, a study conducted in Spain observed that 7.2% of COVID-19 patients experienced bacterial, fungal, or other viral co-infections, with *Streptococcus pneumoniae* and *Staphylococcus aureus* being the predominant bacterial pathogens. These co-infections significantly impacted clinical outcomes, especially in patients suffering from either community-acquired or nosocomial pneumonia.[4]

While viral pneumonia caused by SARS-CoV-2 remains the dominant infection in COVID-19 patients, clinicians must still consider other possible pneumonia etiologies, particularly in the high-risk population, especially in the elderly. Studies have shown a decrease in community-acquired pneumonia cases during the pandemic, particularly among the elderly, while others have suggested that COVID-19 patients rarely develop bacterial community-acquired pneumonia.[5,6] This divergence indicates that further exploration of co-infection trends and clinical outcomes in elderly COVID-19 patients is necessary.

Despite the relevance of bacterial co-infections, data on the incidence, microbiological characteristics, C-reactive protein (CRP) levels, and patient outcomes—particularly stratified by age groups such as elderly versus non-elderly—also remain scarce in Indonesia. Given the unique physiological and psychological changes that occur with aging, understanding the clinical implications of co-infections in the elderly is critical.

Thus, this study aimed to investigate the relationship between age, oxygen supplementation, oxygen saturation, and clinical markers, including procalcitonin and CRP levels, and recovery outcomes in COVID-19 patients with bacterial pneumonia co-infections. By addressing this gap in knowledge, the research will contribute valuable data to inform clinical practices and improve treatment strategies for COVID-19 patients, particularly the elderly, who are more vulnerable to co-infections and adverse outcomes.

METHODS

This predictive multivariate analytic study employed a cross-sectional design and used secondary data from the medical records of COVID-19 patients with bacterial pneumonia co-infection who were hospitalized in an inpatient ward. The research was conducted at Universitas Mataram Hospital and the Regional General Hospital of West Nusa Tenggara Province from July 2021 to February 2022. This study was approved by the Ethics Committee of the Provincial Hospital of West Nusa Tenggara, Lombok, Indonesia (approval number: 5175/UN18.F7/PM/2022).

The population comprised elderly (>60 years) and non-elderly (18 years to <60 years) patients diagnosed with COVID-19 who developed bacterial pneumonia co-infection. Patients were included if they had a positive RT-PCR result confirming COVID-19 and evidence of bacterial pneumonia co-infection, supported by clinical, radiological, and microbiological findings from sputum gram-stain examination before 48 hours of hospitalization. Only those who had been hospitalized at Universitas Mataram Hospital and the Regional General Hospital of West Nusa Tenggara Province during the specified period and had complete medical records were considered for inclusion. Exclusion criteria included patients with confirmed COVID-19 but without bacterial pneumonia co-infection and those with incomplete medical records, missing the variables relevant to this study.

The sample size for this study was calculated using formulas for bivariate and multivariate predictive analyses. Specifically, for bivariate analysis, the sample size was determined using the formula for categorical comparative unpaired analysis with a single measurement. The minimum required sample size for each independent variable was 50 patients. Consecutive sampling was used to recruit all eligible patients who met the inclusion criteria during the study period.

The variables in this study included age, classified into elderly and non-elderly categories; clinical presentation; microbiological profiles; and CRP levels, which were taken on the early day (first or second day) of hospitalization, as independent variables, while the dependent variable was the recovery status, defined as either discharged after recovery or death. The diagnosis of secondary bacterial infection was determined based on clinical presentation, chest X-ray findings indicative of pneumonia, white blood cell counts, and CURB-65 scores.

Data collection was performed by extracting relevant demographic, clinical, and microbiological information from medical records, including patient characteristics, clinical presentation, radiological and microbiological findings, CRP levels, and patient outcomes. Data analysis involved descriptive statistics to summarize patient characteristics, followed by bivariate analysis to examine the relationship between the independent variables (age, microbiological profile, and CRP levels) and recovery status. Chi-square or Fisher's exact tests were used as appropriate. Additionally, multivariate predictive analysis was conducted using logistic regression to identify factors independently associated with patient recovery. All data analyses were performed using SPSS version 22.0.

