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Research Article

Risk Factors Analysis for Rapid In-Hospital Mortality among Covid-19 Patients in a Tertiary Care Hospital in Indonesia

Analisis Faktor Risiko Kematian pada Pasien Covid-19 Rawat Inap di Rumah Sakit Tersier di Indonesia

Juwita Febriawati, Ngakan Putu Parsama Putra, Aditya Sri Listyoko, Susanthy Djajalaksana

Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Brawijaya Malang

ABSTRACT

Systemic inflammation plays an important role in pathogenesis of Covid-19, especially in development of ARDS which is characterized by decrease of PaO2/FiO2 ratio. CRP and procalcitonin are inflammatory markers that are closely associated with severity and mortality of Covid-19. Although several studies have addressed benefit of CRP and procalcitonin as markers on Covid-19 severity, the benefit of these inflammatory markers for in-hospital mortality remain inadequately understood. The aim of this study was to analyze PaO2/FiO2 ratio,comorbidity,CRP,and procalcitonin as risk factors that affect time of in-hospital mortality Covid-19 patient. This was a retrospective observational cohort study of 250 Covid-19 patients who died during hospitalization and data was retrieved from medical record. Laboratory data was collected from three different times, including at time of admission,third day of hospital care,and before patient's death. Data were analyzed using Chi square test,Mann Whitney test,Wilcoxon test, Friedman test, and binary logistic regresion. There were significant differences between CRP and procalcitonin at admission and time of in-hospital mortality (p<0.001; p=0.007). Binary logistic regression analysis revealed significant relationship between CRP and time of in-hospital mortality with p=0.007. ROC curve showed optimal threshold of 11.75mg/L with sensitivity 72.3%; specificity 59.6%, RR 3.24(95% CI: 1.84-5.70). Significant changes were observed regarding PaO2/FiO2 ratio,CRP,and procalcitonin at admission as compared to before patient's death with p<0.001;p=0.017;p<0.001 respectively. This study showed significant decrease of PaO2/FiO2 ratio, elevated CRP and procalcitonin at admission as compared to before patient's death. The increase of CRP could serve as predictor for time of in-hospital mortality for Covid-19 patient.

Keywords: *Covid-19, CRP, PaO2/FiO2 ratio, procalcitonin, time of in-hospital mortality*

ABSTRAK

Inflamasi sistemik memegang peranan penting pada patogenesis Covid-19 terutama dalam berkembangnya ARDS yang ditandai dengan penurunan rasio PaO2/FiO2. CRP dan prokalsitonin merupakan marker inflamasi yang sering dikaitkan dengan severitas dan mortalitas Covid-19. Meskipun banyak studi terkait CRP dan prokalsitonin sebagai marker severitas Covid-19, namun hubungannya dengan waktu kematian masih belum sepenuhnya dipahami. Tujuan penelitian ini adalah untuk menganalisis Rasio PaO2/FiO2, komorbiditas, CRP dan Prokalsitonin terhadap waktu kematian pasien Covid-19. Desain penelitian ini adalah cohort observational retrospektif dengan sampel 250 pasien yang meninggal dunia saat rawat inap menggunakan data rekam medis. Data laboratorium diambil pada tiga waktu pengamatan yaitu pada saat awal masuk rumah sakit, perawatan hari ketiga, dan sebelum pasien meninggal dunia. Data dianalisis menggunakan Uji Chi Square, Uji Mann Whitney, Uji Wilcoxon, Uji Friedman, serta regresi logistik biner. Terdapat perbedaan signifikan antara CRP dan prokalsitonin saat awal masuk rumah sakit dengan waktu kematian pasien (p<0,001; p=0,007). Analisis regresi logistik biner menunjukkan CRP berpengaruh signifikan terhadap waktu kematian dengan p=0,007, kurva ROC menunjukkan optimal threshold 11,75mg/L dengan sensitivitas 72,3% dan spesifisitas 59,6%, RR 3,24(95% CI:1,84-5,70). Rasio PaO2/FiO2, CRP, dan Prokalsitonin awal didapatkan perubahan signifikan dibandingkan sebelum pasien meninggal dengan p berturut-turut <0,001; 0,017; <0,001. Terdapat penurunan Rasio PaO2/FiO2, peningkatan CRP dan Prokalsitonin yang signifikan pada saat awal masuk rumah sakit dibandingkan sebelum pasien meninggal. Peningkatan CRP bisa digunakan sebagai prediktor waktu kematian pasien Covid-19.

