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CRP-Albumin Ratio Predicts in Hospital Survival of Infected COVID-19 Patient: Study in South Kalimantan, Indonesia

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Abstract: Until the end of 2022, Indonesia had a case fatality rate (CFR) of 2.4% in COVID-19, higher than the global CFR of 1%. South Kalimantan, as one province in Indonesia, had CFR reached 2.9%. Improved treatment options and a better understanding of prognostic markers may reduce case fatality. Because of that, we decided to analyze CRP, albumin, and CRP-Albumin Ratio as prognostic markers in COVID-19. We conducted a retrospective study of 980 COVID-19 patients at Ulin Hospital Banjarmasin. The demographic data of the patients were analyzed and separated into two groups (survivors and non-survivors). We found that age, sex, and comorbidities such as hypertension, diabetes mellitus, and obesity correlated with mortality. CRP, albumin, and CRP-Albumin Ratio also correlated with mortality ($p < 0.001$) with an OR of 1.011, 0.468, and 1.032 respectively using univariate analysis. On multivariate analysis, we found that CRP, albumin, and CRP-Albumin Ratio are independent prognostic markers for mortality. ROC curve analysis shows that the CRP cut-off point was > 61,2 (sensitivity 70,2%, specificity 67,9%) with AUC 0.750 ($p < 0.001$) in predicting mortality. For the albumin, the cut-off point was < 3,25 (sensitivity 64,6%, specificity 54,1%) with AUC 0.628 ($p <0.001$). Furthermore, in the CAR, the cut-off point was > 26,2 (sensitivity 62,4%, specificity 77,7%) with AUC 0.753 ($p <0.001$). In conclusion, our study found that CRP, albumin, and CRP-Albumin ratio had a significant connection with mortality, with CRP-albumin ratio being a better predictor. It could be a substantial predictor of mortality in hospitalized COVID-19 patients, which is very easy and cheap.

Keywords: Covid-19, mortality, prognostic markers, CRP-albumin ratio, Indonesia.

协调研究计划-白蛋白比值预测受感染新冠肺炎患者的医院存活率：在印度尼西亚南加里曼丹进行的研究

摘要：到 2022 年底，印度尼西亚的新冠肺炎病死率(病死率)为 2.4%，高于全球 1%的病死率。南加里曼丹作为印度尼西亚的一个省份，病死率达到 2.9%。改进治疗方案和更好地了解预后标志物可能会降低病死率。因此，我们决定分析协调研究计划、白蛋白和协调研究计划-白蛋白比率作为新冠肺炎的预后标志物。我们对马辰乌林医院的 980 名新冠肺炎患者进行了回顾性研究。分析患者的人口统计数据并将其分为两组（幸存者和非幸存者）。我们发现

年龄、性别和高血压、糖尿病和肥胖等合并症与死亡率相关。协调研究计划、白蛋白和协调研究计划-白蛋白比率也与死亡率相关(p < 0.001)，单变量分析的或者分别为 1.011、0.468 和 1.032。在多变量分析中，我们发现协调研究计划、白蛋白和协调研究计划-白蛋白比率是死亡率的独立预后标志物。鹏曲线分析表明，协调研究计划截止点 > 61,2（敏感性 70,2%，特异性 67,9%），AUC 0.750（p < 0.001）预测死亡率。对于白蛋白，截止点为 < 3.25（灵敏度 64.6%，特异性 54.1%），AUC 为 0.628（p < 0.001）。此外，在车中，截止点为 > 26.2（灵敏度 62.4%，特异性 77.7%），AUC 为 0.753（p < 0.001）。总之，我们的研究发现协调研究计划、白蛋白和协调研究计划-白蛋白比率与死亡率有显着联系，协调研究计划-白蛋白比率是更好的预测因子。它可能是住院新冠肺炎患者死亡率的重要预测指标，这非常容易且便宜.

关键词：新冠肺炎、死亡率、预后标志物、协调研究计划-白蛋白比率、印度尼西亚.

