Association Between Ferritin Levels and Sepsis in Patients with COVID-19 at Dr. M. Djamil Hospital

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Abstract

Background: Ferritin is an important mediator of immunomodulatory dysregulation and pro-inflammatory effects, which contribute to cytokine storms that could lead to sepsis in a critically ill patients with COVID-19. The role of ferritin as a biomarker of sepsis in those patients is yet fully understood. The aim of this study is to investigate an association between ferritin levels and sepsis in patients with COVID-19.

Method: This study was a retrospective, cross-sectional study of 474 COVID-19 hospitalized patients at DR M Djamil Hospital.

Result: Most of the COVID-19 patients in this study were between the ages of 18 and 49 (38,61%), female (55,91%), with moderate clinical illness (40,50%), and had one comorbidity (41,14%) with obesity as the most common comorbidity (37,97%). More than half of patients (54,22%) had ferritin levels of ≥ 500 ng/mL (median 1,201 ng/mL with a range of 503–12,010 ng/mL). The incidence of sepsis was significantly higher in the group whose ferritin level was ≥ 500 ng/ml compared to those with less ferritin level (OR = 3,33, 5.99% vs 17.91%, CI 95% 1,74-6,36, p <0.001).

Conclusion: There is a statistically significant association between the ferritin level and sepsis in patiens with COVID-19 at DR M Djamil Hospital.

Keywords: COVID-19, ferritin, sepsis, pro-inflammatory, hyperferritinemia

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[1] Coronavirus 2019 (COVID-19) virus is an enveloped positives single-stranded RNA virus. Coronavirus can cause respiratory, digestive, and nervous system disorders.[2] According to the Global Sepsis Alliance, SARS-CoV-2 can cause sepsis.[3,4]

Sepsis is diagnosed in 19 million people annually and Most patients survive, but approximately one-third of sepsis patients die within 1 year, and up to 40% of patients require rehospitalization within 90 days of discharge.[5] SARS-CoV-2 can induce cytokines storms in patients, resulting in high inflammatory mediators in COVID-19 patients, which is associated with severity and mortality.[6,7]

Brandtner's study suggests that there are changes in iron homeostatic parameters along with inflammation, and also changes that are driven by infection. This study also showed a median high serum ferritin level (567.5 ng/mL, 254.5–1.381 ng/mL) had a statistically significant association with Sequential Organ Failure Assessment (SOFA) score at hospital admission (*P*=0.044), and also there was a statistically significant association with another prognostic score, the Simplified Acute Physiology Score (SAPS II).[5,8]

A study by Garcia et al in pediatric patients with sepsis in Brazil reported that ferritin levels >500 ng/mL had a mortality rate of 58%, a risk of death of 3.2 times, and it predicted death with a sensitivity of 64% and a specificity of 84%. Furthermore, a study by Bennett et al showed that elevated ferritin levels above 1,000 ng/mL and 3,000 ng/mL in hospitalized children were associated with an increased risk of admission to

Pediatric Intensive Care Unit (PICU) and death in the first 5 years.[9,10]

Abumayyaleh MS et al, a cohort study in 2021 of 624 COVID-19 patients with sepsis and 5,213 COVID-19 patients without sepsis found that 69.8% of COVID-19 patients with sepsis and those without sepsis, It was found that 57.7% had elevated ferritin levels. Univariate analysis revealed that increased ferritin was associated with sepsis (odds ratio (OR)=1.88 (95% CI=1.59–2.24; $P<0.001$).[11]

In the study where the ferritin level cut-off value of ≥300 ng/ml as a useful sepsis marker, there was a 60% increase in ferritin from a total of 40 septic patients, but 30% of a total of 20 patients without sepsis also showed the level of ferritin ≥300 ng/ml (sensitivity of 60% and specificity of 70%). Meanwhile, in a study where the ferritin level cut-off value of ≥600 ng/ml as a useful sepsis marker, 27.5% of 40 sepsis patients had increased ferritin, but 10% of a total of 20 patients without sepsis also had ferritin ≥600 ng/ml (sensitivity of 35% and specificity of 90%). In an acute phase, serum ferritin, as a substance in sepsis due to extracellular bacteria, is elevated, but its level is generally not high.[12] Kell in a 2014 study, suggests that ferritin may be a direct signal of cell injury as well as being related to inflammatory processes, particularly when their values are above 600 ng/mL, which indicates a direct association between organ injury and increased ferritin level.[8,13]