Kata Kunci: Covid-19, CRP, waktu kematian, rasio PaO2/FiO2, prokalsitonin

Correspondence: Juwita Febriawati. Department of Pulmonology and Respiratory Medicine Faculty of Medicine Universitas Brawijaya, Jl. Veteran Malang, Jawa Timur, 65145 Tel. +6281230124080 Email: juwitafe@student.ub.ac.id

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INTRODUCTION

An outbreak of pneumonia known as Coronavirus Disease 2019 (Covid-19) emerged in Wuhan in December 2019, and Indonesia alone recorded a total of 6,086,212 confirmed cases, resulting in 156,731 deaths (1). The clinical presentation of Covid-19 varied from mild symptoms like fever and malaise to severe conditions, including hypoxia, respiratory failure, sepsis leading to multi-organ damage, and even death (2). According to research conducted by Wu et al, approximately 80% of Covid-19patients experienced mild to moderate symptoms, 13.8% had severe symptoms, and 6.1% were critically ill. In severe cases, the progression of Covid-19 pneumonia can lead to acute respiratory distress syndrome (ARDS), which occurred in 41.8% of cases and carried a mortality rate of 52.4% (3). Some Covid-19 patients required intensive care unit (ICU) treatment due to ARDS, and the case fatality rates for such patients ranged from 30% to 60% (4). Lower levels of the PaO2/FiO2 ratio in the critical stage compared to the severe stage of Covid-19 patients indicate lower survival rates and are associated with an increased risk of death, while another study demonstrated hypoxemia as a risk factor for mortality (5,6). A previous study has underscored the significant roles of CRP and procalcitonin in the context of Covid-19. CRP, possessing both pro-inflammatory and anti-inflammatory properties, is proposed to function as an immunoregulator (7,8). Elevated CRP levels not only signify a pro-inflammatory state but can also serve as a valuable prognostic marker for tracking the progression of the disease (8). A study conducted by Liu et al demonstrated that serum CRP levels increase significantly in cases of severe Covid-19 compared to moderate cases (9). Furthermore, elevated serum CRP levels exhibit a positive correlation with the severity of Covid-19 as indicated by CT findings, and higher CRP levels are associated with extended hospitalization periods (10). On the other hand, procalcitonin levels tend to be elevated in the presence of bacterial infections and relatively low in viral infections, making them useful for distinguishing between these two types of infections (11). Procalcitonin is synthesized within tissues during inflammation, and bacterial toxins, along with cytokines like IL-6 and TNF α, are known to commonly trigger its synthesis. High levels of these cytokines have been observed in severe Covid-19 cases. A meta-analysis conducted by Lie et al reported the predictive value of death with a single procalcitonin measurement, demonstrating a sensitivity of 76% and a specificity of 64% (12).The study conducted by Vanhomwegen et al showed that high procalcitonin levels were associated with high mortality in Covid-19 pneumonia and also in critically ill patients in general (13).

In addition to CRP, Procalcitonin, and PaO2/FiO2 ratio, The presence of comorbid conditions can serve as a risk factor linked to adverse outcomes in Covid-19 cases. A study conducted by Djaharuddin *et al.*, involving 454 hospitalized Covid-19 patients, revealed that hypertension (42.31%), cardiovascular disease (30.77%), and diabetes (28.21%) were the most prevalent comorbidities. Other conditions, such as chronic kidney failure, malignancy, chronic lung disease, chronic liver disease, autoimmune diseases, and obesity, were also observed among the patients. Notably, more than half of the Covid-19 patients who succumbed to the disease had at least two comorbidities (14).The reasons behind these poor outcomes may be attributed to the use of multiple medications (polypharmacy) and a weakened immune system. Additionally, individuals with diabetes and hypertension who were being treated with ACE inhibitors and angiotensin II type-I receptor blockers exhibited a high expression of ACE2 receptors in epithelial cells of the lungs, intestines, kidneys, and blood vessels. These receptors act as entry points for the SARS-CoV-2 virus, potentially increasing the binding of the virus and, consequently, raising the risk of severe and fatal outcomes among Covid-19 patients with comorbidities (15).

The average length of stay for Covid-19 patients who survived was around 10-13 days (16). Research conducted by Alwafi *et al*., showed that several factors were associated with increased length of stay, including comorbidities, D dimer value >0.5, leukocytes >10,000, ESR >10mm/h, CRP >0.3mg/dl, ferritin >400mcg/L , procalcitonin >0.5ug/L, LDH>230U/L, creatinine >115umol/L, and blood type O (17). The presence of bilateral pulmonary infiltrates on radiological examination is also often associated with a longer hospital stay (16).