RESULTS

The study included data from 77 COVID-19 patients with bacterial co-infection treated at Universitas Mataram Hospital and the Regional General Hospital of West Nusa Tenggara Province from January to December 2021. The descriptive characteristics of the subjects are summarized in Table 1.

The median age was 58 years (range=25–82). Most patients were under 60 years (57.14%) and included slightly more males (53.2%). As many as 42.5% had a body mass index (BMI) of 25 or higher, indicating an overweight status. Comorbidities were present in 58.4% of patients. The majority (68.8%) had a CURB-65 score <2 and elevated CRP levels (>75 mg/L) were present in 62.3% of patients. Procalcitonin levels were available for 26 patients, with a median value of 0.39 ng/mL (range=0.05-40.00 ng/mL).

Regarding oxygen support, 50.6% required <6 liters per minute, 18.2% required>6 liters per minute, and 27.3% received high-flow oxygen or non-invasive ventilation (NIV). The median hospital stay was 10 days (range=1-77), and the median oxygen saturation was 94% (range=48-100). In terms of clinical outcomes, 50.6% died, with an estimated 95% confidence interval (CI) ranging from 39.43% to 61.77%. A total of 16.9% recovered and were discharged, while 32.5% showed improvement and were isolated for further recovery.

Table 1. Characteristics of the subjects

Variable	n (%)
Sex	
Male	41 (53.20%)
Female	36 (46.80%)
Age, median (min-max)	58 (25-82)
<60	44 (57.14%)
≥60	33 (42.86%)
Body mass index (BMI)	
≥25	17 (42.50%)
<25	27 (57.50%)
Comorbidities	
Yes	45 (58.40%)
No	32 (41.60%)
CURB-65 score	
≤2	53 (68.80%)
>2	24 (31.20%)
C-reactive protein (CRP)	
<75	29 (37.70%)
≥75	48 (62.30%)
Procalcitonin	0.39 (0.05-40.00)
Oxygen support	
≤6 liters per minute	39 (50.60%)
>6 liters per minute	14 (18.20%)
>10 liters per minute	21 (27.30%)
High flow/NIV	3 (3.90%)
Oxygen saturation, median (min-max)	94 (48-100)
Length of stay in days, median (min-max)	10 (1-77)
Status Outcome	
Recovered and discharged	13 (16.90%)
Clinical improvement and self-isolation	25 (32.50%)
Died	39 (50.60%)

The bivariate analysis assessed associations between categorical variables and patient outcomes using Chi-square tests. To ensure compatibility, numerical variables such as age, procalcitonin levels, oxygen supplementation, oxygen saturation, and outcome were categorized based on clinical guidelines. Counts, percentages, value of *P*, odds ratios (OR), and 95% confidence intervals (CI) were reported for the results. The analysis also employed the Mann-Whitney U test for length of stay, as the data did not meet the normality assumption. Chi-square tests met the assumption for expected cell counts.

Table 2. Association between variables and patient outcomes

Variables	Status Outcome: Recovered and discharged, Clinical improvement and self-isolation	Status Outcome: Died	*P*	OR (95% CI)
Sex				
Male	23 (56.1%)	18 (43.9%)	0.206 [a]	1.79 (0.72-4.42)
Female	13 (39.4%)	21 (58.3%)		
Age, median (min-max)				
<60	25 (56.8%)	19 (43.2%)	0.130 [a]	2.02 (0.81-5.07)
≥60	13 (39.4%)	20 (60.6%)		
Body mass index (BMI)				
≥25	10 (58.8%)	7 (41.2%)	0.680 [a]	0.76 (0.21-2.77)
<25	15 (65.2%)	8 (34.8%)		
Comorbidities				
Yes	23 (51.5%)	22 (48.9%)	0.714 [a]	1.19 (0.48-2.94)
No	15 (41.7%)	17 (53.1%)		
CURB-65 score				
≤2	29 (54.7%)	24 (45.3%)	0.162 [a]	2.01 (0.75-5.41)
>2	9 (37.5%)	15 (62.5%)		
C-reactive protein (CRP				
<75	22 (75.9%)	7 (24.1%)	<0.001[a]	6.29 (2.22-17.80)
≥75	16 (33.3%)	32 (66.7%)		
Oxygen supplementation				
≤6 lpm	28 (71.8%)	11 (28.2%)	<0.001[a]	7.13 (2.61-19.45)
>6 lpm	10 (26.3%)	28 (73.7%)		
Oxygen saturation				
≥95	23 (65.7%)	12 (34.3%)	0.009[a]	3.45 (135-8.84)
<95	15 (35.7%)	27 (64.3%)		
Length of stay in days, median (min-max)	14 (2-28)	6 (1-77)	<0.001[b]	---