1. Introduction

World Health Organization (WHO) declared Coronavirus Disease-2019 (COVID-19) a pandemic on March 11, 2020, and it caused widespread death. Until the end of 2022, Indonesia had a case fatality rate (CFR) of 2.4%, higher than the global CFR of 1%. South Kalimantan, as one province in Indonesia, had CFR reached 2.9% [1]. Since the onset of the pandemic, studies have revealed a considerable rise in death due to infections unrelated to COVID-19 [2]. The facts illustrate the pandemic's far-reaching impact, which extends beyond the mortality attributable to SARS-CoV-2. Some current statistics suggest that case fatality rates are decreasing regardless of confounding factors [3]. According to the study, improved treatment options and a better understanding of prognostic markers may reduce case fatality.

Biochemical markers C-reactive protein (CRP), D-dimer, albumin, and ferritin are widely used to determine prognosis [4-6]. Previous research has shown that uncontrolled inflammation is one of the most significant contributors to the COVID-19 disease's severity. CRP, one of the most often used inflammation indicators, has been reported to be associated with an illness with a severe condition. CRP is a positive acute-phase reactant, and it has been shown that elevated CRP levels relate to uncontrolled inflammation, a dire prognosis, and the severity of the disease [7].

The dietary status of patients influences their immunity, whereas malnutrition weakens the immune system and increases vulnerability to infection. Hypoalbuminemia mainly reflects nutritional status, but it has also been linked to the severity of COVID-19 [8]. Albumin is a negative acute-phase reactant, and low albumin levels have been linked to increased mortality and morbidity in coronavirus and numerous

other serious disorders. CRP elevation and hypoalbuminemia have been used frequently in research predicting the outcome of COVID-19 infection. It has been observed, however, that the CRP-Albumin Ratio (CAR) is a more accurate predictor of outcome in critical conditions such as sepsis and cancer, as well as in COVID-19 infection [9-12]. The CRP-Albumin ratio (CAR) is a recently defined metric indicating the ratio of a positive acute-phase reactant to a negative acute-phase reactant. It is a simultaneous indicator of both the inflammatory and nutritional states [13, 14].

However, it is essential to do more research to fully understand the relationship between albumin, CRP, and mortality in COVID-19. In addition, using the CRP-Albumin Ratio as a prognostic marker in COVID-19 may vary depending on the specific patient population and clinical setting. As a result, we decided to conduct this study to look into the effect of CAR levels on admission concern mortality in hospitalized COVID-19 patients in Indonesia, particularly in the provinces of South Kalimantan.

2. Materials and Methods

The study was to be conducted retrospectively at Ulin Hospital Banjarmasin in South Kalimantan, Indonesia. The ethical committee approved the study (No. 20/11-Reg Riset/RSUDU/23). The research involved all patients in the hospital between March 2020 and December 2021 who had positive COVID-19 PCR testing, was hospitalized in the isolation unit, aged
> 18, and had CRP and albumin testing when admitted. The patients excluded from this study are those with incomplete medical records or discharged by their own will. Totally 980 patient files were collected. The patients were separated into two groups: those who survived and those who did not.

Age, gender, comorbidities, number of comorbidities, the severity of illness, and body mass index (BMI) are demographic characteristics. The patients' blood test parameters, including albumin and C-reactive protein (CRP) on the first day of admission, were compared in terms of survival. CAR was calculated by dividing the CRP level on the first day of hospitalization by the albumin level. Categorical variables are presented as frequency and percentage. Continuous variables were tested for distribution using the Kolmogorov–Smirnov. The Mann–Whitney U test was performed in analyzing independent quantitative data. In examining independent qualitative data, the chi-square test was applied, and Fisher's Test was used if the chi-square test requirements were not met. With the use of ROC curve, the effect level and cut-of/f value were analyzed. The magnitude of the effect was assessed using univariate and multivariate with forward likelihood ratio logistic regression. A P value < 0.05 is considered statistically significant. SPSS 28.0 was used to conduct data analysis.

3. Result

In this retrospective study, we collected 980 patients' data, with 778 survivors, whereas 205 were non-survivors. The median age of the non-survivors was higher than the survivor's group ($p < 0.001$). There was also a difference in terms of gender distribution ($p = 0.014$).

