
**FERRITIN LEVEL AS INDEPENDENT PREDICTOR
OF COVID-19: A CROSS-SECTIONAL STUDY**

**Nur Komariah^{1,2}, Salbiah², Betha Ariessanthy Anggraini Nugroho¹, Suliati¹,
Aninda Dinar Widiyanti¹, Farida Murtiani^{1*}**

¹ National Infection Center Prof. Dr. Suliati Saroso, Jakarta, Indonesia

² Medical Laboratory Technology, Politeknik Kesehatan Kemenkes Jakarta III, Jakarta, Indonesia

*Correspondence email: idoel_fh@yahoo.com

ABSTRACT

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). In severe cases of COVID-19, it is often accompanied by a syndrome known as cytokine storm or cytokine release syndrome (CRS). Serum ferritin levels increase as the disease worsens. This study aims to see the relationship between ferritin levels and the degree of COVID-19 and evaluate ferritin levels as a predictor of severity in COVID-19 patients at RSPI Prof. Dr. Suliati Saroso. This type of research is quantitative with a cross-sectional approach. Data analysis using Kruskal Wallis test. Secondary data from medical records of confirmed COVID-19 patients based on the results of PCR examinations from March 2020 to December 2020 at RSPI Prof. Dr. Suliati Saroso, who examined ferritin levels of as many as 554 patients. The results showed that the average ferritin level was 164.78, moderate was 524.13, severe was 1377.52, and critical was 1592.46. The analysis results with the Kruskal Wallis test obtained a P-value = 0.000 < (0.05), so it can be explained that there are differences in ferritin levels of the four degrees of disease. The result shows that the relationship between ferritin levels and the degree of disease in COVID-19 patients is significant.

Keywords: COVID-19; Ferritin Serum; Severity

INTRODUCTION

Coronavirus Disease 2019 (Covid-19) is a communicable disease that is caused by *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2). SARS-CoV-2 is a coronavirus which never been identified in humans. In January 30th2020, WHO determined Covid-19 as a Public Health Emergency of International Concern (PHEIC) and on Mar 11 as a pandemic. As noted on May 2, 2021, Covid-19 spread to 222 countries, with 161,5 million cases and 3.352.109 (2,1%) deaths. As of May 16, 2021, the covid-19 incidence in Indonesia was 3.080 cases and kept increasing, while the total confirmed cases was 1.739.750 cases, and the mortality rate was 2,8% (48.093 cases).¹

In severe cases of covid-19, a syndrome called Cytokine Release Syndrome (CRS) is usually found.² Cytokine storm is a condition when an uncontrollable immune response and immunopathy mechanism dysfunction occur while battling this disease. The release of TNF- α , IL-6, IL-12, and IL-8 in a huge amount cause *Acute Respiratory Distress Syndrome (ARDS)* and systemic organ failure.³

Discovering ferritin serum in the covid-19 case is essential as it is correlated to the Iron mechanism in the body. Iron is an important substance and part of the hemoglobin structure whose responsibility is to deliver oxygen to organs. The deficiency of iron causes muscle weakness and decreases lung capacity, which worsens the infection.

Hepcidin escalation (as a result of IL-6 increasing) will block iron absorption in the gut and hinder Iron release from the macrophage. Most people who are inpatient due to respiratory disorders have low Iron serum.⁴

High ferritin serum is found during infection and can be a virus replication marker. Increasing ferritin rate due to cytokine storm and sHLH (secondary hemophagocytic lymphohistiocytosis) has been reported in a severe case of covid-19.³ According to Zhou et al., hepcidin and ferritin serum was found higher in severe cases. Measuring Iron homeostasis specifically and sensitively has proven to be an early prediction of the severity in this case. Qeadan et al. stated cytokine storm is mediated by proinflammatory cytokine, which causes acute lung injury and multiorgan failure.⁵

Some studies have proven the correlation between blood ferritin to covid-19 severity. Ahmed et al., in their study, evaluated ferritin serum to predict severity and mortality. In a study in Medina, it was affirmed that there was a significant escalation of ferritin, neutrophile, and leukocyte in severe cases of covid-19.⁶ A study by Bozkurt et al. showed ferritin was the only significant predictor of the disease's severity ($p=0,004$).⁷

It is necessary to evaluate potential biomarkers that influence the pathology of the disease. Thus, investigating the correlation between ferritin and the severity of covid-19 is our priority in this study.

