Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 05; 10(B):1056-1061.
https://doi.org/10.3889/oamjms.2022.8777
eISSN: 1857-9655
Category: *B - Clinical Sciences*
Section: *Infective Diseases*

OPEN ACCESS

Serum Ferritin Levels for the Prediction of Mortality among COVID-19 Patients in an Indonesia's National Referral Hospital

Yoshie Anto Chicamy[1]*, Annisa Safitri[1], Ricvan Dana Nindrea[2]

[1]Department of Clinical Pathology and Medical Laboratory, Faculty of Medicine, Andalas University, Dr. M. Djamil General Hospital, Padang, Indonesia; [2]Department of Education and Research, Dr. M. Djamil General Hospital, Padang, Indonesia

Edited by: Sinisa Stojanoski
Citation: Chicamy YA, Safitri A, Nindrea RD. Serum Ferritin Levels for the Prediction of Mortality among COVID-19 Patients in an Indonesia's National Referral Hospital. Open-Access Maced J Med Sci. 2022 May 05; 10(B):1056-1061. https://doi.org/10.3889/oamjms.2022.8777
Keywords: COVID-19; Ferritin; Outcome; Prediction
***Correspondence:** Yoshie Anto Chicamy, Department of Clinical Pathology and Medical Laboratory, Faculty of Medicine, Andalas University, Dr. M. Djamil General Hospital Padang, Indonesia.
E-mail: yoshieanto@gmail.com
Received: 27-Jan-2022
Revised: 22-Mar-2022
Accepted: 26-Apr-2022

Funding: This research did not receive any financial support
Competing Interest: The authors have declared that no competing interest exists

Abstract

BACKGROUND: Early identification of clinical outcomes is necessary for risk classification in COVID-19 patients. This study help in evaluating the progression of the disease and the patient's therapy.

AIM: This study aims to determine serum ferritin levels for the prediction of mortality among COVID-19 patients in an Indonesia's National Referral Hospital.

METHODS: A retrospective cohort study was conducted on 142 confirmed positive COVID-19 patients between March 2020 until March 2021 at Dr. M. Djamil General Hospital as a National Referral Hospital in Indonesia. Data obtained from medical record documents and examination of ferritin levels was carried out at the beginning of treatment. The Chi-square test and survival analysis with the log-rank test and Kaplan–Meier methods were used to analyze the data. The SPSS version 15 was used to analyze the data.

RESULTS: The serum ferritin cutoff point for COVID-19 patients that can be used to predict poor outcomes was >651.02 ng/mL with sensitivity 79.3%, specificity 80.5%, and accuracy 85.0%. Age, comorbid diabetes mellitus, number of comorbidities, symptoms of trouble breathing, oxygen saturation, severity, and mortality outcome were all associated to ferritin levels >651.02 ng/mL. The Kaplan–Meier curve showed that ferritin levels >651.02 ng/mL were associated for risk of poor outcome COVID-19 patients (HR = 8.84, [95% CI 3.59–21.73]).

CONCLUSION: The ferritin cutoff point for predicting poor prognosis in COVID-19 patients was 651.02 ng/mL. However, ferritin serum levels cannot be used as a single predictor in determining the poor outcome of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China, and is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which is transmitted to humans. The SARS-CoV-2 virus spreads quickly around the world. On March 11, 2020, the World Health Organization proclaimed COVID-19 a worldwide epidemic. On September 20, 2020, there were 30,675,675 verified cases and 954,417 fatalities, according to reports [1], [2].

COVID-19 symptoms range from asymptomatic, moderate symptoms such as illness, cough, fever, shortness of breath, and shortness of breath to severe symptoms including respiratory failure, acute respiratory distress syndrome, and death. The severity of COVID-19 outcomes is linked to the existence of a cytokine storm, and variations in clinical symptoms are linked to the release of cytokines generated in inflammatory situations. The liver produces ferritin, an acute-phase protein. Increased ferritin levels have been associated to inflammatory conditions in the previous study. Ferritin is a protein that binds iron. Increased ferritin levels indicate an inflammatory condition induced by viruses or bacteria in the body, whereas decreased ferritin levels indicate iron deficiency anemia [2]. Inflammation activates macrophages, which emit inflammatory cytokines and send signals to the immune system, hence, ferritin may be used as a marker of inflammation in addition to being a marker of iron accumulation [2], [3], [4].

