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Potential Role of Ferritin Levels in Distinguish the Severity and Predict the Outcome of COVID-19 Patients

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Abstract

Ferritin is a key mediator of immune dysregulation through its direct pro-inflammatory effects, which contribute to inflammatory cytokine storms and tissue damage. This study aims to analyze ferritin roles in distinguish the severity and predict the outcome of COVID-19 patients. An observational analytic study, using a cross-sectional design, enrolled 142 patients which subsequently divided into a non-severe (mild to moderate cases) and a severe (severe to critically ill cases) group. The levels of ferritin was examined using Enzyme Immunoassay Test Kit on the first day patients was hospitalized. Mann Whitney test was used to analyze the correlation between ferritin levels with severity and outcome of COVID-19 patients. ***Results:*** *The median of ferritin level was higher in the severe group (1532.1 ng/ml, SD= 1715.552) compared to non-severe group (413.3 ng/ml, SD= 459.804) with a statistically significant difference (p< 0.001), cut off point of 865.1 ng/ml, sensitivity of 86.96% (95% CI: 76.68%–93.86%), and specificity of 87.67% (95% CI: 77.88%–94.20%). Ferritin levels were also higher in non-survivors (1496.55 ng/ml, SD = 1798.677) than in survivors (662.05 ng/ml, SD = 1293.026), with a significant difference (p < 0.001), cut off point of 1032.85 ng/ml, sensitivity of 63.33% (95% CI: 43.86% to 80.07%), and specificity of 63.39% (95% CI: 53.76% to 72.29%). This results showed that ferritin levels may not good enough to predict the outcomes, with Contingency coefficient of 0.244 that showed a very weak correlation. The baseline ferritin levels at admission was closely related to the severity of COVID-19, thus it may be considered a potential biomarker for assessing disease severity. However, ferritin levels appear to be insufficiently accurate for predicting clinical outcomes in COVID-19 patients.*

Keywords**:** COVID-19 severity; Serum ferritin; SARS-CoV-2

INTRODUCTION

SARS-CoV-2, a virus that caused COVID-19, was first identified on December 2019 in Wuhan (Hubei, China). The virus outbreak spread rapidly across the world, including Indonesia, and has since become a global pandemic (G. Chen et al., 2020). The World Health Organization (WHO) reported, as of 31 January 2021, there were 102,083,344 confirmed cases and 2,209,195 deaths globally (WHO, 2021b). Similarly, in Indonesia, the number of confirmed COVID-19 cases has continued to increase, with 1,024,298 cases reported by 27 January 2021, including 28,855 deaths and 831,330 recoveries (WHO, 2021a). The pathogenesis of COVID-19 and the effects in immune system has not completely understood, however,

evidences showed that COVID-19 has characteristic of a very progressive virus and associated with uncontrolled inflammation. Ferritin, the main intracelluler iron storage protein, is an acute reactan phase which elevates in many conditions of inflammation, including acute infection. Extreme high levels of ferritin are the hallmark of hyperferritinemic syndrome, a common term for macrophage activation syndrome, onset Still's disease, catastrophic antiphospholipid syndrome, and septic shock (Feld et al., 2020). Ferritin acts as a key mediator of immune dysregulation, especially in extreme hyperferritinemia, through direct immunosuppressive and inflammatory effects, leading to the generation of inflammatory cytokine storms (Vargas-Vargas & Cortés-Rojo, 2020). In general, extremely high level of ferritin indicates a poor prognosis of hospitalized patients. Several studies have suggested that higher ferritin levels, in combination with other pro-inflammatory markers such as C-reactive protein (CRP) and Interleukin 6 (IL-6), correlate with worse prognosis. Nevertheless, ferritin levels may assist in predicting patient prognosis (G. Chen et al., 2020); (Feld et al., 2020).

