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Comparison of the Level of C-Reactive Protein (CRP) and Ferritin among COVID-19 Patients with Critical Diseases that Survive and Do Not Survive at Wahidin Sudirohusodo Hospital

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Abstract— The outbreak of COVID-19 had a significant impact in terms of economic and social health. Because of the high mortality rate and the emergence of this health emergency condition, all scientists worldwide are attempting to investigate all types of biomarkers and markers that can be used as good indicators of symptoms, therapy, prognosis, and outcome COVID-19 patients. This study aims to compare Ferritin and CRP (C-Reactive Protein) levels in COVID-19 patients treated with pneumonia who survive and do not survive in the ICU Infection Center at WahidinSudirohusodo Hospital. The research uses a quantitative design with a cross-sectional study approach. The sample was taken from COVID-19 patients treated with pneumonia. Both survived and did not survive in the March-September 2020 period at the ICU Infection Center, Dr. WahidinSudirohusodo in Makassar.The research found no relationship between CRP levels and the ability to survive in the study sample group. Meanwhile, the ferritin levels of patients in the survival and non-survival groups showed a significant difference. The ferritin results in patients who did not survive were much higher than the ferritin levels in surviving patients. In this study; it was found that Ferritin is an essential factor affecting the severity of COVID-19. Ferritin is one of the factors that can be used as an indicator to assess the severity of patients with COVID-19.

Keywords— C-Reactive Protein, Ferritin, Survive Patients, Non-Survive Patients, COVID-19

1. Introduction

The emergence of COVID-19 as a new infectious disease has significantly impacted health, resilience, and economic stabilization(Pak et al., 2020).Until recently, no treatment could be patented as a cure for COVID-19. Data from the World Health Organization (WHO) shows that on May 16, 2021, globally, there were 162,177,376 positive confirmed cases of COVID-19 with a dead level of 3,364,178 people. The Americas have the most COVID-19 cases, with 64,757,485 cases (WHO, 2021a).

To be precise, on May 16, 2021, the Government of Indonesia announced 1,739,750 people who had been confirmed as COVID-19. Forty-eight thousand ninety-three deaths were recorded related to COVID-19 with a case fatality rate of 2,8%, and 1,600,857 patients recovered from the disease (WHO, 2021b)(Indonesian Health Ministry, 2021).

The high mortality rate and the emergence of this health emergency condition make all scientists explore all forms of biomarkers and markers that can be good indicators in terms of symptoms, therapy to prognosis, and outcome of patients with COVID-19(Zhang & Guo, 2020). The data shows clear evidence of changes in biomarker levels based on the severity of the COVID-19 infection (Kermali et al., 2020). The increasing number of COVID-19 cases causes the number of scientific publications on COVID-19 research; however,

among the many studies related to COVID-19, few limited publications related to COVID-19 biomarkers (Zhang & Guo, 2020).

The pathological process, diagnostic tools, and prognostic methods of COVID-19 are still developing. Several markers were measured in COVID-19 patients to find any marker that could be used accurately to predict the progression of this disease. Research shows that inflammatory markers have a significant relationship with the severity of COVID-19. Therefore, clinicians can measure inflammatory markers to facilitate monitoring and assessing the prognosis of COVID-19 patients (Zeng et al., 2020).

Markers of infection, which are laboratory results used to evaluate the infection process, such as Neutrophil to Lymphocyte Ratio (NLR), C-Reactive Protein (CRP) levels, and blood lactate levels, have been widely studied, with varying significant results(Ali, 2020)(Liu et al., 2020)(Luo et al., 2020).CRP levels as a marker of infection are believed to be related to the excessive production of informational cytokines, which also occurs in COVID-19 patients whose concentrations are not affected by age and sex(Zeng et al., 2020)(Bilgir et al., 2015)(Razanamahery et al., 2020). Several studies have been conducted and obtained significant results (Ali, 2020)(Sharifpour et al., 2020).

Ferritin levels are also believed to be associated with the deterioration code for COVID-19 patients (Cheng et al., 2020), but research related to this is still limited and needs to be clarified(Zeng et al., 2020).Research that explores ferritin levels in patients with COVID-19 is still limited, while the number of COVID-19 sufferers continues to increase. Globally, the COVID-19 Pandemic has caused at least more than 3 million deaths in 2020(WHO, 2021c). This condition is a global crisis that requires the handling of all human beings (Cheng et al., 2020). Therefore it is essential to study more about the COVID-19 biomarkers related to CRP and Ferritin.