Ferritin has been examined extensively as an external predictor of COVID-19 patients as an inflammatory marker. COVID-19 patients with severe symptoms had greater ferritin levels than those with mild symptoms. Ferritin levels in severe symptoms were higher (2817.6 ng/mL) than in non-severe symptoms (708.6 ng/mL) [4]. Ferritin levels were found to be higher in patients with severe symptoms (>1300 ng/mL) than in individuals with mild symptoms (821.1 ng/mL) in another study. In COVID-19 patients, elevated ferritin levels can be utilized as a prediction of poor prognosis. Ferritin levels more than 400 ng/mL were identified to be a risk factor for COVID-19 illness development in one hospital at Beijing, China [5].

However, because the cutoff value for ferritin levels as an outcome prediction marker does not yet exist at one of the Indonesia's national referral

hospitals, researchers are interested in conducting this study. The objective of this study is to provide an overview of the features of COVID-19 patients at one of the Indonesia's national referral hospitals, as well as to evaluate ferritin cutoff as a predictor of prognosis for COVID-19 patients so that doctors may be more alert to disease progression.

Methods and Materials

Study design

This study used a retrospective cohort analysis on confirmed positive COVID-19 inpatients at Dr. M. Djamil General Hospital in Padang, which is one of the Indonesia's national referral hospitals. From March 2020 to March 2021, data were gathered from patient medical records. Clinical factors such as medical history, comorbidities, clinical symptoms, and laboratory examinations of ferritin levels were gathered from medical records, as were demographic data such as age, sex, and body mass index. RT-PCR analysis of nasopharyngeal swab tissues yielded positive findings for COVID-19. Patients with severe COVID-19 are identified by clinical symptoms and an oxygen saturation of less than 93 percent. At the outset of therapy, patients' ferritin levels were examined. Patients with autoimmune illnesses who did not get a ferritin screening during their initial hospitalization were excluded from this study.

Data collection

In this study, demographic data, clinical features, test findings, and patient outcomes were gathered from medical record documents. Blood samples are examined using an automated analysis system to obtain laboratory examinations. The enzyme-linked fluorescent assay (ELFA) technique was used to evaluate ferritin levels on the VIDAS Biomerieux instrument. In adults, the standard range for normal ferritin levels was 68–434 ng/mL.

Ethical approval

This study was approved by the Dr. M. Djamil General Hospital, Padang, Indonesia, ethics committee in 2021.

Operational definition

Positive cases were verified using nasopharyngeal swab specimens and RT-PCR. The ELFA technique was used to determine ferritin levels. In adults, the standard range for normal ferritin levels was 68–434 ng/mL. This study consisted of several variables such as gender (male and female), age, body mass index (underweight 25 Kg/mm^2, overweight 25–27 kg/m^2, and obesity >27 Kg/m^2), clinical symptoms (cough, fever, shortness of breath, hyposmia, and anosmia), comorbidities (cardiovascular disease, respiratory disease, malignancy, liver, and kidney disease), oxygen saturation, and length of stay. The severity of the disease was divided into mild (symptomatic without viral pneumonia), moderate (patients with clinical symptoms of pneumonia without difficulty breathing or SpO2 > 93%), and severe (patients with pneumonia and one of whom had a respiratory rate > 30×/min, distressed heavy breathing or SpO2 < 93%).

Data processing and analysis

For categorical data, frequency and percentage were used, while for numerical variables, the mean was used. The Chi-square test for categorical variables and the independent sample t-test for numerical variables were used to evaluate bivariate analysis hypotheses. Cutoff value analysis was determined based on area under curve using receiver operating characteristic (ROC) curve and survival analysis was assessed using Cox regression and Kaplan–Meier. Odds ratio values are interpreted as OR > 1.00 (risk factor), OR < 1,00 (preventive factor), and OR = 1.00 (reference). $p < 0.05$ was considered statistically significant. SPSS software version 15 was used to analyze the data.