Previous studies of COVID-19 patients have investigated several inflammatory markers, including procalcitonin, CRP, erythrocyte sedimentation rate (ESR), and serum amyloid A, but only a few have particularly explored ferritin. Although hyperferritinemic has been proven to be associated with complications on other virus diseases such as dengue fever, however its utilization to predict clinical outcome has not been acknowledged (Feld et al., 2020). Wu et al. reported that higher ferritin serum correlated with the condition of acute respiratory distress syndrome (ARDS) (Wu et al., 2020), while Zhou et al. demonstrated a correlation between higher ferritin concentrations and mortality (Zhou et al., 2020). Liu et al. suggested, that ferritin and interleukin-6 (IL-6) levels decreased as patients began to recover, supporting the hypothesis that hyperferritinemia is linked to the inflammatory state in SARS-CoV-2 infection. This finding implies that ferritin may serve as a potential parameter to predict the disease severity and the extent of cytokin storm (Liu et al., 2020). The study by Huang et al. (Huang et al., 2020) in Indonesia found that independent higher ferritin serum level was associated with ARDS, mortality, and severe COVID-19. On another hand, Feld et al. (Feld et al., 2020) reported that although higher ferritin level was correlated with all of the cause of death cases, however ferritin was unreliable to predict some of critical outcomes, including death. Currently, researches about ferritin levels and its roles on COVID-19 patients are still controversial and minimally conducted in Indonesia and other countries. Therefore, authors are interested to investigate the correlation of ferritin levels with severity degree of COVID-19 patients.

RESEARCH METHOD

The Design and Subjects of Study

This was an observational analytic study with a cross-sectional design, conducted in the COVID-19 Isolation Ward of Dr. Soetomo General Academic Hospital, Surabaya, from May to October 2020. The subjects were COVID-19 patients, male or female by age ≥ 21 years old.

COVID-19 infection was confirmed by PCR swab examination (Roche cobas Z480 and Lepgen 96). The severity of COVID-19 was assessed based on WHO criteria (WHO, 2020), which differentiate into:

a. Mild disease: Patients with symptoms and meet the case definition for COVID-19 but no evidence of viral pneumonia or hypoxia;
b. Moderate disease (pneumonia): Adolescent or adult with clinical signs of pneumonia (fast breathing, cough, dyspnea, fever) but without the signs of severe pneumonia, including SpO2 ≥ 90% on room air;
c. Severe disease (severe pneumonia): Adolescent or adult with clinical signs of pneumonia (fast breathing, dyspnea, cough, fever) plus one of the following: severe respiratory distress; SpO2 < 90% on room air; or respiratory rate > 30 breaths/min;
d. Critically disease: Patients who had ARDS, sepsis, or septic shock

We categorized these criteria into two groups: non-severe group which consist of patients who had mild and moderate cases; and severe group which consist of patients who had severe and critically ill cases. This study was conducted in accordance with the principles of the Declaration of Helsinki and received ethical approval from the Ethics Committee of Dr. Soetomo General Hospital prior to the study (Ethical Clearance Number 1953/KEPK/IV/2020).

Ferritin Analysis

Peripheral blood samples were collected and sent to the Laboratorium of Clinical Pathology of Dr. Soetomo General Academic Hospital, Surabaya. Serum ferritin levels were measured using an immunoassay test kit with a chemiluminescence immunoassay reagent, following the manufacturer's guidelines (ADVIA Centaur, Siemens, Germany).

Analysis and Statistical Data

Statistical analysis was performed using statistical SPSS software package for Windows, version 17.0 (SPSS, Inc., Chicago, IL). Data normality was assessed using the Kolmogorov–Smirnov test. Normally distributed data was analyzed using independent t test, while the data which non-normally distributed was analyzed using Mann Whitney. A p-value of less than 0.05 was considered statistically significant.