Comorbidities such as hypertension, diabetes mellitus, and obesity correlate with the survivability of COVID-19 patients ($p = 0.004$, 0.001, and 0.042, respectively), and the number of comorbidities in the patients also play a significant role in survivability ($p < 0.001$). The severity of COVID-19 also affects the outcomes of patients ($p < 0.001$). The detailed information is listed in Table 1.

From Table 2, we can see that the non-survivor group had significantly higher CRP ($p < 0.001$), while the albumin was lower ($p < 0.001$). Because of that, the CRP-Albumin Ratio (CAR) was higher in the non-survivor group ($p < 0.001$).

The univariate analysis showed that CRP, Albumin, and CRP-Albumin Ratio (CAR) significantly correlated with mortality in COVID-19. In contrast, multivariate analysis identified that CRP, Albumin, and CAR are independent prognostic markers for mortality (Table 3).

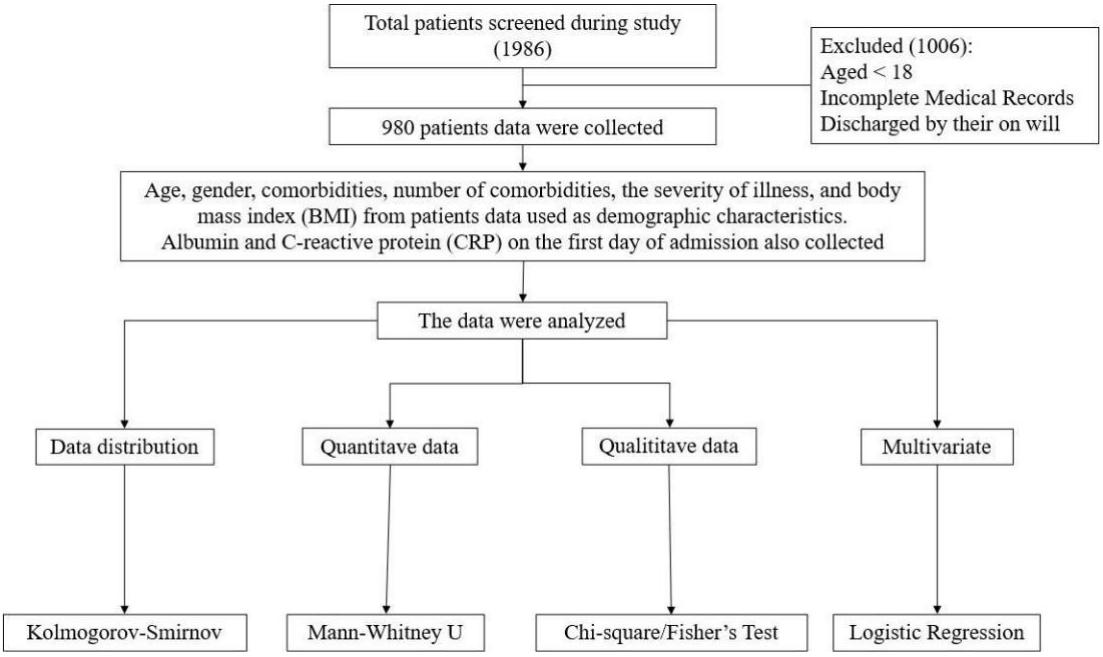

Fig. 1 The schematic pathway of collecting samples and analysis (Elaborated by the authors)

Table 1 Demographic characteristics of patients hospitalized with the diagnosis of COVID-19 in survivors and non-survivors groups (Elaborated by the authors)

Variable	All patients (n = 980)	Survivors (n = 775)	Non-Survivors (n = 205)	*p*
Age, median (IQR), year	54 (44-62)	52 (43-60)	58 (49.5-65)	$< 0.001^{*}$
- Male	54 (44-62)	53(43-61)	60(49-66)	$< 0.001^{*}$
- Female	53 (43-61	52(42-60)	57(49-64)	0.001^{*}
Sex, no (%)				0.014^{α}
- Male	542 (55.3)	413 (42.1)	129 (13.2)	
- Female	438 (44.7)	362 (36.9)	76 (7.8)	
Comorbidities, no (%)				
- Hypertension	446 (45.5)	334 (34.1)	112 (11.4	0.004^{α}
- Diabetes Mellitus	323 (33)	235 (24)	87 (9)	0.001^{α}
- Chronic Kidney Disease	102 (10.4)	74 (7.6)	28 (2.9)	0.095^{α}
- Cardiovascular disease	80 (8.1)	60 (6.1)	20 (2.0)	0.389^{α}
- Stroke	39 (4)	30 (3.1)	9 (0.9)	0.841^{α}

