




**REKOMENDASI PERSETUJUAN ETIK**

Nomor : 318/UN4.6.4.5.31/ PP36/ 2022

Tanggal: 29 Juni 2022

Dengan ini Menyatakan bahwa Protokol dan Dokumen yang Berhubungan Dengan Protokol berikut ini telah mendapatkan Persetujuan Etik :

No Protokol	UH22050220	No Sponsor Protokol	
Peneliti Utama	<b>dr. Ivo Ariandi</b>	Sponsor	
Judul Peneliti	KORELASI KADAR FERRITIN DAN CRP PADA BERBAGAI TINGKAT KEPARAHAN COVID-19		
No Versi Protokol	2	Tanggal Versi	27 Juni 2022
No Versi PSP	2	Tanggal Versi	27 Juni 2022
Tempat Penelitian	RSUP Dr. Wahidin Sudirohusodo Makassar		
Jenis Review	<input type="checkbox"/> Exempted <input checked="" type="checkbox"/> Expedited <input type="checkbox"/> Fullboard Tanggal	Masa Berlaku 29 Juni 2022 sampai 29 Juni 2023	Frekuensi review lanjutan
Ketua KEP Universitas Hasanuddin	Nama <b>Prof.Dr.dr. Suryani As'ad, M.Sc.,Sp.GK (K)</b>	Tanda tangan 	
Sekretaris KEP Universitas Hasanuddin	Nama <b>dr. Agussalim Bukhari, M.Med.,Ph.D.,Sp.GK (K)</b>	Tanda tangan 	

Kewajiban Peneliti Utama:

- Menyerahkan Amandemen Protokol untuk persetujuan sebelum di implementasikan
- Menyerahkan Laporan SAE ke Komisi Etik dalam 24 Jam dan dilengkapi dalam 7 hari dan Laporan SUSAR dalam 72 Jam setelah Peneliti Utama menerima laporan
- Menyerahkan Laporan Kemajuan (progress report) setiap 6 bulan untuk penelitian resiko tinggi dan setiap setahun untuk penelitian resiko rendah
- Menyerahkan laporan akhir setelah Penelitian berakhir
- Melaporkan penyimpangan dari protokol yang disetujui (protocol deviation / violation)
- Mematuhi semua peraturan yang ditentukan

# Correlation Of CRP and Ferritin Levels In The Degree Of Severity Of COVID-19

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## Keywords:

Coronavirus Disease 2019 (COVID-19), C-reactive protein, Ferritin.

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## ABSTRACT

New biomarkers are needed to identify Coronavirus Disease 2019 (COVID-19) patients who experience deterioration and have the potential to die. Elevated levels of C-reactive protein (CRP) occur in the early phase of infection when the SARS-CoV-2 virus binds to the ACE2 receptor and infects bronchial epithelial cells. Then, in the hyperinflammatory phase of COVID-19, there was an increase in serum ferritin, where the levels were higher in severe cases of COVID-19. It is recommended that serum CRP and ferritin be tested since they can be used as screening to evaluate the degree of severity and predict the prognosis of COVID-19 in the hospital. This observational study with a cross sectional approach used medical record data at Wahidin Sudirohusodo Hospital. The sample size was 639 people, with 2 subjects excluded due to extreme high levels of CRP and ferritin, thus the number of subjects being 637 people. A significant positive correlation was found between CRP and ferritin levels at all degrees of severity of COVID-19 ( $p < 0.001$ ), where the higher the CRP level, the higher the ferritin level. Based on the value of the correlation coefficient (R), the strongest correlation between CRP and ferritin levels was found in severe cases ( $R = 0.587$ ) and the weakest in very severe cases ( $R = 0.444$ ). CRP levels were positively correlated with ferritin levels at all degrees of severity of COVID-19; the higher the CRP level, the higher the ferritin level.



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## 1. Introduction

The first case of COVID-19 was discovered in Wuhan at the end of 2019, and it has spread rapidly around the world since then [1]. Transmission of Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is through contact with an infected person through droplets, then the virus binds to ACE2 receptors on the surface of arterial and venous endothelial cells, arterial smooth muscle, respiratory tract epithelium, and small intestinal epithelium to enter host cells [2], [3].