Note: [a]Chi-square test; [b]Mann-Whitney U test

Significant associations were observed in three key areas related to patient outcomes, as shown in Table 2. Higher levels of C-reactive protein (CRP) were strongly linked to an increased risk of mortality (*P*<0.001; OR=6.29; 95% CI=2.22–17.8). Similarly, patients requiring greater oxygen supplementation (>6 lpm) demonstrated a significantly higher likelihood of death (*P*<0.001; OR=7.13; 95% CI=2.61–19.45). Furthermore, lower oxygen saturation levels (<95%) were found to be significantly associated with worse clinical outcomes (*P*=0.009; OR 3.45; 95% CI=1.35–8.84).

Additionally, the Mann-Whitney U test highlighted a significant difference in the length of stay, with survivors having a longer median stay (14 days) compared to deceased patients (6 days) (*P*<0.001). Non-significant findings included age, gender, and comorbidities.

To further refine the analysis, a multivariate logistic regression model was developed to identify significant predictors of patient outcomes. Variables with a value of *P* greater than 0.25, such as comorbidities, were excluded from the model. The final regression identified two critical predictors: oxygen supplementation (OR=5.31; 95% CI=1.84–15.31; *P*=0.002) and C-reactive protein (CRP) levels (OR=4.41; 95% CI=1.44–13.51; *P*=0.009), both of which were significantly associated with mortality in patients with COVID-19 pneumonia (Table 3).

Table 3. Multivariable analysis

Variable	Coefficient	*P*	OR (95% CI)
Oxygen supplementation (≤6 lpm)	1.670	0.002	5.311 (1.842-15.311)
C-Reactive Protein (<75)	1.485	0.009	4.413 (1.442-13.510)
Constant (Intercept)	-1.415	0.001	0.243

The equation derived from the model was as follows:

$$\text{logit}(p) = -1.415 + 1.670 \text{ (oxygen supplementation)} + 1.485 \text{ (CRP)}$$

This equation was used to calculate the probability of patient outcomes across different clinical scenarios, based on oxygen supplementation levels and CRP values. The model thus provides a valuable tool for predicting prognosis and guiding clinical decision-making.

The logistic regression model was well-calibrated, as indicated by the Hosmer-Lemeshow test (*P*=0.988), and exhibited strong discriminatory ability, with an area under the curve (AUC) of 0.920 (95% CI=0.865–0.976) as shown in Figure 1.

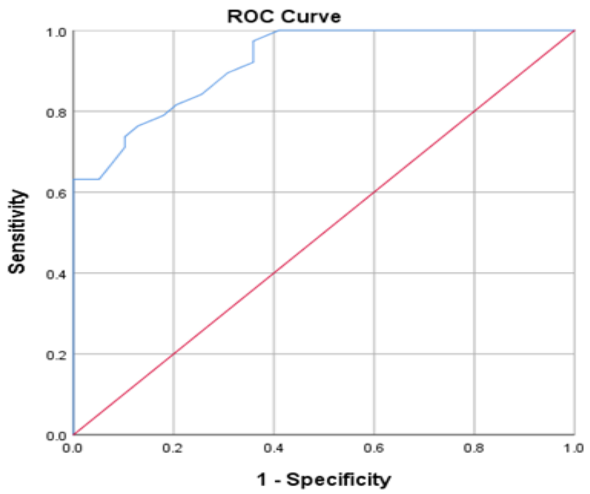

Figure 1. Area under the curve

DISCUSSIONS

The study revealed statistically significant and clinically meaningful associations between oxygen saturation and patient outcomes, particularly concerning mortality. Patients with oxygen saturation levels below 95% had a significantly higher risk of death. This is supported by a study conducted by Xie et al, which found that hypoxemia was independently associated with in-hospital mortality.[7] Additionally, a significant difference in hospital stay duration was observed between survivors and those who passed away, with survivors tending to have longer stays (*P*<0.001). These findings suggest that lower oxygen saturation levels are a critical factor influencing patient outcomes in COVID-19 cases complicated by secondary bacterial infections.