MATERIAL AND METHODS

This study was an analytical correlational descriptive with a cross-sectional approach. Data collection was done simultaneously (point time approach) from medical records, including all covid-19 confirmed cases based on PCR (Polymerase Chain Reaction) from March - December 2020 in National Infection Center Prof. Dr. Sulianti Saroso, Jakarta. Inclusion criteria were inpatient, older than 18 years old, and ferritin tested less than 24 hours from hospital admission. Exclusion criteria were incomplete data and pregnant women. The total sampling method was used in this

study. Univariate and bivariate analysis was done. Normality test was done using Kolmogorov Smirnov test and bivariate analysis using Kruskal Wallis test. The significance rate that used to be the standard for accepting or denying H_0 was 0,05. By drawing the ROC curve, the ferritin rate predicted the disease severity.

RESULT

Between March and December 2020, 554 covid-19 confirmed cases were found in National Infection Center Prof. Dr. Sulianti Saroso. were collected. The mean age was 49,03 years (18-86 years old, $SD = 14,38$). Most of the data were from men, and the rest were from women (57,6%, $n=319$ vs. 44,8%, $n=248$). More than half patients had comorbid, while the others didn't (55,2%, $n=306$ vs. 44,8%, $n=248$). Table 1 describes the category and severity of covid-19 cases investigated in the study.

Tabel 1. Category and Severity Covid-19 Case in National Infection Center Prof. Dr. Sulianti Saroso in March-December 2020

Variable	Frequency (n=554)	%
Category		
▪ Mild	9	1,6
▪ Moderate	415	74,9
▪ Severe	71	12,8
▪ Critical	59	10,8
Severity		
▪ Mild-moderate	424	76,5
▪ Severe-critical	130	23,5

Mean ferritin rate in the study was 741,44 ng/mL (10-3720, $SD=709,36$). Kruskal Willis test was used to analyze the non-parametric test. In each category; mild, moderate, severe, critical, mean ferritin rate was 164,78 ng/mL; 524,13 ng/mL; 1377,52 ng/mL; 1592,46 ng/mL, $p=0,000$. Kruskal Willis test was used to analyze the non-parametric test. It was concluded that the ferritin rate in the critical category was higher than in severe cases. Reciprocally, it was also higher when we compared the ferritin rate in severe to moderate and moderate to mild categories.

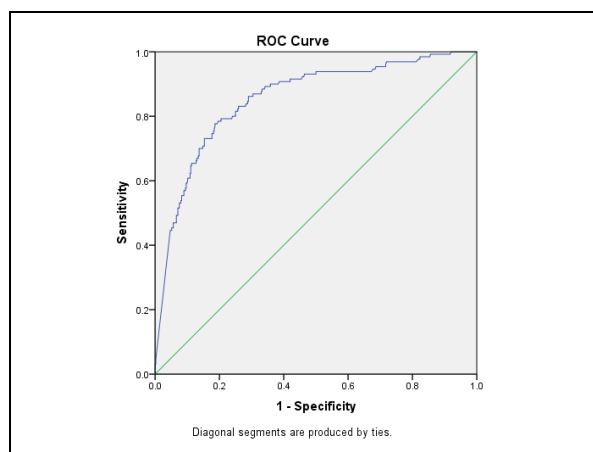


Figure 1. ROC curve was done to describe a correlation between ferritin rate to severity classification

It was pictured in the ROC curve that the ferritin rate could be used to foresee the severity of the disease (AUC 85,4%). Ferritin rate higher than 881 ng/mL was predicted to develop to severe-critical category (sensitivity: 77,7%; specificity: 81,4%).

DISCUSSION

The mean age in this study was 49,03 years old (18-86 years old, SD = 14,38). Ariza et al. found the same age range people in their study conducted in Bandar Lampung in March-September 2020.⁸ Cross-sectional study that was held by Rajanna et al., in Victoria Hospital, Banglore, India also discovered most people aged 43,89 years old in their study.⁹ Research by the Health Ministry of Indonesia showed that people aged 46-65 were the most vulnerable group to get the infection. It was revealed aging process, depressing of immune system function, and comorbid disease was the main cause of the vulnerability. It was proven comorbid disease could increase morbidity and mortality.¹⁰

Most of the data collected in our study were from men. This finding was as concomitant as data gathered by Indonesian Covid-19 Response Acceleration Task Force until Nov 22, 2020, which showed 50,6% were men and 49,4% were women.¹¹ Some studies which had the same results were a study by Kangdra, that stated confirmed

covid-19 was dominated by men (57,9%),¹² a study by Ariza et al., in Bandar Lampung, which found 50 participants were men (63,3%), and another 29 people were women (36,7%).¹² A study by Zhang et al. also described men's domination in a confirmed covid-19 case.¹³ It was hypothesized this phenomenon was caused by their movement pattern that was predominantly much higher than women. Moreover, cigarettes and alcohol consumption that could induce comorbid disease was found more in men than women.