Results

Characteristics of research subjects

Description of the characteristics of the research subjects conducted on 142 COVID-19 patients (Table 1).

Table 1 found based on demographic data, the number of research subjects with female (55.6%) was more than male (44.0%). The mean age of the research subjects was 47.45±15.58 years. BMI of patients who were underweight (12.7%), normal (59.2%), and overweight (28.2%).

Clinical characteristics found that the average subject had two comorbidities with the most comorbid diabetes mellitus (18.3%) followed by hypertension (15.5%). The median value of ferritin levels was 268.6 ng/mL with a minimum level of 5.9 ng/mL and a maximum of 1.200 ng/mL. Ferritin levels <651.02 ng/mL (68.3%), and ferritin levels >651.02 ng/mL (31.7%) were found in research subjects.

The average length of treatment for research subjects was 12 days with the highest degree of disease severity being moderate disease (62.7%). The results of

Table 1: Characteristics of research subjects

Variables	f (%)	Mean ± SD/ median (min-max)
A. Demographics		
Sex, f (%)		
Male	63 (44.4)	
Female	79 (55.6)	
Age (years), mean ± SD		47.45 ± 15.58
Body mass index (BMI), f (%)		
Underweight	18 (12.7)	
Normal	84 (59.2)	22.91 ± 6.23
Overweight	40 (286.2)	
B. Clinical		
Comorbid, f (%)		
Hypertension	22 (15.5)	
Diabetes mellitus	26 (18.3)	
Cancer	5 (3.5)	
Tuberculosis	2 (1.4)	
Number of comorbid, mean ± SD		1.11 ± 1.03
Symptom, f (%)		
Cough	60 (42.3)	
Fever	47 (33.1)	
Difficult to breath	66 (46.5)	
Nausea	8 (5.6)	
Anosmia	24 (16.9)	
Oxygen saturation (%), mean ± SD		95.31 ± 7.66
Ferritin levels group (ng/ml), f (%)		
< 651.02 ng/ml	97 (68.3)	
> 651.02 ng/ml	45 (31.7)	
Ferritin levels group (ng/ml), median (min-max)		268.62 (5.90-1,200)
Length of stay (days), mean ± SD		12.22 ± 6.46
Severity, f (%)		
Severe	26 (18.3)	
Moderate	89 (62.7)	
Mild	27 (19.0)	
Outcome, f (%)		
Life	113 (79.6)	
Death	29 (20.4)	

the study regarding the outcome of subjects who lived or returned home (79.6%) and the outcome was died (20.4%).

Cut-off value of ferritin on COVID-19 patient outcomes (Table 2).

Table 2: Cutoff value of ferritin on COVID-19 patient outcomes

Cutoff	Accuracy (95% CI)	Sensitivity	Specificity
651.02 ng/mL	85.0% (78.0–95.0%)	79.3%	80.5%

Figure 1 shows that the cutoff value of ferritin on the outcome of COVID-19 patients was >651.02 ng/mL