Continuation of Table 1

-	Malignancy	8 (0.8)	6 (0.6)	2 (0.2)	0.676[β]
-	Hepatitis B	11 (1.1)	6 (0.6)	5 (0.5)	0.059[α]
-	Lung tuberculosis	33 (3.4)	24 (2.4)	9 (0.9)	0.383[α]
-	COPD	4 (0.4)	3 (0.3)	1 (0.1)	1.000[β]
-	Asthma	27 (2.8)	21 (2.1)	6 (0.6)	1.000[α]
-	Obesity	478 (48.8)	365(37.2)	113 (11.5)	0.042[α]
Number of Comorbidities, no (%)					< 0.001[α]
-	0	172 (17.6)	159 (16.2)	13 (1.3)	
-	1	330 (33.7)	262 (26.7)	68 (6.9)	
-	2	262 (26.7)	203 (20.7)	59 (6.0)	
-	≥ 3	216 (22)	151 (15.4)	65 (6.6)	
The severity of illness, no (%)					< 0.001[α]
-	Mild	95 (9.7)	92 (9.4)	3 (0.3)	
-	Moderate	242 (24.7)	236 (24.1)	6 (0.6)	
-	Severe	162 (16.5)	148 (15.1)	14 (1.4)	
-	Critically ill	481 (49.1)	299 (30.5)	182 (18.6)	

* Mann–Whitney U test, [α] Pearson's chi-squared test, [β] Fisher exact test

Table 2 Laboratorium characteristics of patients hospitalized with the diagnosis of COVID-19 in survivors and non-survivors groups (Elaborated by the authors)

Parameter	**All patients (n = 980)**	**Survivors (n = 775)**	**Non-Survivors (n = 205)**	***p***
CRP, median (IQR)	45.5 (13-98.9)	33.8 (10.5 -80.5)	105.5 (48-187.7)	< 0.001*
Albumin, median (IQR)	3.4 (3.0-3.8)	3.5 (3.1-3.9)	3.2 (2.8 -3.5)	< 0.001*
CRP-Albumin Ratio, median (IQR)	13.3 (3.9-31.5	10.5 (2.9-23.3)	33.9 (15.2-58.6)	< 0.001*

* Mann–Whitney U test

Table 3 Univariate and multivariate analysis for CRP, albumin, and CRP-albumin ratio (Elaborated by the authors)

Variables	**Univariate**			**Multivariate**		
	OR	**95% CI**	**P**	**OR**	**95% CI**	***P***
CRP	1.011	1.009 - 1.013	< 0.001	1.021	1.011-1.031	< 0.001
Albumin	0.468	0.355 - 0.618	< 0.001	0.498	0.323-0.768	0.002
CRP-Albumin Ratio	1.032	1.026 -1.038	< 0.001	0.968	0.938-0.998	0.035

Table 4 Optimum cut-off points* of CRP, albumin and CRP/albumin ratio in predicting mortality (Elaborated by the authors)

	Cut of Point	**Sens (%)**	**Spec (%)**	**PPV (%)**	**NPV (%)**	**AUC**	**Youden's Index**	**P Value**
CRP	≥ 61.2	70.2	67.9	20.9	79	0.750	0.381	< 0.001
Albumin	≤ 3.25	64.6	54.1	23.6	80.8	0.628	0.188	< 0.001
CRP-Albumin Ratio	≥ 26.2	62.4	77.7	21.3	79.2	0.753	0.401	< 0.001

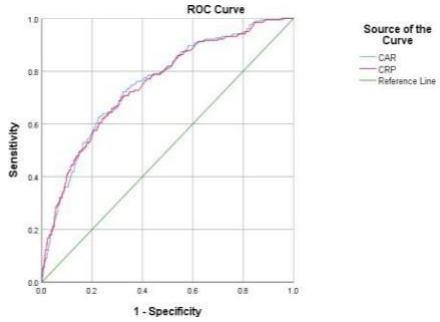

Fig. 2 The ROC curve of CRP and CRP-albumin ratio for mortality (Elaborated by the authors)