Thus, PaO2/FiO2 ratio, comorbidity, CRP, and procalcitonin as predictors of mortality and time of in-hospital mortality for Covid-19 patients may warrant investigations to mitigate poor outcomes in Covid-19 patients. The early identification of biomarkers plays a crucial role in enabling clinicians to provide objective assessments and make informed decisions about appropriate treatments. This, in turn, has the potential to reduce the mortality rate among Covid-19 patients. Despite various studies addressing the potential benefits of CRP and procalcitonin as markers for assessing the severity of Covid-19, the extent of their usefulness in predicting in-hospital mortality remains insufficiently understood. Research concerning on these biomarkers as indicators of time of in-hospital mortality and their value as prognostic indicators is still limited in Indonesia. However, there is a need to investigate the potential of the PaO2/FiO2 ratio, comorbidities, CRP, and procalcitonin as predictors of mortality and the time of in-hospital mortality among Covid-19 patients. Such investigations could prove essential in improving the outcomes for Covid-19 patients. This study aims to analyze the relationships between the PaO2/FiO2 ratio, CRP, procalcitonin, and comorbidities and their impact on the time of in-hospital mortality among Covid-19 patients.

METHOD

Research Design and Subjects

This was a retrospective observational cohort study and a part of the Research Analysis of Inpatient Covid-19 Patient Mortality at Dr. Saiful Anwar General Hospital. The data were obtained from the medical records of patients with confirmed cases of Covid-19 who passed away during their hospitalization at Dr. Saiful Anwar General Hospital from January to July 2021. The patients included in the study met the following criteria: a positive PCR test result from a nasal and oropharyngeal swab or SARS-CoV-2 rapid antigen test, an age of over 18 years, a PaO2/FiO2 ratio of <300 at the time of admission, and treatment received from pulmonologists. Patients with incomplete laboratory data were excluded. Laboratory data were collected during examinations upon the patients' initial admission to the hospital, on the third day of treatment, and during the final examination conducted just before the patients' death. The time of in-hospital mortality is calculated from when the patient was hospitalized (initial admission) until

the patient passed away in hospital. The time of in-hospital mortality was categorized into two groups: ≤48 hours and >48 hours. This category based on data collected at Saiful Anwar General hospital in 2020 that indicate that over 30% of in-hospital Covid-19 patient died in less than 48 hours.

Statistical Analysis

Data analysis was conducted using SPSS version 26 software. The study investigated the relationship between the PaO2/FiO2 ratio, CRP level, procalcitonin level at the patients initial admission and the time of in-hospital mortality. Since the data on PaO2/FiO2 ratio, CRP level, procalcitonin level are continuous data, the Mann-Whitney test has been used for data analysis. Additionally, the binary logistic regression test was adopted to examine how these three parameters (PaO2/FiO2 ratio, CRP, and procalcitonin) influenced the time of in-hospital mortality. ROC curve analysis was used to determine cutoff values, a sensitivity, and a specificity. Relative risk calculations were performed to assess the risk of death within <48 hours and >48 hours. The analysis of changes in the PaO2/FiO2 ratio, CRP, and procalcitonin at the time of initial hospital admission, on the third day of treatment, and prior to the patient's death involved the Friedman Test and the Wilcoxon Test. Furthermore, the analysis of oxygen therapy utilization and its relationship with comorbidities concerning the time of in-hospital mortality was conducted using the Chi-square test. All tests were carried out with a 95% confidence level, α=0.05, and findings were considered significant if p<0.05.

RESULTS

Subject Characteristics

There were 250 COVID-19 patients who died during treatments at dr. Syaiful Anwar Hospital who were included as study subjects. Table 1 shows the characteristics and their distributions among the subjects. More than half (55.6%) of them were male. The age of the subjects ranged from 21 to 86 years old, with an average of 54.18 (SD=13.89) years. Most subjects (66.4%) were high school graduates, followed by 38 subjects (15.2%) who held a diploma, undergraduate, or postgraduate degree. Seventy-one subjects (28.4%) worked in the private sector, 64 subjects (25.6%) did not have jobs, and 38 subjects (15.2%) were housewives. There were 159 subjects (64.6%) who were never smokers, while 58 subjects (23.2%) had a history of active smoking. As shown in table 1 below, 157 subjects (62.8%) had one or more comorbidities, and 93 subjects (37.2%) had no comorbidities. The comorbidity with the most subjects was diabetes mellitus (20.8%), followed by heart disease (9.2%), and hypertension (6%).