RESULT AND DISCUSSION

1. Demography and Characteristic of COVID-19 Patients as Research Subject

A total of 142 patients met the inclusion and exclusion criteria. Based on the WHO classification mentioned above, 19 patients had mild disease (13.4%); 54 had moderate disease (38%); 50 had severe disease (35%); and 19 were critically ill (13.4%). We distributed those four criteria into severe group (n= 73, 51.41%), and non-severe group (n= 69, 48.59%). According to the demography data, there were significant differences between the severe and non-severe groups in age and gender, while comorbidities did not differ significantly. The most common comorbidities in both severe and non-severe groups were diabetes mellitus (64.9% and 47.1%,

respectively) and hypertension (45.9% and 67.6%, respectively). In the severe group, cough was the most frequent symptom (80.0%), while in the non-severe group was shortness of breath (100.0%). Significant difference was observed between both groups in term of symptoms, particularly shortness of breath (p= 0.000) and anosmia (p= 0.006). In the result of laboratory examinations, a significant differences of neutrophils and lymphocytes number count were found in both groups. Neutrophils had a higher median of 79.30 x 10^9 per L, while lymphocytes had a lower median of 11.70 x 10^9 per L in the severe group. Bilateral infiltrations on chest X-rays were noted in all severe cases (100.0%). The survived outcome of the patients was higher in the non-severe group (94.5%) than in the severe group (62.3%) (Table 1).

Table 1. Characteristics of Subjects Based on Severity

Characteristics	**Severity Degree of COVID-19**		
	Non-severe (n=73) (Mild: n=19; Moderate: n=54)	**Severe (n=69) (Severe: n=50; Critically ill: n=19)**	**p Value**
Age			
Mean ± SD	49.30 ± 12.834	55.43 ± 11.042	0.003
Median (min – max)	52.00 (21.00 – 75.00)	55.00 (28.00 – 77.00)	
Gender			
Male	30 (41.1%)	41 (59.4%)	0.029
Female	43 (58.9%)	28 (40.6%)	
Comorbidities			
Malignancy	1 (2.9%)	1 (2.7%)	0.968
Cardiovascular disease	3 (8.8%)	4 (10.8%)	0.642
Diabetes mellitus	16 (47.1%)	24 (64.9%)	0.089
Hypertension	23 (67.6%)	17 (45.9%)	0.363
Tuberculosis	2 (5.9%)	2 (5.4%)	0.954
Bronkhial asthma	3 (8.8%)	1 (2.7%)	0.338
Obesity	4 (11.8%)	3 (8.1%)	0.756
Symptoms			
Fever	53 (75.7%)	45 (65.2%)	0.342
Cough	56 (80.0%)	58 (84.1%)	0.272
Shortness of breath	36 (51.4%)	69 (100.0%)	0.000
Runny nose	7 (10.0%)	3 (4.3%)	0.222
Diarrhea	17 (24.3%)	15 (21.7%)	0.825
Malaise	18 (25.7%)	10 (14.5%)	0.128
Sore throat	8 (11.4%)	6 (8.7%)	0.651
Nausea/vomit	8 (11.4%)	8 (11.6%)	0.905
Anosmia	10 (14.3%)	1 (1.4%)	0.006
Neurological symtoms	5 (7.1%)	2 (2.9%)	0.277
Laboratory Examinations			
Leukocytes, x 10^6 per L			