Ferritin as a useful marker of inflammation in COVID-19, has an influence on poor outcomes and can be used to estimate clinical deterioration in patients with COVID-19. Ferritin levels correlated with clinical grade, chest radiographic severity, and need for high-flow nasal cannula (HFNC) and/or ventilator supplemental oxygen ($P<0.001$).[14] A study by Lu et al showed that high ferritin levels were associated with a higher rate of severe cases, even death, in patients with COVID-19 ($P=0.0016$).[15]

In 2021, Ochoa et al conducted a study on 50 patients with COVID-19 stages II and III, as well as 24 patients with bacterial sepsis. The study found that the mean ferritin value upon admission to the COVID-19 patient group was 1,105 ng/ml, which is higher than the mean ferritin value in the bacterial sepsis group, which was 525 ng/ml. Ferritin is an acute phase reactant that nonspecifically increased in acute and chronic inflammatory processes but is also increased in other diseases.[16] Although underused to establish the diagnosis and assess the prognosis of death in sepsis, a study demonstrated a correlation between low iron and transferrin levels and high serum ferritin levels in sepsis patients. The higher serum ferritin level in COVID-19 patients in this study strengthens the hypothesis that this phenomena can be grouped a hyperferritinemia syndrome.[16]

The role of ferritin as a biomarker of sepsis in pediatric and neonatal patients is well known, but information on its role in adults is still very limited, especially in sepsis with COVID-19. This is because there are still some studies on the association between ferritin levels and sepsis in COVID-19, this study aims to take a closer look into the concept of a laboratory biomarker in the form of ferritin levels on sepsis in COVID-19 patients.

METHODS

This was a retrospective cross-sectional study to determine the association between ferritin levels and sepsis in confirmed COVID-19 patients treated at Dr. M Djamil Hospital. This study was conducted in the COVID-19 isolation room of Dr. M. Djamil Hospital, Padang, from August 2021 to November 2022. The population of this study was all COVID-19 patients treated at the said hospital from January 1, 2021, to December 31, 2021. We used consecutive sampling to generate sample data from the medical records, with a minimum sample size of 52 people.

Inclusion criteria for this study were COVID-19 patients confirmed by SARS-CoV-2 RT-PCR/TCM results from nasopharyngeal swabs, and had to be ≥18 years of age. Exclusion criteria were patients with a confirmed mild clinical degree of COVID-19 and patients diagnosed with sepsis on initial admission. According to the Third International Consensus, sepsis is life-threatening organ dysfunction due to a dysregulated host response to infection.[11] Data collection was based on patient medical records.

Collected data were statistically analyzed using SPSS version 21. Statistical tests were tested using chi-square. The Research and Ethics Committee of Dr. M. Djamil Hospital, Padang approved this study on November 4, 2022, with No. LB. 02.02/5.7/464/2022.

RESULT

This study was conducted from January 2021 to September 2021 in the isolation room for the COVID-19 treatment at Dr. M. Djamil Hospital, Padang. Received first subjects of 612 confirmed COVID-19 patients, meanwhile, the number of eligible subjects were 474 patients.