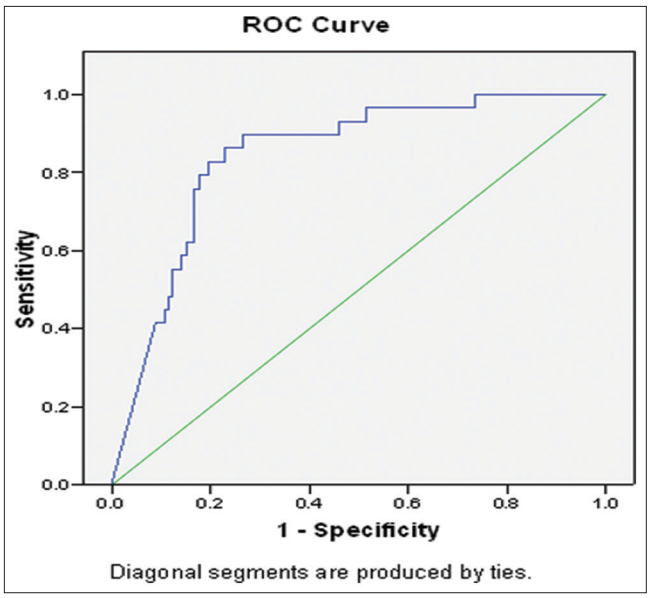

Figure 1: ROC curve of ferritin levels during treatment to predict the outcome of COVID-19 patients

with sensitivity 79.3%, specificity 80.5%, and accuracy 85.0% (78.0%–95.0%).

Research results from the association between ferritin levels and characteristics of COVID-19 patients (Table 3).

Table 3 shows significant results ($p < 0.05$) between the cutoff ferritin value with age, comorbid DM, number of comorbidities, difficult to breath, oxygen saturation, severity, and outcome of the subject. Sex, BMI, comorbid hypertension, TB, fever, cough, nausea, anosmia, and length of stay were not significant with ferritin levels.

Based on the unadjusted hazard ratio, it was found that the highest HR values for increasing ferritin levels were the severity of disease (HR 26.6; 95% CI 5.9–120.42), disease outcome (HR 15.85; 95% CI 5.76–43,6), symptoms of difficulty breathing (HR 3.92; 95% CI 1.84–8.34), comorbid diabetes mellitus (HR 3.27; 95% CI 1.42–7.52), number of comorbidities (HR 1.63; 95% CI 1.14–2.34), and age (HR 1.29; 95% CI 1.01–1.05). COVID-19 patients who are older and have multiple comorbidities show a higher risk and are positively correlated with increased ferritin levels. Difficulty breathing was the only symptom associated with elevated ferritin levels in this study. Patients with severe severity have a greater risk of death compared to moderate or mild cases.

The adjusted hazard ratio value after being tested with other characteristic variables consistently found the severity of disease in COVID-19 patients (HR 37.2; 95% CI 2.34–590.75) followed by death outcome (HR 21.2; 95 % CI 3.66–123.35) which correlates with a higher risk of elevated ferritin levels. Oxygen saturation (HR 1.16; 95% CI 1.01–1.34) was also a variable that correlated with higher ferritin levels after the test was performed.

Research results of ferritin levels during hospitalization and length of hospitalization in predicting outcome of COVID-19 patients (Table 4 and Figure 2).

Based on Table 4, the median length of stay for patients with ferritin levels <651.02 ng/mL was 41 days, while patients with ferritin levels >651.02 ng/mL were 17 days. The incidence of death in patients with ferritin levels <651.02 ng/mL was 6.2% and patients with ferritin levels >651.02 ng/mL were 51.1%. During hospitalization, there were 29 outcomes of death, of which 23 people had ferritin levels >651.02 ng/mL. Based on the results of the survival analysis, it was found that there was an association between the increase in ferritin on the outcome of COVID-19 patients as seen based on the length of stay (p log-rank test = 0.001, $p < 0.05$). Based on the HR value, patients with ferritin levels >651.02 ng/mL had an HR of 8.84 (95% CI; 3.59–21.73) with respect to the outcome, which indicates that patients with ferritin levels >651.02 ng/mL had 8.84 times more risk of experiencing a worse outcome than patients with ferritin levels <651.02 ng/mL.