The dynamic development of science regarding the Coronavirus in 2020 is ongoing. Researchers want to prove previous studies that said that CRP levels are essential in the progression of the COVID-19 patients and confirmed the comparison of ferritin levels in COVID-19 patients who "survivors" and "non-survivors" in the ICU Infection Center WahidinSudirohusodo Hospital. Based on the description above, the problem to be investigated is the comparison of Ferritin and CRP levels in COVID-19 patients treated with pneumonia, who survive and do not survive in the ICU Infection Center WahidinSudirohusodo Hospital.

2. Methods

2.1 Studying Design

This research is a quantitative design with a cross-sectional study approach.

2.2 Population, Samples, and Sampling

The study was conducted by taking data from COVID-19 patients treated with pneumonia at the ICU Infection Center Dr. WahidinSudirohusodo Makassar from March to September 2020. The sample for this study was data from COVID-19 patients treated at the ICU Infection Center, both those who survived (transferred to the standard care room) and those who did not survive (died) in March-September 2020 period.

The variables assessed were COVID-19 patients with pneumonia confirmed positive using a nasopharyngeal swab detection that examined in real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) at the ICU Infection Center Dr. WahidinSudirhohusodo Makassar. Surviving patients have passed a critical period and are transferred to the usual COVID-19 isolation care. Non-surviving patients were patients who

died in the ICU Infection Center.

The flow of this research begins with the identification of all confirmed COVID-19 patients from the results of the swab. Then, the total sampling will be divided into two groups: ICU patients who survive and are transferred to ordinary isolation care and non-surviving / dying patients. CRP and ferritin levels will be compared in both groups at a significance level of P 0.05.

Infection marker variables are laboratory markers used to assess the state of infection. In this study, CRP was used, and Ferritin was examined using a venous blood sample, expressed in mg / L units.

2.3 Analysis Data

This research used the Mann and Whitney U test.

2.4 Ethical Clearance

This research has passed the ethical test issued by the Health Research Ethics Commission, Faculty of Medicine, Hasanuddin University Makassar with the ethical recommendation number: 636/UN4.6.4.5.31/PP36/2020.

3. Results

3.1 Characteristics of Patient

Table 1. Characteristics of Patient (n = 52)

Patient Characteristics	Survive N (%)	Not Surviving	P Value
Age			
- 0- 50 years	8 (25.8)	7 (33.3%)	**0.935**
- 51- 90 years	23 (74.2)	14 (66.7)	
Gender			
- Man	21 (67.8)	14 (66.7)	**0.557**
- Women	10 (32.2)	7 (33.3)	
TOTAL	**31 (59.6)**	**21 (40.4)**	

In this study, it was found that 52 patients were respondents. Fifty-two respondents were divided into two groups, namely 31 respondents who survived and 21 respondents who did not survive. Respondents were aged 51-90 years, with a total of 23 people (74.2%) in the survival group and 14 people (66.7%) in the non-survival group. Men outnumbered women, with 21 (67.8%) in the survival group and 14 (66.7%) in the non-survival group. This study showed no significant relationship between age and gender with the ability to survive and not survive at WahidinSudirohusodo Hospital.

3.2 Comparison of CRP and Ferritin Levels in Surviving and Non-surviving Patients in the ICU of WahidinSudirohusodo Hospital

Table 2. Comparison of CRP and Ferritin Levels (n = 52)

CRP Levels	N	Mean	Min	Maximum	P value
CRP levels					
- Survive	31	157.39	22	549	**0.450**
- Not Survive					

	21	210.44	4	1200	
Ferritin levels					
- Survive	31	1239.40	22	549	**0.018 ***
- Not Survive	21	2358.81	56	7333	

Description: *Ferritin levels in the survival and non-survival groups differed significantly

This study showed no relationship between CRP levels and the ability to survive in the study sample group. Meanwhile, the Ferritin levels in the survival and non-survival groups differed significantly. The ferritin results in patients who did not survive were much higher than the ferritin levels in surviving patients.