Table 1. Characteristics of COVID-19 Subjects treated at RSUP Dr. M. Djamil Hospital, Padang

Characteristic	n (%)
Age (years)	
18–49 years	183 (38.61%)
50–59 years	112 (23.63%)
60–69 years	106 (22.36%)
≥70 years	73 (15.40%)
Gender	
Male	209 (44.09%)
Female	265 (55.91%)
Clinical Degree of Disease	
Moderate	192 (40.50%)
Severe	151 (31.86%)
Critical	131 (27.64%)
Comorbidity	
None	167 (35.23%)
1 comorbid	195 (41.14%)
Patient with comorbid:	
Obesity	180 (37.97%)
Hypertension	86 (18.14%)
Diabetes mellitus	84 (17.72%)
Cardiovascular Disease	29 (6.12%)
Chronic Kidney Disease	17 (3.58%)
Malignancy	13 (2.74%)
Chronic Lung Disease	10 (2.11%)
Cerebrovascular Disease	24 (5.06%)
Chronic Liver Disease	11 (2.32%)
Length of treatment	
<14 days	273 (57.60%)
≥14 days	201 (42.40%)
End of treatment status	
Survive	442 (93.25%)
Died	32 (6.75%)

Table 1 shows the characteristics of subjects with COVID-19 at Dr. M. Djamil Hospital, Padang. Most of the patients were aged 18–49 years (38.61%) and

female (55.91). Most of the subjects had moderate clinical degrees (40.5%), with obesity as the most common type of comorbid i.e. 37.97% of subjects, followed by hypertension (18.14%), and diabetes mellitus (17.72%). The length of treatment was <14 days for most of the subjects. The majority of patients survived (93.25%) at the end of treatment.

Table 2. The Ferritin Levels of COVID-19 Subjects at Dr. M. Djamil Hospital, Padang

Ferritin Levels	n (%)	Median (min – max)
<500 ng/ml	217 (45.78)	130.1 (1–493)
≥500 ng/ml	257 (54.22)	1,201.0 (503 – 1,201)

Table 2 shows an overview of the ferritin levels obtained. There were 217 subjects (45.78%) with ferritin levels <500 ng/mL, with a median ferritin level of 130,1 ng/mL (range 1–493 ng/mL). However, more than half (54.22%) of all subjects had ferritin levels ≥500 ng/mL, with a median ferritin level of 1.201 ng/mL and a range of 503–1,201 ng/mL.

Table 3. Sepsis Incidence in COVID-19 Subjects at Dr. M. Djamil Hospital, Padang

Group	n (%)
Sepsis	58 (12.23%)
Not sepsis	416 (87.76%)

Table 4. Association between Ferritin Levels and Sepsis in Patients with COVID-19 at Dr. M. Djamil Hospital, Padang

Ferritin Levels	Incidence of Sepsis		P	OR
	Sepsis	Not sepsis		
<500 ng/ml	13 (5.99%)	204 (94.01%)	<0.001	3.331
≥500 ng/ml	45 (17.51%)	212 (82.49%)		

Table 3 shows the sepsis incidence was in 58 subjects (12.23%) and 418 subjects were not sepsis (87.76%). Table 4 shows that the incidence of sepsis in COVID-19 patients with ferritin levels ≥500 ng/mL was 17,51%, and the incidence of sepsis in patients with ferritin levels <500 ng/mL (5.99%), the chi-square test showed a value of $P<0.001$, indicating a statistically significant association between ferritin levels and sepsis in subjects with COVID-19 at Dr. M. Djamil Hospital, Padang. The OR was 3.331, which means that patients in the ferritin level group of ≥500 ng/mL have a 3.331 times higher chance of developing sepsis.

DISCUSSION

This study yielded 474 selected subjects that met the inclusion criteria for COVID-19 patients treated

at Dr. M. Djamil Hospital, Padang. The average age of COVID-19 subjects ranged from 18–49 years for 183 people (38.61%) and >50 years for a total of 291 people (61.39%). This is consistent with the study of Wuryantari et al. In 2022, a sample aged 40 and older was found to have a higher prevalence of COVID-19 than other age groups.[17] According to McLaughlin et al in 2020, age is another factor that needs to be considered in COVID-19.[18] Jing et al in 2020 stated that the elderly is more susceptible to COVID-19 compared to the younger ones.[19]