Table 3: The association between ferritin levels and characteristics of COVID-19 patients

Characteristics	Ferritin levels (ng/mL)		p-value	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
	< 651.02	> 651.02			
A. Demographics					
Sex, f (%)			0.199[a]		
Male	39 (40.2)	24 (53.3)		0.58 (0.28–1.20)	2.43 (0.77–7.64)
Female	58 (59.8)	21 (46.7)		1.70 (0.83–3.46)	0.41 (0.13–1.29)
Age (years), mean ± SD	45.3 ± 15.9	52.09 ± 13.69	0.015[b]*	1.29 (1.01–1.05)	1.02 (0.98–1.06)
Body mass index (BMI), f (%)			0.683 a		
Underweight	13 (13.4)	5 (11.1)		1.01 (0.29–3.51)	2.18 (0.36–13.09)
Normal	55 (56.7)	29 (64.4)		1.38 (0.60–3.17)	0.86 (0.23–3.23)
Overweight	29 (29.9)	11 (24.4)		0.98 (2.84–3.14)	0.46 (0.07–2.75)
B. Clinical					
Comorbid, f (%)					
Hypertension	14 (14.4)	8 (17.8)	0.792a	1.28 (0.49–3.31)	0.71 (0.13–3.86)
Diabetes mellitus	14 (14.4)	16 (35.6)	0.008a*	3.27 (1.42–7.52)	0.87 (0.19–3.99)
Cancer	3 (3.1)	2 (4.4)	0.652a	1.47 (0.23–9.04)	1.20 (0.11–12.22)
Tuberculosis	0 (0)	2 (4.4)	0.099a	n/a	n/a
Number of comorbid, mean ± SD	0.94 ± 0.89	1.47 ± 1.21	0.004b*	1.63 (1.14–2.34)	1.22 (0.64–2.33)
Symptom, f (%)					
Cough	42 (43.3)	18 (40)	0.851a	0.87 (0.42–1.79)	0.33 (0.89–1.22)
Fever	30 (30.9)	17 (37.8)	0.538a	1.35 (0.64–2.84)	1.52 (0.40–5.72)
Difficult to breath	35 (36.1)	31 (68.9)	0.001a*	3.92 (1.84–8.34)	2.42 (0.56–10.46)
Nausea	3 (3.1)	5 (11.1)	0.109a	3.91 (0.89–17.17)	7.49 (0.91–61.26)
Anosmia	14 (14.4)	10 (22.2)	0.362a	1.69 (0.68–4.17)	2.60 (0.53–12.77)
Oxygen saturation (%), mean ± SD	96.85 ± 6.95	92 ± 8.12	0.001b*	0.91 (0.85–0.96)	1.16 (1.01–1.34)
Length of stay (days), mean ± SD	12.61 ± 6.49	11.38 ± 6.93	0.293b	0.96 (0.91–1.02)	1.04 (0.95–1.14)
Severity, f (%)			0.001a*		
Severe	24 (24.7)	3 (6.7)		26.6 (5.9–120.42)	37.2 (2.34–590.75)
Moderate	67 (69.1)	22 (48.9)		0.99 (0.35–0.27)	0.01 (0.01–0.16)
Mild	6 (6.2)	20 (44.4)		0.03 (0.08–0.16)	0.02 (0.01–0.42)
Outcome, f (%)			0.001a*		
Life	91 (93.8)	22 (48.9)		Ref	Ref
Death	6 (6.2)	23 (51.1)		15.85 (5.76–43.6)	21.2 (3.66–123.35)

Ref: Reference; n/a: Not account, a: Chi-square test, b: Independent sample t-test. *p < 0.05, considered significant; HR: Hazard ratio.

Table 4: Ferritin levels during hospitalization and length of hospitalization in predicting outcome of COVID-19 patient

Ferritin levels (ng/mL)	Mean of length of stay (min-max)	Outcome	p-log rank test	HR 95% CI
< 651.02	41 (34-47)	6 (6.2%)	0.001	8.84 (3.59-21.73)
> 651.02	17 (13-21)	23 (51.1%)		

Discussion

The research showed an association between age and higher ferritin levels in this study. Patients over the age of 47 are at risk of having elevated ferritin levels, which can lead to complications. COVID-19 mortality is related with increasing age, according to the previous study. The severity of COVID-19 illness is mostly determined by the patient's age. People above the age of 65 have a 23-fold higher risk of death than those under the age of 65 [6].