A bivariate analysis also identified a strong association between oxygen supplementation and outcomes, indicating that patients receiving oxygen therapy at a rate greater than 6 lpm had a significantly higher risk of death. This association highlights the clinical importance of oxygen requirements in predicting patient prognosis, with a more than 20% difference in recovery rates between patients receiving <6 lpm versus >6 lpm of oxygen supplementation. While there is limited literature on the specific association between oxygen supplementation at this threshold and outcomes, the findings are consistent with research on severe hypoxia, which has been shown to induce cellular apoptosis through mechanisms such as reactive oxygen species (ROS) release, inhibition of repair proteins, and the release of apoptogenic factors.[6–9]

Similarly, CRP levels were significantly associated with outcomes. Patients with CRP levels >75 mg/L had a sixfold higher risk of death compared to those with lower levels. Elevated CRP is a well-established prognostic marker in COVID-19, correlating with disease severity, increased need for mechanical ventilation, and higher mortality rates. Several studies have demonstrated that elevated CRP levels are linked to a greater risk of organ failure, including ARDS, and higher mortality.[6–9] Additionally, CRP levels at hospital admission have been shown to predict mortality, with a threshold of >54 mg/L indicating a poor prognosis.[10]

Previous research, such as that by Daher et al and Xie et al, has supported these findings, noting that high oxygen requirements and elevated inflammatory markers like CRP are linked to worse outcomes in COVID-19 patients. The persistence of systemic inflammation, reflected by elevated interleukin-6 (IL-6) and CRP levels, contributes to respiratory failure and prolonged hospital stays.[7,11] The pathogenesis and clinical manifestations of COVID-19 are strongly influenced by the host's immune response to SARS-CoV-2, with uncontrolled immune activation in severe cases leading to cytokine storms, which can result in ARDS, multiorgan failure, and death.[12] The C19-PNEUMOSCORE study by Tanzarella et al further emphasized the importance of CRP and other markers in predicting bacterial co-infections in COVID-19 patients.[13]

In this study, a multivariate predictive analysis was performed to determine which variables had the strongest association with patient outcomes. The logistic regression analysis identified oxygen supplementation and CRP levels as significant predictors of mortality. The predictive model demonstrated excellent calibration and strong discriminatory power, providing a practical tool for prognostication in clinical settings. The logistic regression equation allows for the calculation of recovery probabilities based on different clinical scenarios. For instance, patients receiving less than 6 lpm oxygen supplementation and with CRP levels less than 75 mg/L had an 85.1% probability of recovery, whereas those receiving more than 6 lpm oxygen and with CRP greater than 75 mg/L had only a 19.5% probability of recovery.

Scenario 1:
oxygen supplementation ≤6 lpm = 1;
CRP <75 mg/L = 1
logit(p) = -1.415 + 1.670 (1) + 1.485 (1) =1.74
probability = $\frac{1}{(1+\exp[-p])} = \frac{1}{(1+\exp[-1,74])}$=0.85 ≈ 85.1%

Scenario 2:
oxygen supplementation >6 lpm = 0;
CRP ≥75 mg/L = 0
logit(p) = -1.415 + 1.670 (0) + 1.485 (0) = -1.415
probability = $\frac{1}{(1+\exp[-p])} = \frac{1}{(1+\exp[1,415])}$=0.195 ≈ 19.5%

LIMITATION

Despite its contributions, this study has several limitations, including its retrospective design, which may introduce bias and limit control over data quality. Additionally, the small sample size and lack of long-term follow-up data restrict the ability to assess longer-term outcomes.

CONCLUSION

This study highlights the significant impact of oxygen supplementation and CRP levels on the outcomes of COVID-19 patients with bacterial pneumonia co-infections. Patients requiring higher oxygen support and exhibiting elevated CRP levels had a markedly increased risk of mortality, making these factors critical prognostic indicators. The predictive model derived from this research offers a practical tool for improving treatment strategies and patient outcomes during the ongoing pandemic.

CONFLICT OF INTEREST

No conflict of interest is declared.

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