COVID-19 patients were categorized into several degrees of severity, namely mild with features without pneumonia on radiological examination, moderate with evidence of pneumonia on radiological examination, severe with blood oxygen saturation of 93%, and critical with respiratory failure and requiring mechanical ventilation [4], [5]. Biomarkers are needed to identify deteriorating cases which can result in mortality [6].

When the inflammation in COVID-19 is not resolved, hyperinflammation occurs and causes more severe tissue damage and organ failure [7]. Severe COVID-19 causes a cytokine storm as an uncontrolled systemic inflammatory response due to the release of proinflammatory cytokines from the immune response which leads to an increase in the inflammatory biomarker, namely CRP. A previous study has shown that CRP has good diagnostic accuracy in early prediction of severe COVID-19 cases [1].

Another prior study linked COVID-19 hyperinflammation with altered iron metabolism, with hyperferritinemia predicting an increased risk of death [8]. In addition to being an indicator of iron status, ferritin is also an inflammatory marker whose levels can increase significantly in response to the inflammation, including in severe COVID-19 where ferritin is a key mediator of immune dysregulation through its immunosuppressive and pro-inflammatory effects that contribute to cytokine storms [9], [10]. Meanwhile, other study suggests that it not only reflects the acute phase response but also plays an important role in inflammation [11].

The mechanism of hyperferritinemia and the severity of COVID-19 are not fully understood. Some explanations of this theory are as follows. First, pro-inflammatory cytokines such as interleukin- $\beta$  (IL- $\beta$ ), tumor necrosis factor-  $\alpha$  (TNF- $\alpha$ ), and interleukin-6 (IL-6) increase ferritin synthesis [9]. Second, cell damage due to inflammation increases intracellular ferritin leakage, thereby increasing serum ferritin [9]. Third, acidosis causes an increase in the production of reactive oxygen species (ROS) that can release iron from ferritin [9].

The increase in CRP occurs in the early phase of infection, then develops in the hyperinflammatory phase of COVID-19 where there is an increase in serum ferritin, which is higher in severe COVID-19 cases [1]. Serum CRP and ferritin tests are recommended to evaluate the severity and predict the prognosis and mortality of COVID-19 in hospital [12]. The above explanation motivated this study on the suitability of CRP and ferritin levels in COVID-19 patients.

## **2. Research Objectives**

This study aims to determine the correlation of CRP levels with Ferritin at various degrees of severity of COVID-19.

## **3. Research Methods And Subjects**

### **3.1 Research Methods**

This study is an observational study with a cross-sectional approach using medical record data of COVID-19 patients at Wahidin Sudirohusodo Hospital Makassar, South Sulawesi, Indonesia. The inclusion criteria for this study were confirmed COVID-19 patients with complete medical record data including CRP and ferritin tests. The sample size was 639 people, with 2 subjects excluded due to extremely high levels of CRP and ferritin, thus the number of subjects being 637 people. The COVID-19 patients were confirmed by a positive PCR nasopharyngeal swab examination. Serum CRP levels were measured using the immunoturbidimetric method with the normal value of CRP < 5 mg/l, while serum ferritin levels were

measured using the ELFA (Enzyme Linked Fluorescent Assay) method with the normal value of ferritin being 13 ng/ml – 400 ng/ml. Meanwhile, the degree of severity was based on the COVID-19 treatment guidelines.

### 3.2 Statistical Analysis

The data analysis was carried out by statistical tests using SPSS version 25. The statistical tests used were the Kruskal-Wallis test and the Spearman’s Correlation test. The results of statistical tests are considered significant if the p value <0.001.

## 4. Results

The research subjects (Table 1) consisted of 266 (4.8%) men and 371 (58.2%) women. Based on CRP levels, subjects were divided into normal and increased categories, where the number of subjects with normal CRP levels was 450 (70.6%) and the number of those with increased CRP levels was 187 (29.4%). For the ferritin levels variable, subjects were also divided into normal and increased categories, with those with normal ferritin levels being 293 (46%) and those with increased ferritin levels being 344 (54%). Meanwhile, the severity of COVID-19 was divided into moderate, severe, and very severe categories, with moderate cases being 399 (62.6%), severe cases being 127 (19.9%), and very severe cases being 111 (17.4%).