Table 1. Clinical characteristics of subjects

Characteristics	N	(%)
Number of comorbidities		
0	93	37.20%
≥1	157	62.80%
Comorbidity		
Asthma	3	1.20%
Chronic bronchitis	1	0.40%
COPD	10	4.00%
Pulmonary TB	4	1.60%
Heart disease	23	9.20%
Chronic kidney disease	13	5.20%
Hypertension	15	6.00%
Diabetes mellitus	52	20.80%
Hyperthyroid	1	0.40%
Obesity	7	2.80%
HIV	2	0.80%
Pregnancy	10	4.00%
CVAs	9	3.60%
Chronic gastritis	1	0.40%
Malignancy	1	0.40%
Disease severity		
Mild	6	2.40%
Moderate	41	16.40%
Severe	137	54.80%
Critical	66	26.40%
Clinical symptoms		
Fever	183	73.2%
Cough	201	80.4%
Nasal congestion	227	90.8%
Anosmia, augesia	42	16.8%
Diarrhea	28	11.2%
Weakness	135	54.0%
Myalgia	71	28.4%
Nausea and vomiting	116	46.4%
Other symptoms	71	28.4%
Initial oxygenation therapy		
Nasal cannula	23	9.20%
Simple mask	4	1.60%
Non-rebreathing mask	168	67.20%
Jackson Reese	44	17.60%
HFNC	1	0.40%
Ventilator	10	4.00%
Time of in-hospital mortality		
≤48 hours	82	33.20%
>48 hours	168	66.80%

The Relationship between the PaO2/FiO2 ratio, CRP, and Procalcitonin Levels at the Time of Hospital Admission and the Time of In-Hospital Mortality

As shown in Table 2, the lowest PaO2/FiO2 ratio on the initial admission was 20.44 and the highest PaO2/FiO2 ratio was 297.79 with an average of 100.54. The PaO2/FiO2

Table 2. Comparison of parameters on initial admission, third day of treatment, and before death

Parameter		Initial admission (n=250)	Third day of treatment (n=136)	Before Death (n=105)
PaO2/FiO2 ratio	Mean (SD)	100.54(63.19)	76.78(32.80)	66.48(26.60)
	Median (min-max)	94.02(20.44-297.78)	70.20(32.63-196.67)	60.30(26.06-174.95)
CRP	Mean (SD)	13.71(10.39)	15.97(19.77)	16.71 (16.57)
	Median (min-max)	11.02(0.31-68.7)	12.04(0.20-65.59)	10.67(0.19-78.65)
Procalcitonin	Mean (SD)	4.21(15.31)	5.73(2.46)	6.93 (19.03)
	Median (min-max)	0.43(0.03-100.00)	0.595(0.04-100.00)	0.76 0.05-100.00)

ratio at the time of initial hospital admission largely varied (SD=63.19). The average PaO2/FiO2 ratio on the third day of treatment and before the patients died were 76.78 and 66.48, respectively. Meanwhile, the average CRP level at the initial examination was 13.72. The average procalcitonin level at the initial assessment was 4.21, with the highest reaching 100 or more.

Table 3 shows that the CRP levels had a significant effect on time of in-hospital mortality, with an odds ratio value of 0.959 (95% CI: 0.933-0.985). This means patients with high CRP levels tended to have a shorter time of in-hospital mortality (≤48 hours). On the other hand, if the CRP level decreased by 1 unit, it will significantly extend the time of in-hospital mortality by 0.959 times. Thus, patients with low CRP levels tend to have a longer time of in-hospital mortality (>48 hours).

Table 3. Regression analysis of PaO2/FiO2 Ratio, CRP and procalcitonin on time of in-hospital mortality

Parameter	OR	95%CI	p-value	B
PaO2/FiO2 ratio	1.004	1.000-1.009	0.072	0.004
CRP	0.959	0.933-0.985	0.002*	-0.042
Procalcitonin	0.987	0.968-1.005	0.174	-0.013

Note: *p<0.05 is considered statistically significant

The difference in the initial CRP examination between both groups of time of in-hospital mortality analyzed using the Mann-Whitney test was significant (p<0.001) as shown in Figure 1. Measured at the time of hospital admissions, the average value of CRP levels in the group of patients with a time of in-hospital mortality within 48 hours (≤48 hours) was 153.19 points higher than the CRP levels in the group of patients with a time of in-hospital mortality of more than 48 hours (>48 hours).