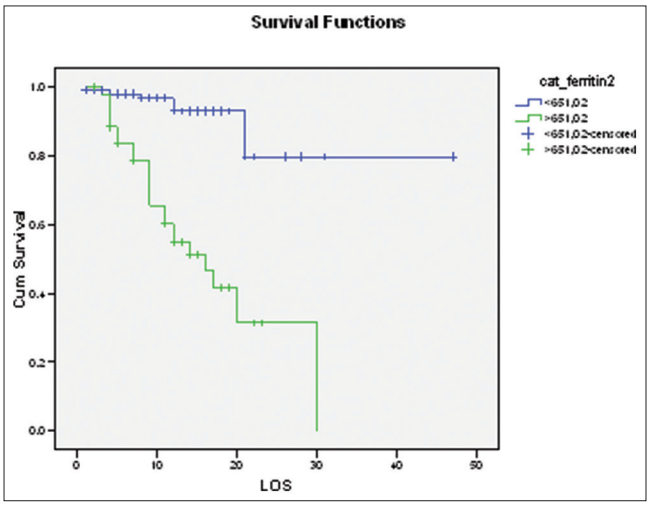

Figure 2: Kaplan–Meier of ferritin levels during hospitalization and length of hospitalization in predicting outcome of COVID-19 patient

With advancing age, the immune system's reaction decreases and slows, disrupting the process of pathogen detection, signaling, destruction, and clearance. More infected cells and the production of greater inflammatory cytokines result from defects in macrophages and T cells, which can cause more harm to organ systems [6]. In monkeys, inoculation with SARS-CoV-2 elicited a higher innate immune response in the young than in the young adults, with variations in the expression of genes linked to inflammation. Interferon beta-type 1 expression dropped, but T- and B-cell production and activity increased, making them less able to regulate viral replication and prolonging inflammation [5].

This study found that diabetes mellitus was the only statistically significant risk factor. COVID-19 patients who have one or more comorbid diseases have significantly higher ferritin levels than patients without comorbidities, indicating a poor prognosis in patients with comorbidities [2]. One previous study reported greater inflammation and higher mortality in COVID-19 patients with comorbid diabetes mellitus, another study observed that patients with diabetes mellitus had higher ferritin levels than those without. This study found the second highest frequency of comorbid diabetes mellitus (19.0%) after hypertension (30.0%).

The clinical symptoms of many COVID-19 patients found in this study were difficulty breathing, coughing, and fever, but the only significant

symptom associated with this was difficulty breathing. This is probably due to a bias in the selection of sample criteria. Previously, there were also no reports that explained the effect of difficult of breath symptoms on the outcome of COVID-19 patient [7], [8].

Based on the ROC curve in this study, the cutoff value of ferritin as a marker for the outcome of COVID-19 patients was 651.02 ng/mL. Patients with ferritin levels >651.02 ng/mL had an 8.84 times greater risk of poor outcome and mortality. A previous study found that the cutoff value was not much different, namely, 727 ng/mL to predict a poor outcome in COVID-19 patients [3]. Another study in Utah, USA, found an optimal cutoff of ferritin 714 ng/mL as a predictor of mortality outcome in COVID-19 patients and ferritin levels of 502 ng/mL as a predictor of ventilator dependence [9], [10]. Slightly different from other study, the ferritin cutoff level was higher for the mortality outcome, namely, 1.873 ng/mL [11].

A study showed that patients with elevated ferritin (≥500 ng/mL) had a risk of disease severity and death in COVID-19 patients because bilateral pulmonary infiltration was more easily and the disease was more severe, because serum ferritin levels correlated with the degree of systemic and pulmonary inflammation [12], [13]. Other study reported that COVID-19 patients with high ferritin levels had a higher proportion of disease severity and mortality ($p = 0.016$) [14]. COVID-19 patients with severe cases who did not receive treatment had a higher proportion of elevated ferritin than patients with mild cases and received treatment ($p < 0.001$) and stated that ferritin is a potential risk factor for the poor prognosis of COVID-19 patients [15].