Cases with the comorbid disease were found in 306 participants (55,2%). Most of them were diabetes mellitus and hypertension. A study in Wuhan showed the most common comorbidity found in Covid-19 were diabetes mellitus (20%), hypertension (15%), and cardiovascular disease (15%).² Patients with comorbid were correlated more to severe infection and worst outcomes than a patient without the comorbid disease.¹⁴

In this study, we found mean average ferritin rate was 741,44 ng/mL. Earlier research by Boslurtz et al. in Mehmet Akif Inan Research and Training Hospital in March-June 2020 showed mean ferritin in mild-moderate was 110,9 ng/mL and 756,2 ng/mL in a severe-critical stage.¹⁵ A study by Al Meani et al., 2020 in Anbar Governorate of Iraq mentioned mean ferritin in covid-19 confirmed case was $551,70 \pm 194,59$ ng/mL.¹⁶ Ferritin rate in the covid-19 case was influenced by several factors (1) older age, which increases the ferritin rate, (2) sex, men were higher in ferritin rate than women, (3) genetic; hereditary hemochromatosis caused accumulation of blood iron; thus ferritin rate was higher, (4) iron consumption, an iron supplement could increase ferritin rate.¹⁷

Zhou et al. confirmed the covid-19 patient had higher hepcidin and ferritin serum. Iron homeostasis has a strong relationship to severe covid-19. They confirmed iron homeostasis could predict specifically and sensitively predict the pathogenesis of the disease.⁵

Most of the data covid-19 confirmed in National Infection Centre was a moderate

stage on admission day. Our hospital was a national center for a covid-19 referral. Thus, inpatients commonly come in the late stage of covid-19. This also happened in Alrajhi Liver University hospital and Assiut University hospital Mesir on 30 Mei-30 June 2020. Ramadan et al., 2020 mentioned that 51,54% were patients in the moderate stage, and 23,08% were in the severe-critical stage.¹⁹ This finding was in contrast to Bozkurt's research that stated inpatients were mostly in the mild-moderate stage.¹⁵

In this study, the mean ferritin rate in the mild, moderate, severe, and critical stages was 174,78 ng/mL; 524,13 ng/mL; 1377,52 ng/mL; and 1592 ng/mL, which was known statistically by the Kruskal Willis test different. In conjunction with our research was a study in the Sino-French New City Branch of Tongji Hospital. It was concluded the difference among these four categories was scientifically proven by $p < 0,005$.¹⁹

A high ferritin rate during infection could be a biomarker of virus replication. High ferritin rate had also been reported during cytokine storm and sHLH, mainly in severe and critical cases. Cytokine storm is a syndrome causing inflammation in the immune system. Therefore, multiorgan failure and death occur. In contrast to this statement, hyperferritinemia was used as an acute-phase reaction to investigate therapeutical response by clinician.²⁰

During cytokine storm in covid-19, inflammatory cytokine mass production, including TNF- α , IL-1 β , IL-12, and IFN- γ , stimulates hepatocyte, Kupffer cell, and macrophage to induce ferritin production. Ferritin also has a pathogenic role in the inflammation process to promote expression from some pro-inflammation mediators via its binding to immunoglobulin T-cell and mucin-2 (TIM-2).³

In line with this study, Bozkurt et al. mentioned ferritin rate was the only scientifically proven predictor of covid-19 severity ($p=0,004$).¹⁵ Binary regression logistic showed ferritin was the independent predictor of all death causes, completed AUC 69% in their ROC curve. Rajanna et al.'s study

also mentioned ferritin was correlated to clinical symptoms. Their ROC curve showed AUC 80,08%, with cut off 352 ng/ml, specificity and sensitivity were 76,3% and 74,6%.⁹ Zhou et al., in their study, also revealed ferritin was one of the independent predictors of covid-19 severity.⁵

CONCLUSION

This study showed there was a significantly different among ferritin in each category of disease category. A ferritin rate of more than 881 ng/mL was predicted to develop into severe-critical covid-19.