**Table 1.** Category of research variables

	Variable	n	%
Sex	Male	266	41.8
	Female	371	58.2
CRP Level	Normal	450	70.6
	Increased	187	29.4
Ferritin Level	Normal	293	46.0
	Increased	344	54.0
Degree of Severity of COVID-19	Moderate	399	62.6
	Severe	127	19.9
	Very Severe	111	17.4

Variable Descriptive Statistics (n=367); CRP: C-reactive protein, COVID-19: Coronavirus Disease 2019

In the comparison of CRP levels according to the severity of COVID-19 (Table 2), it was found that the mean CRP levels with the highest significance was in very severe cases (83.79) and the lowest in moderate cases (19.51), thus indicating a significant correlation between CRP levels and the severity of COVID-19 ( $p < 0.001$ ). Similarly, in the comparison of ferritin levels according to the severity of COVID-19 (Table 3), the mean ferritin levels with the highest significance was found in very severe cases (669.54) and the lowest in moderate cases (243.28). This indicates a significant correlation between ferritin levels and the severity of COVID-19 ( $p < 0.001$ ).

**Table 2.** Comparison of CRP level by degree of severity

Degree of Severity	n	Mean	SD	p
Moderate	399	19.51	42.91	0.000
Severe	127	56.98	78.61	
Very Severe	111	83.79	93.86	

Kruskal-Wallis test

**Table 3.** Comparison of ferritin level by degree of severity

Degree of Severity	n	Mean	SD	P
Moderate	399	243.28	317.10	0.000
Severe	127	628.17	501.87	
Very Severe	111	669.54	551.12	

Kruskal-Wallis test

Correlation analysis of CRP and ferritin levels according to the severity of COVID-19 (Table 4) found a significant positive correlation between CRP and ferritin levels at all degrees of severity of COVID-19 ( $p < 0.001$ ), where the higher the CRP level, the higher the ferritin level. Based on the values of the correlation coefficient (R), the strongest correlation between CRP and Ferritin levels was found in severe cases ( $R = 0.587$ ) and the weakest in very severe cases ( $R = 0.444$ ).

**Table 4.** Correlation of CRP and ferritin levels according to the degree of severity of COVID-19

Degree of Severity	Type	Variables	Statistics	CRP
Moderate	Spearman's rho	Ferritin	R	0.458
			p	0.000
			n	399
Severe	Spearman's rho	Ferritin	R	0.587
			p	0.000
			n	127
Very severe	Spearman's rho	Ferritin	R	0.444
			p	0.000
			n	111

Spearman's Correlation test; CRP: C-reactive protein

## 5. Discussions

In this study, the analysis of CRP levels found a significant correlation between CRP levels and the severity of COVID-19 ( $p < 0.001$ ). Similar findings were found in a study conducted by Wang who reported a significant increase in CRP levels in the early stages of COVID-19 infection, with the increase in CRP levels being correlated with the severity of the disease and the degree of lung tissue damage. The CRP level was found to be higher in the severe group than in the moderate - mild group, while the CRP level in the critical group was found to be higher than the severe group. [13] similarly, the ferritin analysis found a significant correlation between ferritin levels and the severity of COVID-19 ( $p < 0.001$ ). The same results were also found in a study by [14] where both the severe and very severe COVID-19 groups showed an

increase in ferritin levels, but ferritin levels in the very severe COVID-19 group was significantly higher than that in the severe group. In a retrospective study by the National Health Commission of the PRC on 21 patients with COVID-19, patients were classified as severe and moderate (11 and 10 cases, respectively). The results found that 12 patients showed increased Ferritin levels, with 9 patients classified as severe cases and 3 patients as moderate cases [15].

Correlation analysis of CRP levels with ferritin levels according to the severity of COVID-19 found a significant positive correlation between CRP levels and independent ferritin on the severity of COVID-19, where the higher the CRP level, the higher the ferritin level. This is in line with a study carried out by [12] on 100 hospitalized COVID-19 patients in India which showed that ferritin and CRP levels were significantly increased in severe cases of COVID-19 compared to mild cases. Therefore, these two examinations are used as important predictors of the severity of COVID-19 disease at the time the patient is admitted to the hospital.

## **6. Conclusions**

CRP levels had a significant positive correlation with independent Ferritin levels on the severity of COVID-19, with the strongest correlation between CRP and Ferritin was found in severe COVID-19.

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