Mean ± SD	4927.90 ± 4661.666	9357.23 ± 26801.734	0.167
Median (max-min)	4270.00 (40.00 – 22580.00)	5630.00 (54.00 – 224000.00)	
Hemoglobin g/L			
Mean ± SD	13.12 ± 1.484	13.21 ± 1.771	
Median (max-min)	13.20 (8.40 – 17.70)	13.20 (9.00 – 18.40)	0.739
Neutrophils, x 10^9 per L			
Mean ± SD	71.03 ± 11.752	79.42 ± 9.055	
Median (max-min)	74.30 (39.10 – 89.20)	79.30 (51.20 – 94.30)	0.000
Limphocytes, x 10^9 per L			
Mean ± SD	19.79 ± 9.602	13.11 ± 7.600	
Median (max-min)	17.40 (5.80 – 48.40)	11.70 (0.69 – 39.70)	0.000
Platelet x 10^9 per L			
Mean ± SD	268.84 ± 92.490	294.87 ± 109.837	
Median (max-min)	256.00 (107.00 – 541.00)	269.00 (85.00 – 618.00)	0.125
Chest X-ray			
Normal	19 (26.0%)	0 (0%)	< 0.001
Unilateral	6 (8.2%)	0 (0%)	
Bilateral	48 (65.8%)	69 (100.0%)	
Antivirus Therapy			
No antiviral drugs	8 (38.1%)	13 (62.0%)	
Isoprinosine	47 (54.0%)	40 (46.0%)	
Oseltamivir	7 (58.3%)	5 (41.7%)	
Lopinavir-Ritonavir	16 (40.0%)	24 (60.0%)	
Hydroxychloroquine	30 (52.6%)	27 (47.4%)	
Favipiravir	8 (80.0%)	2 (20.0%)	
Remdesivir	2 (100.0%)	0 (0%)	
Other Therapy			
Dexamethasone	6 (24.0%)	19 (76.0%)	
Tocilizumab	1 (100.0%)	0 (0%)	
Invasive ventilator	1 (10.0%)	9 (90.0%)	
Non-invasive ventilator	0 (0%)	1 (100.0%)	
ECMO	0 (0%)	0 (0%)	
Outcomes			
Survived	69 (94.5%)	43 (62.3%)	
Non-survived	4 (5.5%)	26 (37.7%	

Sources: Author, 2022

2. Ferritin Levels and Severity Degree of COVID-19 Research Subjects

In this study, the median ferritin level in COVID-19 patients was 841.60 ng/mL (SD = 1434.99), ranging from 12.00 to 9328.00 ng/mL. Based on disease severity, higher median ferritin level was observed in the severe group by 1532.10 ng/mL (SD = 1715.55), compared to 413.30 ng/mL (SD = 459.80) in the non-severe group (Table 2). Normality test of ferritin levels using Kolmogorov Smirnov resulted that the data was not distributed normally ($p< 0.05$), thus the Mann–Whitney U test was applied to assess differences between the groups. The test showed a meaningful and significant difference of ferritin levels between severe and non-severe patients ($p< 0.001$). Receiver operating characteristic (ROC) curve analysis identified a cutoff value of 865.1 ng/mL, with an area under the curve (AUC) of 0.918, sensitivity of 86.96% (95% CI: 76.68–93.86%), specificity of 87.67% (95% CI: 77.88–94.20%), positive predictive value of 86.96%, and negative predictive value of 87.67% (Figure 1). This results suggested that ferritin may be potential to predict disease severity, with Contingency Coefficient of 0.598 which showed a moderatae correlation. Further analysis using Cohen's kappa coefficient inter-rater agreement to assess the suitability between ferritin levels and COVID-19 severity based on WHO criteria was resulted in 0.746, indicating strong correlation (Table 3).

Table 2. Ferritin levels in COVID-19 patients

Severity Degree of COVID-19	Ferritin Levels			
	Mean ± SD	Median (min – max)	p Value	Contingency coefficient
All (n= 142)	1207.70 ± 1434.991	841.60 (12.00 – 9328.00)		
Non-severe (n=73) (Mild: n=19; Moderate: n=54)	501.17 ± 459.804	413.30 (12.00 – 3073.40)	0.000	0.598
Severe (n=69) (Severe: n=50; Critically ill: n=19)	1955.18 ± 1715.552	1532.10 (188.40 – 9328.00)		

Sources: Author, 2022

Table 3. The Suitability of Ferritin Levels with WHO criteria

	Non-severe	Severe	Kappa coefficient
High Ferritin (≥865.1 µg/L)	9	60	0.746
Low Ferritin (<865.1 µg/L)	64	9	