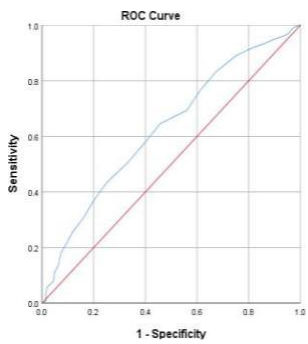

Fig. 3 The ROC curve of albumin for mortality (Elaborated by the authors)

ROC curve analysis in Fig. 2 and 3 shows that the CRP cut-off point was > 61,2 (sensitivity 70,2%, specificity 67,9%) with AUC 0.750 (p < 0.001) in predicting mortality. For the albumin, the cut-off point was < 3,25 (sensitivity 64,6%, specificity 54,1%) AUC 0.628 (p < 0.001). Furthermore, in the CAR, the cut-off point was > 26,2 (sensitivity 62,4%, specificity 77,7%) with AUC 0.753 (p < 0.001).

4. Discussion

We reported the baseline demographic and laboratory information of our COVID-19 patients in this study. First, we found that age correlated with mortality (p < 0.001). Aging can have various effects on the human body and the immune system [15]. Lung muscular atrophy is expected in the elderly. Airway clearance, lung reserve, and defense barrier function were also reduced [16]. According to one study, every five years of age increased the mortality rate by 1.55 times [17]. Another result that we found is that gender also affects mortality. Males tend to have higher mortality (p < 0.014). As we know, the Centers for Disease Control and Prevention (CDC) already

reported that 54% of deaths by COVID-19 were male [18]. It stated that males had higher angiotensin-converting enzyme 2 (ACE2) expression, which made the male patients more at risk for SARS-CoV-2 infections and poor clinical outcomes [19]. It is also hypothesized that female patients may have a slower progression of SAR-CoV-2 infection and less severe outcome conditions due to x-linked heterozygous alleles called sex dimorphism [20]. For the comorbidities, we found that hypertension, diabetes mellitus, and obesity had higher mortality ($p = 0.004$, 0.001, and 0.042, respectively). The number of comorbidities also affect mortality ($p < 0.001$). The relationships between hypertension and COVID-19 are not fully discovered, but they could be related to endothelial dysfunction and renin-angiotensin system (RAS) imbalance. It stated that RAS axis activation parallels non-conventional axis down-regulation in COVID-19, leading to a severe clinical condition. The endothelial dysfunction related to hypertension also plays a role in the proinflammatory state and causes a higher level of chemokines, cytokines, and tumor necrosis factor-α in COVID-19 [21]. In diabetes mellitus patients, the rapid progression of diseases and severe clinical outcomes may be due to hyperglycemia affecting immune function. It also causes macrovascular complications [22]. Increased blood glucose also promotes lung fibrosis, chronic inflammation, and inflammatory cytokine release [23]. The last one, for obesity comorbidities, generally has an impaired innate and adaptive immune response. People with obesity tend to have chronic low-grade inflammation, which leads to abrupt systemic metabolic alteration (higher levels of leptin and lower adiponectin). Obesity also enhanced the production of several proinflammatory cytokines. This condition will lead to poor outcomes of COVID-19 [24]. The mortality rate of COVID-19 patients also increased if the patient had more than one comorbid [25].

For this study, we focus on the laboratory results on CRP and albumin. We also counted the CRP-Albumin Ration (CAR) and analyzed with mortality in COVID-19. CRP is an acute-phase pentametric protein. It is synthesized in the liver, and induced by IL-6, in response to inflammation. It is a crucial player in recognizing and clearance of pathogens [26]. Although albumin is the major protein in human plasma, it accounts for less than a quarter of the plasma oncotic pressure. It is produced by the liver and fulfills multiple crucial functions. Albumin distributes many molecules through the bloodstream, acts as an antioxidant and suppresses platelet aggregation. It is essential in numerous processes, particularly inflammation [27].