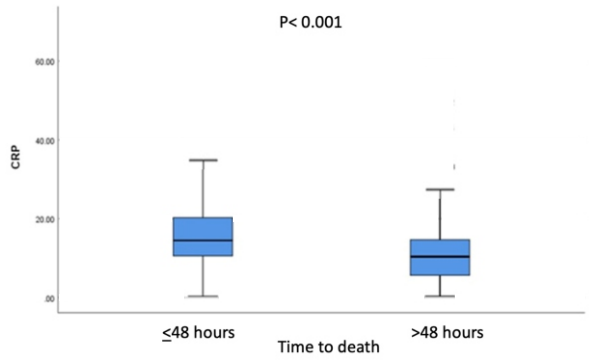

Figure 1. The relationship between CRP levels and time of in-hospital mortality

Note: The figure showed a comparison on the initial examination of patients with the time of in-hospital mortality divided into before 48 hours and equals to or more than 48 hours since admission

Figure 2 shows the initial procalcitonin test of patients with a time of in-hospital mortality within 48 hours (≤48 hours) and patients with a time of in-hospital mortality beyond 48 hours (>48 hours) with a significant difference of p=0.007 using the Mann-Whitney test. The mean value at the initial procalcitonin test in the group of Covid-19 patients who died within 48 hours (≤48 hours) was 159.02 points higher than the initial examination of procalcitonin in the group of patients with Covid-19 who died with a time of in-hospital mortality beyond 48 hours (>48 hours).

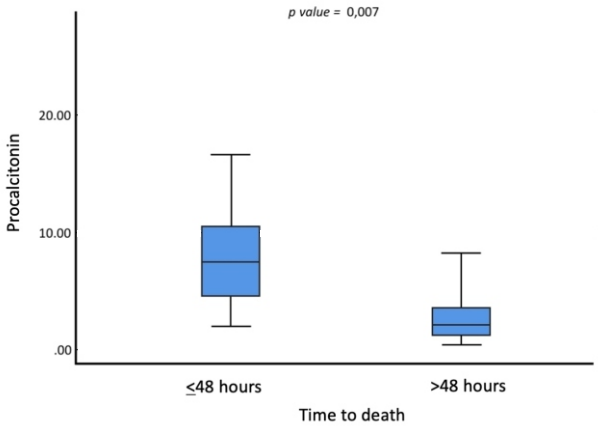

Figure 2. The relationship between procalcitonin levels and time of in-hospital mortality

Note: The figure showed a comparison on the initial examination of patients with the time of in-hospital mortality divided into before 48 hours and equals to or more than 48 hours since admission

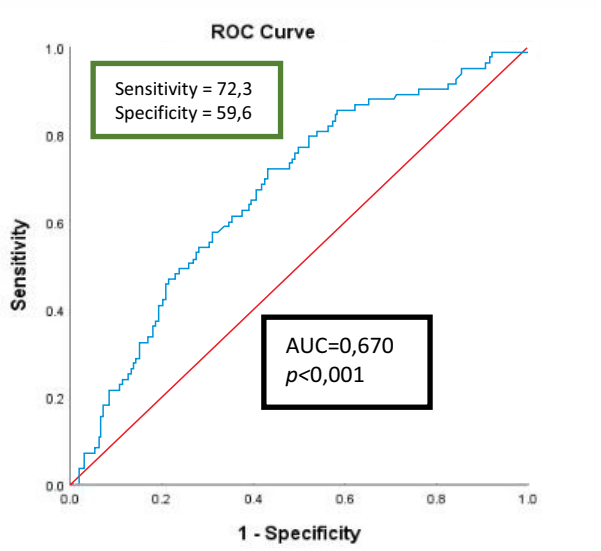

Figure 3. ROC curve of CRP levels to predict time of in-hospital mortality

Note: an AUC of 0.670 and an optimal threshold of 11.75 mg/L have a sensitivity of 72.3% and a specificity of 59.6%

Figure 3 shows the prediction of time of in-hospital mortality using CRP levels. The ROC curve describes the relationship between the level of sensitivity (true positive rate) and the level of specificity (1-false positive rate) by changing the threshold on the test result variable. In this case, the higher the value of the test outcome variable, the stronger the evidence to support a negative actual condition (time of in-hospital mortality ≤48 hours). The ROC curve in Figure 3 showed a relative risk (RR) of 3.24 (95% CI: 1.84-5.70) which means that patients with CRP levels ≥11.75mg/L are at risk of having a shorter time of in-hospital mortality (≤48 hours) 3.24 times compared to

Table 4. Changes in the PaO2/FiO2 ratio, CRP and procalcitonin levels at initial admission and before death

	Initial Admission	Before Death	n	Negative Mean Rank	n	Positive Mean Rank	p
PaO2 / FiO2 ratio	106.89±68.02	66.48±26.60	75	59.68	30	36.30	<0.001
CRP	11.84±9.4	16.71±16.56	44	46.31	61	56.86	0.017
Procalcitonin	1.51±9.78	6.86±18.95	30	29.11	75	61.85	0.000

Note: *p<0.05 is considered statistically significant

patients with CRP levels <11.75mg/L.