Sources: Author, 2022

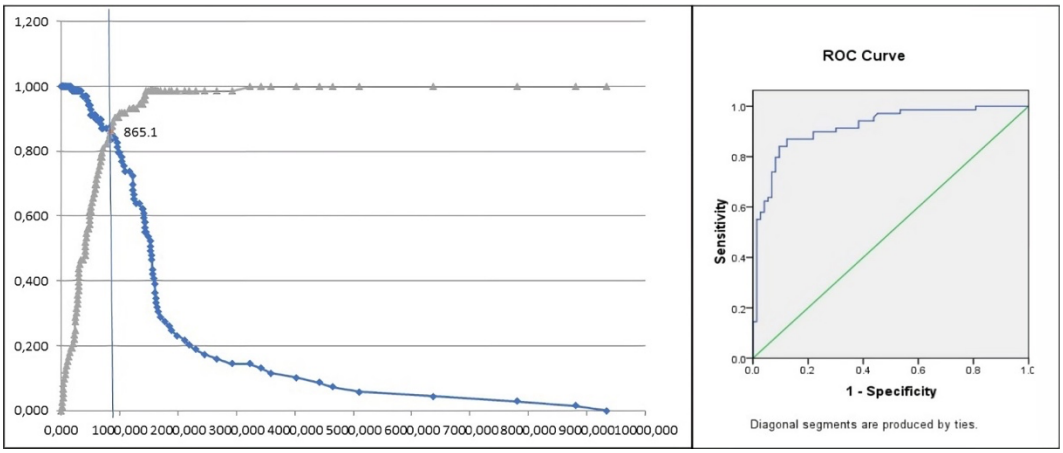

Figure 1. ROC curve and Area Under Curve (AUC) graphic of ferritin levels and severity degree.

3. The Correlation Between Comorbidity Factor with Ferritin Levels and Severity of COVID-19 Research Subjects

This study analyzed the influence of comorbidities factor towards COVID-19 severity. The most comorbidity found was hypertension in non-severe group, and diabetes mellitus in severe group (Table 1). A significant correlation between comorbidities and severity of COVID-19 was observed ($p < 0.001$) (Table 4). Median of the ferritin levels in COVID-19 patients with comorbidities was found to be 892.60 ng/ml (SD= 1781.152), with a maximum level of 9328.00 ng/ml (SD= 1781.152). In contrast, patients without comorbidities had a lower median ferritin level of 711.20 ng/mL (SD = 926.82), with a maximum level of 4467.50 ng/mL. Statistical analysis revealed no significant difference in ferritin levels between patients with and without comorbidities (p= 0.110) (Table 5).

Table 4. Comorbidities and severity degree of COVID-19 patients.

Severity Degree of COVID 19	Comorbidities		p Value
	Present	Absent	
Non-severe (n=73) (Mild: n=19; Moderate: n=54)	34	39	0.000
Severe (n=69) (Severe: n=50; Critically ill: n=19)	37	32	

Sources: Author, 2022

Table 5. Ferritin Levels and Comorbidities of COVID-19 Subjects

Comorbidities	Mean ± SD	Median (min – max)	p Value
Without comorbidities (n= 50)	968.20 ± 926.823	711.20 (12.00 – 4467.50)	0.110