Ferritin levels increased in patients who died with COVID 19, the average ferritin level in severe severity was >800 g/L, which was 1.5–5.3 times higher than in cases with mild severity [8]. Ferritin levels were 327.7 ng/mL in mild cases, 1.555 ng/mL in moderate cases, and 2817.6 ng/mL in severe cases. There was a significant difference between mild cases compared to moderate cases and severe cases ($p = 0.006$ and $p = 0.005$) [3]. A study involving 141 patients with COVID-19 reported that hyperferritinemia (serum ferritin > 500 g/L) was observed in all severe cases at admission, and mild cases had normal mean ferritin levels (303 ± 224 g/ml); In addition, severe cases and ICU patients had higher ferritin levels than mild patients [16].

Serum ferritin is composed of a heavy subunit “H” and a light subunit “L,” these subunit proteins play an important role in many diseases, such as autoimmune diseases and inflammation. Secreted by hepatocytes and macrophages, ferritin can also activate macrophages, which increases the secretion of pro-inflammatory cytokines. Therefore, ferritin is known as an acute-phase protein. Serum ferritin concentrations have been found to be elevated in viral diseases, such as H5N1 influenza and hepatitis B and C [5], [11].

Elevated ferritin levels could be indicative of a strong inflammatory reaction associated with viral entry into the human body, cytokine storm syndrome causing multiorgan failure so that elevated ferritin levels could be associated with mortality and progression of severe outcomes in COVID-19 patients [5]. An increase in ferritin level >700 ng/mL should prompt additional diagnostic testing so that a therapeutic approach can be taken without delay and it has been shown to result in a better patient outcome. Ferritin can be used as an early identification and risk management for COVID-19 patients for the occurrence of disease worsening [17], [18].

This study has several limitations: First, it did not compare ferritin to other inflammatory markers in predicting COVID-19 outcome; second, because it was a retrospective study, hospitalization data such as laboratory results and previous medical history may be incomplete, contributing to study bias, and thus, the characteristics of eligible patients may not be representative. Third, because the data in this study came from patients treated at Dr. M. Djamil General Hospital, which is one of Indonesia’s national referral hospitals, additional validation for geographical diversity, prospective, and cohort studies is required.

Based on the findings of several studies, ferritin has increased as an acute-phase protein in COVID-19 instances, where a cytokine storm can cause damage to various organs and result in poor outcomes, suggesting that ferritin could be utilized as an outcome predictor in COVID-19 patients to enhance COVID-19 patients’ clinical approaches.

Conclusion

The ferritin cutoff point for predicting poor prognosis in COVID-19 patients was 651.02 ng/mL. However, ferritin serum levels cannot be used as a single predictor in determining the poor outcome of COVID-19.

Acknowledgments

The authors would like to thank Director of resources, education, and general Dr. M. Djamil General Hospital, Padang, Indonesia, for to facilitate the implementation of this research.