Physiological changes are associated with aging. The aging process, here called immunosenescence, causes T-cell depletion and accumulation of memory T-cells, which alters the recognition and elimination of pathogens, which causes a disparity in the functioning of many systems, especially the immune system, become susceptible to inflammatory processes that result in death. Older patients have higher levels of angiotensin converting enzyme 2 (ACE2) (encoded by the ACE2 gene) and other factors such as weakened immunity, reduced organ function, and underlying conditions that increase the risk of morbidity and mortality. Furthermore, aging results in an ineffective antiviral response due to a disturbance in cytokine release.[20]

Females were found to suffer from COVID-19 more often than males, i.e. 265 subjects (55.91%) is consistent with the study of Chicamy et al in 2021 which found more female (55.6%) than male (44.4%).[21] According to a study by Wuryantari et al in 2022 showed that 95.5% of her sample were in the age group of 18 years and older (n=61,403) and 61.6% (n=39,477) were female.[17] This is also in line with a study by Tao et al in 2020 on the subject of 69 severe cases of COVID-19, 52.17% were females.[22] Furthermore, a study by Chen et al in ACE2 expression has been reported to be increased by up to 100% in the adrenal glands, esophagus, lungs, adipose tissue, heart, blood vessels, and colon in Asian women.[23]

Data from The Chinese National Reporting System in 2020 and the results of Lino et al's study in Brazil in 2020 reported the opposite result, where the ratio of male subjects was higher than females. This difference in results may be due to the ACE2 gene

found on the X chromosome, and circulating levels of ACE2 in males than in females. Differences in the proportion of the sex group of the population in each study location also influenced the results of this study.[24,25]

Our study showed that the majority of patients had at least 1 comorbidity, i.e. 192 patients (41.14%), this is in an accordance with a study by Cheng et al in 2020 which showed that COVID-19 patients who have one or more comorbidities show a poor prognosis.[26] Sepsis is understood to be associated with severity and mortality in which Organ failure that happened in patients with sepsis increases in-hospital mortality by greater than 10%.[11]

The most common comorbidity found in this study was obesity, i.e. 180 subjects (37.97%). Cheng et al's study obtained different results that the most common comorbidity was hypertension (18.14%).[26] Meanwhile, a study Lino et al in 2021 found 38.6% of COVID-19 patients had diabetes.[24] Furthermore, a study by Chicamy et al in 2021, found that two of the commonest comorbidities were diabetes mellitus in 18.3% and hypertension in 12.7% of their subjects.[21]

Obesity is known to have the effect of increasing the risk of experiencing serious and significant clinical events requiring intensive care and poor outcomes. Ilham et al in their study found a statistically significant association between obesity and mortality in COVID-19 subjects in a February 2022 study of 96 subjects in the intensive care unit of M. Djamil Hospital, Padang (P<0.05; OR=2.84; 95% CI=1.12–7.18). There was also a statistically significant correlation with conversion time in COVID-19 subjects (P<0.05; OR=30.00; 95% CI=2.85–31.61), with a statistically significant association with length of stay in COVID-19 subjects (P<0.05; OR=3.67; 95% CI=1.09–12.35).[27] Patients with obesity and overweight tend to have comorbid diseases, i.e. metabolic diseases and cardiovascular diseases.[18]

Bello-Chavola et al in a cross-sectional study of 8,261 COVID-19 subjects showed that obese patients with body mass index >30 kg/m^2 had a higher mortality rate of 13.6% compared to 7.1% in non-obese patients.[28] Adipose or fat tissue can be a reservoir for virus generation. Obesity may increase ACE2

expression, which promotes SARS-CoV-2 cellular entry. Obesity is associated with immune dysfunction that weakens the body and fails to inhibit viral replication. Obesity also reduces lung capacity, which in turn makes ventilation more complicated.[29]