With comorbidities (n= 50)			1447.18 ± 1781.152	892.60 (37.10 – 9328.00)	
Comorbidity Diseases	Malignancy	Yes	4995.45 ± 6127.157	4995.45 (662.90 – 9328.00)	0.283
		No	1153.59 ± 1268.606	841.60 (12.00 – 8280.60)	
	Cardiovascular disease	Yes	883.93 ± 436.887	828.20 (255.30 – 1437.50)	0.917
		No	1224.49 ± 1467.127	855.00 (12.00 – 9328.00)	
	Diabetes mellitus	Yes	1402.76 ± 1390.941	972.55 (188.40 – 7340.50)	0.072
		No	1131.21 ± 1451.439	690.25 (12.00 – 9328.00)	
	Hypertension	Yes	1323.44 ± 1673.376	640.55 (132.60 – 9328.00)	0.637
		No	1162.31 ± 1336.442	865.10 (12.00 – 8280.60)	
	Tuberculosis	Yes	780.33 ± 939.838	476.75 (37.10 – 2130.70)	0.416
		No	1220.09 ± 1447.236	859.10 (12.00 – 9328.00)	
	Bronkhial asthma	Yes	2366.55 ± 3946.805	509.65 (166.30 – 8280.60)	0.684
		No	1174.11 ± 1318.282	859.10 (12.00 – 9328.00)	
	Obestity	Yes	606.89 ± 389.056	509.30 (166.30 – 1267.00)	0.208
		No	1238.85 ± 1462.927	863.20 (12.00 – 9328.00)	

Sources: Author, 2022

4. Ferritin Levels and Outcomes of COVID-19 Research Subject

The median of ferritin levels was higher in patients who did not survived (1496.55 ng/ml, SD= 1798.677) compared to those who survived (662.05 ng/ml, SD= 1293.026) (Table 6). Statistical analysis using Mann-Whitney Test was resulted in a significant result ($p< 0.001$), indicating a significant difference between non-survived and survived patients. ROC curve analysis identified a cutoff value of 1032.85 ng/mL, with AUC of 0.701, sensitivity of 63.33% (95% CI: 43.86–80.07%), specificity of 63.39% (95% CI: 53.76–72.29%), positive predictive value of 31.67%, and negative predictive value of 86.59% (Figure 2). This results showed that ferritin level may not good enough to predict disease outcome, with Contingency coefficient of 0.244 which showed a very weak correlation.

Table 6. Ferritin Levels and Outcomes of COVID-19 Subjects

Outcomes	Ferritin Levels			
	Mean ± SD	Median (min – max)	p Value	Contingency coefficient
Survived	1063.97 ± 1293.026	662.05 (12 – 9328)		
Non-survived	1744.23 ± 1798.637	1496.55 (236.6 – 8280.6)	0.001	0.244

Sources: Author, 2022

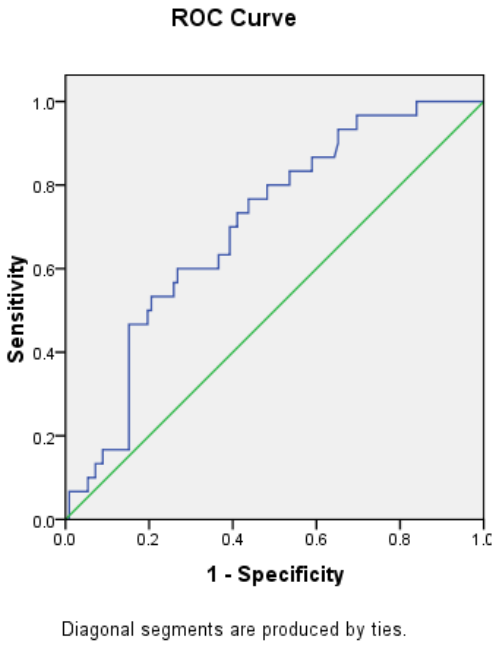

Figure 2. ROC curve of ferritin levels and outcomes

5. Discussion

The subject of this study was COVID-19 patients hospitalized in Isolation Ward of Dr. Soetomo General Academic Hospital, Surabaya, with a total of 142 patients included. According to the demography data, male patients with older age were more prevalent in severe group than in non-severe group. This data is in line with the study by Jin et al., who reported that cases in male with older age were tended