REFERENCES

1. Kemenkes RI. Pedoman Pencegahan dan Pengendalian Corona Virus deases (Covid-19). Kementerian Kesehatan Republik Indonesia. 2020;5:178.
2. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
3. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, Li Y. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Lab Anal*. 2020;34(10):1-18
4. Alipour R, Hashemi SH, Mikaeili F. Serum iron level in patients with COVID-19: a case report study. *Int J Res Med Sci*. 2020;8(7):2658–2662.
5. Zhou C, Chen Y, Ji Y, He X, Xue D. Increased Serum Levels of Hepcidin and Ferritin Are Associated with Severity of COVID-19. *Med Sci Monit*. 2020;26(26):e926178-1–e926178-6.
6. Mohammedsaeed W, M. Surrati A, Q. Alnakhli H, Alharbi M, Syeed N. Alteration of Ferritin Levels and Lymphocytes Counts in Saudi Patients with COVID-19 Infection in Al Madinah Al Munawarah. *Int J Diabetes Endocrinol*. 2020;5(4):61–66.

7. Bozkurt FT, Tercan M, Patmano G, Bingol Tanriverdi T, Demir HA, Yurekli UF. Can Ferritin Levels Predict the Severity of Illness in Patients With COVID-19? *Cureus*. 2021 Jan;13(1):1–8.
8. Ariza R, Messah AD, Sinaga F, Wahyudi A, Pratama SA, Annisa I. Korelasi Gambaran Radiografi Toraks dengan Karakteristik Klinis Pasien Terkonfirmasi Covid-19. *Arter J Ilmu Kesehat*. 2021;2(1):15–22.
9. Rajanna AH, Krishnegowda R, Govindaiah RM. To Correlate Serum Ferritin Levels with Clinical Outcome in Covid-19 Patients. *Asian J Med Sci*. 2021;12(5):25–29.
10. Kemenkes RI. COVID-19 INDONESIA Per 16 Mei 2021. INFEKSI EMERGING Media Inf Resmi Terkini Penyakit Infeksi Emerg [Internet]. 2021; Available from: <https://infeksiemerging.kemkes.go.id/dashboard/covid-19>.
11. Satuan Satgas Penanganan COVID-19. Analisa Data COVID-19 Indonesia [Internet]. 2020. Available from: <https://covid19.go.id>
12. Kangdra WY. Karakteristik Klinis Dan Faktor Komorbid Pada Pasien Dalam Pengawasan (PDP) Coronavirus Disease 2019 (COVID-19) di RS Mitra Medika Amplas [Internet]. Medan: Universitas Sumatra Utara; 2021. Available from: <http://repositori.usu.ac.id/handle/123456789/30672>
13. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, Song Q, Jia Q, Wang J. . Clinical characteristics of 82 cases of death from COVID-19. *PLoS One*. 2020;15(7):1–13.
14. Wang W, Knovich MA, Coffman LG, Torti FM, Torti S V. Serum ferritin: Past, present, and future. *Biochim Biophys Acta*. 2020;1800(8):760–769.
15. Bozkurt FT, Tercan M, Patmano G, Bingol Tanriverdi T, Demir HA, Yurekli UF. Can Ferritin Levels Predict the Severity of Illness in Patients With COVID-19? *Cureus*. 2021;13(1):1–8.
16. Al Meani SAL, Abdulkareem AH, Ibrahim MO, Ahmed MM, Mukhlif MY. Assessment the Correlation of D-dimer and Ferritin Level in Patients Infected with Covid-19 in Anbar Governorate of Iraq. *Syst Rev Pharm*. 2020;11(9):1130–1133.
17. McKinnon EJ, Rossi E, Beilby JP, Trinder D, Olynyk JK. Factors That Affect Serum Levels of Ferritin in Australian Adults and Implications for Follow-up. *Clin Gastroenterol Hepatol*. 2014;12(1):101-108.
18. Ramadan HKA, Mahmoud MA, Zakaria M, Aburama, Elkhawaga AA, El-Mokhtar MA, et al. Predictors of severity and co-infection resistance profile in COVID-19 patients: First report from upper Egypt. *Infect Drug Resist*. 2020;13:3409–34022.
19. Deng F, Zhang L, Lyu L, Lu Z, Gao D, Ma X, et al. Increased levels of ferritin on admission predicts intensive care unit mortality in patients with COVID-19. *Med Clin (Barc)*. 2021;156(7):324–331.
20. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol*. 2017;29(9):401–409.