The Kolmogorov Smirnov test showed a skewed distribution in all variables therefore the non-parametric statistical analysis was used. The Mann-Whitney test showed no significant relationship between the PaO2/FiO2 ratio, CRP, and procalcitonin levels at the time of admission to the hospital and the time of in-hospital mortality (p=0.078). However, there was a significant difference between the initial CRP examination and the time of in-hospital mortality (p<0.001). The average value at the initial examination of CRP levels in the group of patients with a time of in-hospital mortality within 48 hours (≤48 hours) was 153.19 points higher than at the initial examination of CRP levels in the group of patients with a time of in-hospital mortality of more than 48 hours (>48 hours).

Analysis of the Relationship between the Use of Oxygen Therapy Devices and Time of In-Hospital Mortality

There were 162 patients (64.8%) who received non-ventilator oxygen therapy for more than 48 hours (>48 hours). Six patients (2.4%) were put on ventilators for equals to or less than 48 hours (≤48 hours) and 4 patients (1.6%) were more than 48 hours. The Chi-Square test showed no significant relationship between the use of oxygen therapy equipment in deceased Covid-19 patients and the time of in-hospital mortality (p=0.07).

Analysis of the Relatioship between Comorbidities and PaO2/FiO2 ratio, CRP, Procalcitionin and Time of In-Hospital Mortality

Eighty-eight subjects (35.2%) had no comorbidities, 57 of them (22.8% of all subjects) died after being treated for more than 48 hours (>48 hours), while the remaining 31 subjects (12.4% of all) died before or at 48 hours (≤48 hours). Almost half of the subjects (44.4%) had comorbidities and died after 48 hours of treatment (>48 hours). Fifty-one subjects (20.41%) died within 48 hours after admission (≤48 hours). The Chi-Square test showed no significant relationship between the comorbidities and the time of in-hospital mortality (p=0.547).

The relationship between comorbidities and the PaO2/FiO2 ratio, CRP, and procalcitonin in Covid-19 patients who died was also observed using bivariate analysis. The Mann-Whitney test showed no significant relationship between comorbidity and the PaO2/FiO2 ratio (p=0.826). The test also showed no significant relationship between comorbidity and CRP (p=0.134). Furthermore, there was no significant relationship between comorbidity and procalcitonin (p=0.216). Thus, the highs and lows of the PaO2/FiO2 ratio were not associated with comorbidities, nor were those of CRP and procalcitonin.

DISCUSSION

This study observed a predominance of male subjects, comprising 55.56% of the sample, while nearly half (44.4%) of the participants fell within the 40-59 year age group. Moreover, the >60 year age category accounted for 39.6% of the subjects. It is well-established that elderly individuals are particularly vulnerable to diseases when exposed to viruses, owing to age-related changes in their immune systems. The prevalence of low CD4/CD8 ratios often serves as an indicator of immune system aging, and it substantially increases with advancing age, with individuals over 80 years experiencing a threefold higher prevalence compared to those in their 50s and 60s. This aging-related shift can result in reduced numbers of naïve T cells and alterations in the CD4/CD8 T cell ratio, ultimately leading to a diminished ability to respond to new pathogens, which may be linked to a poor response to Covid-19. Furthermore, this decreased ability to combat viral infections may heighten the risk of hyperinflammation, cytokine storms, and mortality (18).

In this study, a noteworthy 36.4% of the subjects encompassed active smokers, passive smokers, and former smokers. Extensive research, including meta-analyses, has illuminated the adverse impact of active smoking on Covid-19 severity and mortality. Smoking is believed to contribute to these negative outcomes by inducing mechanical and structural changes in the respiratory tract and affecting the humoral immune response. Furthermore, smoking has been associated with heightened hospitalization and intensive care unit (ICU) admissions in cases of influenza, RSV infections, and increased mortality in viral pneumonia (19). It is essential to acknowledge that individuals with a smoking history are twice as likely to require hospitalization due to Covid-19 when compared to non-smokers, although this relationship is influenced by various factors such as age, body mass index, and comorbidities (20). However, an insightful meta-analysis conducted by Lippi and Hendry in 2020 suggested that active smoking is not significantly linked to the severity of Covid-19, as the severe cases are notably prevalent in the elderly population (aged over 65) with comorbidities, a group with significantly lower smoking rates compared to the general population (21).