to be more serious than in female's (Jin et al., 2020). In patients on admission, the most common symptoms in both groups were cough, shortness of breath, and fever. The most common symptom that found in non-severe group was cough (80%), while in severe group was shortness of breath (100%). These results are supported by Guan et al. (Guan et al., 2020) that reported fever as the most common symptoms, then followed by cough, which occured in two–thirds of COVID-19 cases. Similarly, a meta-analysis study encompassing 148 studies with 24,410 confirmed COVID-19 patients across nine countries reported that the most common symptoms were fever (78%), cough (57%), and fatigue (31%) (Grant et al., 2020).
There was no significant difference in term of comorbidity factor between both groups, with diabetes mellitus and hypertension representing the most frequent comorbid conditions. This results were in line with a meta-analysis study which identified the most common comorbidities on COVID-19 were hypertension (15.8%), cardiovascular and cerebrovascular disease (11.7%), and diabetes (9.4%) (Paudel, 2020). In this study, we found that 53.4% patients in non-severe group had no comorbidities, and 46.6% patients had comorbidities. Meanwhile, in severe group, 46.4% patients had no comorbidities, and 53.6% patients had comorbidities. Based on correlation test, a significant correlation was found between comorbidity and COVID-19 severity. This findings are parallel with the study by Luo et al. (Luo et al., 2020) which suggested that comorbidities aggravate the risk of COVID-19 severity. A retrospective study by Shi et al. (Shi et al., 2020) reported a higher prevalence of hypertension on severe cases than mild cases of COVID-19 (53.1% vs 16.7%, $p< 0.0001$).
A significant difference were observed in neutrophils and lymphocytes count number in both groups. The median neutrophil count was higher in the non-severe group than in the severe group, whereas the median lymphocyte count was higher in the severe group compared to the non-severe group. There was no significant difference in leukocytes and platelets count number. A study by Zhou et al. also showed median of lymphocyte count was significantly different in non-survivor and survivor group (Zhou et al., 2020). Kong et al. (Kong et al., 2020) proved a significant increase of leukocytes and neutrophils in the group with severe cases compared to mild cases ($p< 0.0001$). In this study, the most common found in chest X-ray of both groups was infiltrate bilateral. This result supported by Lomoro et al.'s and Chen et al.'s study who reported bilateral pneumonia as the most common finding in chest X-ray of COVID-19 patients (N. Chen et al., 2020); (Carcillo et al., 2020). In this study, the highest ferritin level was 9328 ng/ml in severe group. This is similar with a retrospective study by Guang Chen who investigated 21 COVID-19 patients and found an elevation of ferritin levels in severe cases than in moderate cases (G. Chen et al., 2020). Analysis test resulted a significant difference between ferritin levels with COVID-19 severity, with cut off point was 865.1 ng/ml, the value of sensitivity and specificity also showed a good enough value. This results showed that ferritin level is potential to predict severity of disease.
A study by Zhou et al. (Zhou et al., 2020) showed a higher and signficantly different median of ferritin levels in non-survivor and survivor group. Dahan et al. (Dahan et al., 2020) found that ferritin levels were highest in patients with severe COVID-19 (mean: 2817.6 ng/ml), compared to those with moderate (1555 ng/ml) and mild

disease (327.27 ng/ml). In hyperferritinemic condition, it was reported to be associated with the severity of the disease. Their study also showed a significant increase of ferritin levels in moderate and severe group compared to mild group ($p= 0.006$ and $p= 0.005$, respectively) (Huang et al., 2020). A study by Lin et al. (Lin et al., 2020) which involved 147 patients of confirmed COVID-19 found that ferritin levels during initial period of hospitalization was an independent risk factor for COVID-19 severity. Patients were categorized by ferritin levels of ≥ 500 ng/ml as hyperferritinemic group, in which had a higher proportion of severe cases compared to patients without hyperferritinemic (Guan et al., 2020). This study also analyzed if the elevation of ferritin levels was associated with comorbidity presence. According to the stastical analysis, no significant correlation between ferritin levels and comorbidities in COVID-19 patients was observed ($p= 0.110$). This contrasts with meta-analysis study by Cheng et al. which stated that COVID-19 patients with comorbid conditions like diabetes, thromboembolism, and cancer had higher levels of ferritin than COVID-19 patients without comorbidities ($p < 0.01$). However, there were no significant differences of ferritin levels in COVID-19 patients with comorbidities of cardiovascular disease, anemia, bleeding complication, and cerebral ischemia (Cheng et al., 2020).