In SARS-CoV-2 infection, inflammation plays a central role. This virus can generate a broad spectrum of clinical manifestations [28]. SARS-CoV-2 causes the destruction of lymphocytes, making lymphopenia conditions and serum albumin decrease while inducing an increase in CRP and ferritin [29]. In our study, we found that CRP, albumin, and CAR correlated with mortality ($p < 00.1$). Let us break down the mechanism one by one. CRP is indispensable for the identification of foreign compounds. In inflammatory or infectious disorders, the adaptive immune system is activated by interaction with foreign molecules. CRP is also a scavenger for damaged membranes, decaying nuclear material, and autoantigens. Because of that, the CRP level in serum is directly proportional to disease severity and outcomes [30]. For albumin, recent studies show that COVID-19 patients with hypo albumin had a poor prognosis compared with patients with normal albumin [31, 32]. Hypothesized mechanisms for hypoalbuminemia during sepsis could explain the decrease in albumin. Inflammatory activities that generate cytokines (IL-1, IL-6, and TNF-) result in hypoalbuminemia due to decreased albumin synthesis and increased hormone catabolism. During severe SARS-CoV-2 infection, inflammatory processes and mediator levels are enhanced. In severe inflammatory circumstances, there is an increase in capillary permeability, which may contribute to hypoalbuminemia due to an increase in interstitial albumin release and an increase in filtration rate. Reduced albumin levels may therefore indicate a robust inflammatory response and, in more advanced cases, systemic involvement comparable to that seen in sepsis [33]. CRP/Albumin Ratio (CAR) is already been utilized as a prognostic biomarker in various disorders. CRP and albumin are both generated in the liver and regulated by IL-6. CRP is positively affected by this mechanism, and albumin is negatively affected. Due to this, the ratio between these can be used to measure disease severity. In COVID-19 cases, it has been established that a greater CAR correlates with death [34]. Then in univariate analysis, CRP, albumin, and CAR had OR 1.011, 0.468, and 1.032, respectively, with $p < 0.001$. These data show that while CRP and albumin can be used as prognostic factors, CAR has proven to be a better tool. However, when we analyzed with multivariate, we found that CRP was a better independent factor for mortality (OR 1.021 and $p < 0.001$). Although if we look at the ROC curve, the CAR has a better AUC than CRP (0.753 vs. 0.750). It resembles a study from Lucijanic et al. [37], which calculates the 30-day survival of COVID-19 patients using CAR. [34] Another study that supports our result is [35]. In that study, not only the CAR has better AUC, but it also has better sensitivity and specificity rather than CRP or albumin alone.

The CRP, albumin, and CAR cut-off that correlates with mortality in our study were > 61.2, < 3,25, and > 26.2, respectively. In another study, the cut-off was > 33,9, < 3,8, and >8,9, respectively [35]. The other study showed that the cut-off CAR value was reported to be 5.4 [36]. We propose that the disparity in cut-off values can be attributed to differences in patient

characteristics and the diverse methodology used in the studies.

Our research has limitations. It is a retrospective and single-center study, resulting in inherent limitations. Evidence suggesting a connection between CAR and mortality might be strengthened if prospective studies were conducted across multiple centers. Additionally, our research was carried out in a province that only covers a small geographical area, making it impossible to generalize our findings nationally or internationally. Nevertheless, since our findings correlated with those of other research, it would indicate that our findings are consistent with the findings of the larger community of COVID-19 patients.

5. Conclusion

CRP and albumin are already been used as inflammation markers in COVID-19. Many studies have proved their relationship with disease severity. However, studies about their correlation with mortality still need to be completed. There are already studies on the CRP-albumin ratio correlation with mortality in COVID-19, but it's still minimal. That's why our study can help other researchers in their research on CRP and albumin.

In conclusion, our study found that CRP, albumin, and CRP-Albumin ratio had a significant connection with mortality, with CRP-albumin ratio being a better predictor. It could be a substantial predictor of mortality in hospitalized COVID-19 patients. We can estimate the probability of death based on the CAR level at admission, which is very easy and cheap, especially in countries with limited sources such as Indonesia.

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