References

1. Gómez-Pastora J, Weigand M, Kim J, Wu X, Strayer J, Palmer AF, *et al*. Hyperferritinemia in critically ill COVID-19 patients - Is ferritin the product of inflammation or a pathogenic mediator? Clin Chim Acta. 2020;509:249-51. https://doi.org/10.1016/j.cca.2020.06.033
   PMid:32579952
2. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, *et al*. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal. 2020;34(10):e23618. https://doi.org/10.1002/jcla.23618
   PMid:33078400
3. Dahan S, Segal G, Katz I, Hellou T, Tietel M, Bryk G, *et al*. Ferritin as a marker of severity in COVID-19 patients: A fatal correlation. Isr Med Assoc J. 2020;22(8):494-500.
   PMid:33236582
4. Kappert K, Jahić A, Tauber R. Assessment of serum ferritin as a biomarker in COVID-19: Bystander or participant? Insights by comparison with other infectious and non-infectious diseases. Biomarkers. 2020;25(8):616-625. https://doi.org/10.1080/1354750X.2020.1797880
   PMid:32700561
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. https://doi.org/10.1016/S0140-6736(20)30566-3
   PMid:32171076
6. Mueller AL, McNamara MS, Sinclair DA. Why does COVID-19 disproportionately affect older people? Aging (Albany NY). 2020;12(10):9959-81. https://doi.org/10.18632/aging.103344
   PMid:32470948
7. Wang Z, Du Z, Zhu F. Glycosylated hemoglobin is associated with systemic inflammation, hypercoagulability, and prognosis of COVID-19 patients. Diabetes Res Clin Pract. 2020;164:108214. https://doi.org/10.1016/j.diabres.2020.108214
   PMid:32416121
8. 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):324-31. https://doi.org/10.1016/j.medcli.2020.11.030
   PMid:33422296
9. Akdur G, Daş M, Bardakci O, Akman C, Sıddıkoğlu D, Akdur O, *et al*. Prediction of mortality in COVID-19 through combing CT severity score with NEWS, qSOFA, or peripheral perfusion index. Am J Emerg Med. 2021;50:546-52. https://doi.org/10.1016/j.ajem.2021.08.079
   PMid:34547696
10. Qeadan F, Tingey B, Gu LY, Packard AH, Erdei E, Saeed AI. Prognostic values of serum ferritin and D-dimer trajectory in patients with COVID-19. Viruses. 2021;13(3):419. https://doi.org/10.3390/v13030419
    PMid:33807920
11. Lino K, Guimarães GM, Alves LS, Oliveira AC, Faustino R, Fernandes CS, *et al*. Serum ferritin at admission in hospitalized COVID-19 patients as a predictor of mortality. Braz J Infect Dis. 2021;25(2):101569. https://doi.org/10.1016/j.bjid.2021.101569
    PMid:33736948
12. Tang JW, Young S, May S, Bird P, Bron J, Mohamedanif T, *et al*. Comparing hospitalised, community and staff COVID-19 infection rates during the early phase of the evolving COVID-19 epidemic. J Infect. 2020;81(4):647-79. https://doi.org/10.1016/j.jinf.2020.05.029
    PMid:32442455
13. Nindrea RD, Djanas D, Warsiti W, Darma IY, Hendriyani H, Sari NP. The risk factors and pregnant women's willingness toward the SARS-CoV-2 vaccination in various countries: A systematic review and meta-analysis. Clin Epidemiol Glob Health. 2022;14:100982. https://doi.org/10.1016/j.cegh.2022.100982
    PMid:35169659
14. Zeng Z, Yu H, Chen H, Qi W, Chen L, Chen G, *et al*. Longitudinal changes of inflammatory parameters and their correlation with disease severity and outcomes in patients with COVID-19 from Wuhan, China. Crit Care. 2020;24(1):525. https://doi.org/10.1186/s13054-020-03255-0
    PMid:32854750
15. Sun Y, Dong Y, Wang L, Xie H, Li B, Chang C, *et al*. Characteristics and prognostic factors of disease severity in patients with COVID-19: The Beijing experience. J Autoimmun. 2020;112:102473. https://doi.org/10.1016/j.jaut.2020.102473
    PMid:32439209
16. Gao YD, Ding M, Dong X, Zhang JJ, Kursat Azkur A, Azkur D, *et al*. Risk factors for severe and critically ill COVID-19 patients: A review. Allergy. 2021;76(2):428-55. https://doi.org/10.1111/all.14657
    PMid:33185910
17. Nindrea RD, Usman E, Katar Y, Sari NP. Acceptance of COVID-19 vaccination and correlated variables among global populations: A systematic review and meta-analysis. Clin Epidemiol Glob Health. 2021;12:100899. https://doi.org/10.1016/j.cegh.2021.100899
    PMid:34746514
18. Cecconi M, Piovani D, Brunetta E, Aghemo A, Greco M, Ciccarelli M, *et al*. Early predictors of clinical deterioration in a cohort of 239 patients hospitalized for Covid-19 Infection in Lombardy, Italy. J Clin Med. 2020;9(5):1548. https://doi.org/10.3390/jcm9051548
    PMid:32443899