Ferritin is an iron storage protein, thus elevation of its levels reflects normal iron level and helps to diagnose iron deficiency anemia. Ferritin levels in the circulation also increases during virus infection and may serves as a marker for virus replication (Li et al., 2020). The elevations of ferritin levels due to cytokine storm and secondary haemophagocytic lymphohistiocytosis (sHLH) has been reported in severe COVID-19 patients (Velavan & Meyer, 2020). Cytokine storm in COVID-19 is characterized by the increase of inflammatory cytokines productions, such as IL-6, tumor necrosis factor-α (TNF-α), IL-1β, IL-12, and interferon-γ (IFN-γ), which subsequently stimulate hepatocytes, Kupffer cells, and macrophages to release ferritin (Torti & Torti, 2002). Beyond being a result of excessive inflammation, ferritin itself plays pathogenic roles in the inflammation process through binding with T cell immunoglobulin and TIM-2 via pro-inflammatory mediator expressions (Kernan & Carcillo, 2017). Several studies also show that H chain of ferritin activates macrophages to release inflammatory cytokines (Perricone et al., 2020). The mechanism of hyperferritinemic and severity of disease correlation in COVID-19 patients may caused by: 1) Upregulation of ferritin synthesis by pro-inflammatory cytokines (e.g IL-1β, TNF-α, and IL-6); 2) Cellular damage caused by inflammation, resulting in leakage of intracellular ferritin into the circulation; 3) In acidosis, microvascular environtment and elevated reactive oxygen species (ROS) may free iron from ferritin and is creating hydroxil radical which lead to severe tissue damage and perpetuate the circle of inflammation (Lin et al., 2020).

The survival rate in this study was higher in the non-severe group, with 94.5% of patients surviving compared to 62.3% in the severe group. The median of ferritin levels in COVID-19 patients was higher in patients who did not survived compared to the survived patients. Statistical analysis showed a significant difference between both groups with $p< 0.001$, however further analysis showed that ferritin levels may not good enough to predict disease outcome. This is different with several studies

that reported ferritin levels can be an outcome predictor. A retrospective multicenter studies identified ferritin and IL-6 levels as mortality predictor on 150 cases of confirmed COVID-19 (Dahan et al., 2020). A study by Wu et al. (Wu et al., 2020) also showed that high ferritin levels in patients of confirmed COVID-19 was an independent factor risk associated with ARDS and mortality. Another study showed that patients with dengue fever, Ebola, and COVID-19 could not survived with hyperferritinemic sepsis (Carcillo et al., 2020). Management of COVID-19 patients is one of essential factor which affects the result of the outcomes. Different management in every hospital may contributes to these differencess.

CONCLUSION

This study demonstrated that ferritin levels may serve as a potential biomarker for assessing disease severity, as they were significantly higher in patients with severe COVID-19, thereby indicating the need for more aggressive therapy and closer monitoring. However, ferritin level is a poor predictor to assess outcome of COVID-19 patients.

ABBREVIATIONS

Acute respiratory distress syndrome (ARDS); area under curve (AUC); C-reactive protein (CRP); erythrocyte sedimentation rate (ESR); interferon (IFN); interleukin (IL); receiver operating charecteristics (ROC); reactive oxygen species (ROS); secondary haemophagocytic lymphohistiocytosis (sHLH); tumor necrosis factor (TNF)

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CONSENT FOR PUBLICATION

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The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.