4. Discussion

The impact of COVID-19 is a new challenge that has a significant impact on existing health systems worldwide. Cases of COVID-19 that show severity will generally display many aspects of common disorders, including hyperferritinemia syndrome. Ferritin can increase the inflammatory burden, leading to a vicious pro-inflammatory cycle (Ruscitti et al., 2020). Therefore, treatment efforts require a multidisciplinary approach and broad knowledge.

We found that Ferritin significantly differs between the survival and non-survival groups. The ferritin results in non-survival patients were much higher than those in survival patients. The results of this study are the same as those conducted by Parimoo et al. (2021), showing that a high serum ferritin value before the terminal condition more significantly indicates death as a result. Higher levels of the inflammatory marker ferritin were associated with patients who did not survive (Parimoo et al., 2021).

The cytokine storm syndrome accompanies the worst outcome of COVID-19. Ferritin, dominant in the hyperferritinemia condition, is the primary mediator of immune dysregulation. Its role in suppressing immunity and causing pro-inflammation contributes to cytokine storms(Kernan & Carcillo, 2017)(Vargas-Vargas & Cortés-Rojo, 2020). Many people with diabetes show elevated serum ferritin levels and a higher likelihood of developing complications of death from COVID-19(Vargas-Vargas & Cortés-Rojo, 2020). Therefore, it is presumed that cytokine storm syndrome determines the severity of the COVID-19 disease.

The relationship between serum ferritin levels and clinical presentation of COVID-19 patients, including disease severity, mortality, comorbidities, and specific treatment, has been revealed by a meta-analysis (Cheng et al., 2020). A study conducted by Gomez found that ferritin levels found in non-survivors were 3-4 times higher than in survivors (Gómez-Pastora et al., 2020). Ferritin serum levels are nonspecific markers in the acute phase for most physicians who treat inflammation syndrome. They are frequently ignored or unmeasured if the patient presents for the acute phase. Ferritin levels may be extremely high in some diseases, and while this is nonspecific, it may be helpful as a prognostic factor (Rosário et al., 2013).
Research conducted by Deng et al. (2021) shows that in critically ill patients in the ICU, inflammatory cytokines such as IL-6, IL-8, IL-10, TNF-, CRP, and PCT are nearly 2-10 times higher than in non-critical patients. Ferritin concentration is also positively related to inflammatory cytokines such as IL-8, IL-10, TNF-, and CRP. Furthermore, the ferritin concentration was 3.43 times higher in the death group than in the survival group. These findings suggest that hyperferritinemia may be a marker of disease severity and death by COVID-19. So far, Ferritin and cytokines have linked in a vicious circle, and targeting Ferritin may be a novel way to reduce pro-inflammatory presence (Deng et al., 2021).

Ferritin levels are a promising predictor of mortality, with statistically significant results and widespread availability; It is a valuable risk marker in COVID-19 and can be used following other clinical details and

laboratory tests when developing a patient-centered treatment plan (Ahmed et al., 2021). Research conducted by Deng et al. (2021) suggested that using serum ferritin alone or combined with CRP can improve accuracy in predicting in-hospital mortality in clinical practice, particularly in the ICU ward. Elevated ferritin levels are associated with mortality, and Ferritin is an independent predictor of in-hospital mortality in COVID-19 patients in the ICU (Deng et al., 2021).

On the other hand, we found no relationship between CRP levels and survival in the study sample group in this study. CRP is still identified as a risk factor independent of adverse outcomes in severe or critical illness (Luo et al., 2020). Contrary to other research conducted by Ahnach (2020) shows that CRP level at admission is a simple and independent factor that can be useful for early detection of severity during COVID-19 and simple primary care guidance (Ahnach et al., 2020). Serum CRP levels can be used to predict the progression and severity of COVID-19. Patients with higher CRP levels should be closely monitored throughout their disease (Sadeghi-Haddad-Zavareh et al., 2021).

5. Conclusion

The research found no relationship between CRP levels and survival in the study sample group. Meanwhile, ferritin levels differ significantly between the survival and non-survival groups. The study shows that Ferritin is an essential factor affecting the severity of COVID-19. Ferritin is one factor that can use as a marker for determining the severity of COVID-19.

6. References

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