In this study, the majority of participants (62.8%) had underlying comorbidities, with diabetes mellitus being the most prevalent (20.8%), followed by heart disease (9.2%), and hypertension (6%). This aligns with findings from a comprehensive meta-analysis conducted by Thakur et al on 125,446 patients, which identified hypertension (32%), obesity (25%), diabetes (18%), and cardiovascular disease (16%) as the most common comorbidities in Covid-19 patients. Notably, the symptoms observed in this study were characterized by shortness of breath (90.8%), cough (80.4%), and fever (73.2%). These findings closely mirror previous studies, which also indicated that the most frequent symptoms in Covid-19 patients included fever (81.2%), cough (58.5%), fatigue (38.5%), and shortness of

breath (26.1%) (22). It's interesting to note that in the Indonesian context, cough (77.7%), fever (42.8%), and shortness of breath (34.8%) predominated as the primary symptoms (23). In this study, a severe degree of COVID-19 was determined by specific criteria, including shortness of breath, a respiratory rate of ≥30 breaths/minute, oxygen saturation of ≤93% on room air, a PaO2/FiO2 ratio of <300 mmHg, or lung infiltrates covering more than 50% of the lung area within 24-48 hours after symptom onset. Consequently, a significant proportion of the subjects in this study were found to be in severe and critical stages, comprising 54.8% and 26.4%, respectively.

The average initial PaO2/FiO2 ratio in this study was measured at 100.54, indicating a rather severe condition. It is noteworthy that no statistically significant association with the time of in-hospital mortality was observed (p=0.078). This finding underscores the notion that relying solely on the PaO2/FiO2 ratio may have limited utility when it comes to assessing the full scope of severity in ARDS patients. This limitation arises from the fact that the PaO2/FiO2 ratio fails to account for various other critical factors that influence ARDS severity, such as mechanical ventilation settings, changes in lung compliance, and the presence of pulmonary shunts. Numerous studies have consistently shown that the PaO2/FiO2 ratio, when considered in isolation, is not an independent predictor of mortality in ARDS when other parameters of disease severity are controlled for in multivariate analysis (24).

An additional study emphasized that PaO2/FiO2 values may not serve as early indicators of death in cases of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Instead, a consistent and persistent decline in the PaO2/FiO2 ratio emerges as a more reliable marker of a poor outcome. In a contrasting approach, the Oxygenation Index (OI) emerges as a superior predictor of mortality compared to the PaO2/FiO2 ratio. This enhanced predictive power is attributed to the OI's consideration of mean airway pressure in addition to FiO2. Notably, OI assessments during hospitalization have proven to be particularly effective in predicting outcomes, especially in pediatric patients facing hypoxemic acute respiratory failure (25). The OI outperforms the PaO2/FiO2 ratio by offering a more comprehensive evaluation of oxygenation status and lung severity, taking into account factors such as positive end-expiratory pressure (PEEP), inspiratory and expiratory times, and tidal volume (24).

This study unveiled a significant relationship between CRP levels at the time of initial admission and the time of in-hospital mortality (p<0.001). The Odds Ratio indicated an effect of CRP on the time of in-hospital mortality with a value of 0.959 (95% CI: 0.933-0.985). However, it is essential to recognize that while CRP demonstrated a sensitivity of 72.3% and a specificity of 59.6%, these values also pointed to its limitations in accurately predicting the time of in-hospital mortality in COVID-19 patients. The relative risk (RR) of 3.24 (95% CI: 1.84-5.70) signified that patients with CRP levels ≥11.75mg/L faced a 3.24 times higher risk of experiencing early mortality (≤48 hours) compared to those with CRP levels <11.75mg/L. This study's CRP threshold value of 11.75mg/L suggests that any value exceeding this threshold increases the likelihood of a shorter time of in-hospital mortality. Notably, this CRP cutoff was lower than those found in several other studies that used CRP as a predictor of death in Covid-19 patients, where cutoff values ranged from 10mg/L to 76mg/L. Furthermore, it is important to recognize that CRP levels tend to increase more substantially in bacterial infections in comparison to viral infections.

Procalcitonin levels had demonstrated a noteworthy increase, up to fivefold, in severe cases of Covid-19, which underscored its significant correlation with the time of in-hospital mortality in this study (p=0.007). This association aligns with findings from other studies, suggesting that elevated procalcitonin levels compared to baseline values can serve as an indicator of the critical phase of viral infection. In the context of Covid-19, a substantial production and release of procalcitonin into the bloodstream occurs during the course of infection (26). A study by Xu et al emphasized that an increase in serum procalcitonin levels to ≥0.1ng/mL and CRP levels of ≥52.14mg/L were identified as independent risk factors for mortality in hospitalized Covid-19 patients. Moreover, elevated procalcitonin levels were found to be particularly associated with increased mortality in patients aged 60 years or older and those experiencing severe or critical degrees of the disease. These insights emphasize the value of procalcitonin as a potential prognostic marker in the context of Covid-19 (27).

The PaO2/FiO2 ratio and procalcitonin levels displayed significant fluctuations over the course of hospitalization, each with a p-value <0.001. In this study, the PaO2/FiO2 ratio exhibited a consistent decreasing trend, while procalcitonin levels tended to increase when comparing measurements taken at the time of hospital admission, the third day of treatment, and just before patients succumbed to the illness. Notably, among the 105 patients, 32 of them showed lower procalcitonin levels on the third day of treatment, potentially reflecting a positive response to the therapies administered. This observation is in line with findings from Sarfaraz et al, who noted that a decrease in the PaO2/FiO2 ratio and serum albumin levels were associated with mortality, and their study revealed a 50% reduction in mortality for every unit increase in the PaO2/FiO2 Ratio. Additionally, procalcitonin levels were found to increase significantly as the disease progressed (28).

In contrast, CRP levels in this study did not demonstrate significant changes between the first and third days, nor between the third day and the period just before patients' deaths, with p-values of 0.114 and 0.084, and an overall p-value of 0.143. However, CRP levels exhibited a noteworthy increase just prior to the patients' deaths compared to the levels upon admission (p=0.017). Previous studies have consistently pointed out the association between elevated CRP levels and the presence of bilateral pneumonia on chest X-rays or CT scans, particularly in severe Covid-19 cases when compared to those with milder forms of the disease (29). These findings underscore the dynamic nature of these biomarkers and their implications for disease progression and prognosis.

Prior research regarding the use of ventilators in Covid-19 patients has yielded important insights. These studies have indicated that patients placed on mechanical ventilation at the time of their initial hospital admission typically required longer periods of ventilator support compared to those who were only put on mechanical ventilation after several days of treatment. Moreover, patients already on a

ventilator upon hospital admission faced a higher risk of mortality when compared to patients receiving non-ventilator oxygenation. However, it is crucial to note that this particular study incorporated only ten subjects on ventilators out of the total 250 subjects examined. Consequently, the smaller sample size might limit the representativeness of these findings, and no statistically significant correlation with the time of in-hospital mortality was established (p=0.07). This highlights the need for further investigation and a larger sample size to draw more conclusive results regarding the impact of ventilator use in Covid-19 patient outcomes.

This study did not reveal a statistically significant association between comorbidity and the time of in-hospital mortality (p=0.547), aligning with the findings of several prior studies indicating that comorbidities were not necessarily linked to the length of stay or mortality in the context of Covid-19. For instance, research conducted by Jang et al involving 7590 confirmed Covid-19 patients in Korea indicated that individuals with comorbidities such as cancer and ischemic heart disease may be at risk of experiencing shorter times to in-hospital mortality. However, no substantial relationship was found between comorbidities and variables such as the length of hospital stay and high medical costs. Importantly, this study underscored that the severity of Covid-19 appears to be more influenced by a patient's age compared to other indicators (30). Of note, a subset of patients (30%) in this study presented with comorbidities that were associated with elevated CRP and procalcitonin levels. In accordance with this, a separate study demonstrated a clear link between comorbidities and the severity of COVID-19, indicating that comorbid conditions elevate the risk of Covid-19 patients progressing to severe degrees of the disease or facing a fatal outcome (31). As patients with severe Covid-19 cases tend to exhibit lower PaO2/FiO2 ratios, it can be inferred that the PaO2/FiO2 ratio is indirectly intertwined with the presence of comorbidities.

This study has some limitations that need to be considered. First, it lacks a control group, which limits the ability to make direct comparisons and draw more robust conclusions. Additionally, the relatively small number of patients requiring ventilators (only 10 out of 250) may introduce bias into the findings. Furthermore, the study does not account for the impact of specific antiviral or antibiotic therapies administered to the patients, potentially influencing CRP, procalcitonin levels, and changes in the PaO2/FiO2 ratio.

In summary, this study has highlighted the significant correlation between initial CRP and procalcitonin levels and the time of in-hospital mortality in Covid-19 patients. The study identified an optimal threshold value of 11.75 mg/L for CRP, offering a sensitivity of 72.3% and specificity of 59.6%. Therefore, the rise in CRP levels can serve as a potential predictor for the time of in-hospital mortality among Covid-19 patients, providing valuable insights for clinical management and prognosis assessment.

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