This study showed that most subjects (57.60%) were treated for 14 days or more. Results of a study by Surendra et al. that the median length of patient hospital stay was found to be 24 days, with a range of 13 to 36 days. Meanwhile, the median length of stay in the study by Sanyaolu et al was around 12 days. The majority of subjects survived at the end of treatment, with a percentage of 93.25% and a mortality rate of 6.75%. A study by Osibogun et al that mortality (3.34%) was shown to be lower than recovery (78.98%). Furthermore, Guan et al showed mortality is about 3.1%.[30–32]

Most subjects in our study (54.22%) had ferritin levels ≥ 500 ng/mL, with a median ferritin level of 1.201 ng/mL and a range of 503–1.201 ng/mL. This is different from a study by Sari et al in 2022 at Dr. M Djamil Hospital, Padang, in which most of their subjects (52.8%) had ferritin levels of <500 ng/mL. The difference in the results of this study was due to the fact that this study did not involve a sample group of clinically mild COVID-19 patients, while the study by Sari et al involved a relatively large sample of clinically mild COVID-19 patients, i.e. 45.25%.[14]

Kaushal et al found elevated ferritin levels in COVID-19 patients (SMD=0.889; 95% CI=1.201-0.577; I2=85%). Patients with severe to severe COVID-19 had higher ferritin levels (SMD=0.882; 95% CI=0.738-1.026; I2=85%) compared with patients with mild and moderate COVID-19, and serum ferritin levels on died patients were higher than in surviving patients. Patients (SMD=0.992; 95% CI=0.672-1.172; I2=92.33%). Patients requiring intensive care (SMD=0.674; 95% CI=0.515–0.833; I2=80%) and mechanical ventilation (SMD=0.430; 95% CI=0.258-0.602; I2=32%) had lower serum ferritin compared with those who did not level was high. This means that serum ferritin levels can be used as an important biomarker to help manage COVID-19.[33]

Ferritin levels increase in COVID-19 and are associated with clinical degrees where there is an increase of 1.5 to 5.3 times higher in COVID-19 patients who have severe symptoms compared to those with mild/moderate symptoms. Results of a study by Komariah et al. in 2022, an association was shown between ferritin levels and disease severity in patients with COVID-19.[34] Ferritin levels show a positive correlation with disease severity where ferritin levels increased along with the increase in disease severity.[35,36]

Serum ferritin is actively produced by macrophages (the major immune cell in the lung parenchyma), in which ferritin also can act as a cytokine. Ferritin is secreted in the area of infection, thus ferritin takes on a function as a signaling molecule and direct mediator of the body's immunity in addition to its main function as an iron storage protein. Cytokines can induce the expression of ferritin, but ferritin can also induce the expression of pro- and anti-inflammatory cytokines, so there are pro- and anti-inflammatory mediators between ferritin and cytokines. There may be complex feedback mechanisms controlling.[37]

Ferritin can be used to differentiate severity. Persistent hyperferritinemia is more common with critical COVID-19 than mild disease. Elevated ferritin levels have been associated with increased deaths related to COVID-19, with patients who died exhibiting higher mean ferritin levels than the patients who survived.[35] Many in-hospital patients with elevated serum ferritin levels (>300 g/L) have a much higher mortality rate.[7,38]

The sepsis incidence in patients with COVID-19 in our study was 12.23%. A study Abumayyaleh et al in 2021 in Honduras on 5.837 COVID-19 patients showed 624 people (10.69%) with sepsis and 5.213 people (89.31%) COVID-19 patients without sepsis. This study assess COVID-19 patients at increased risk of developing sepsis. Patients he falls into three risk groups. Low risk group (3.1% to 11.8% chance of sepsis). intermediate risk (24.8–53.8%); and high risk (58.3–100%), concluding that sepsis in COVID-19 is associated with high mortality.[11]

Sepsis also can develop secondary due to bacterial, viral, fungal, and other pathogens, with bacterial pathogens most commonly involved. A total

of 42% of sepsis cases had no isolated bacteria, which suggests that the etiology of sepsis is likely to be non-bacterial. The proportion of viruses involved in one study was very low, i.e. 1% of reported sepsis cases. Viral coinfection is common in respiratory tract infections and can also present with clinical features of sepsis but is often neglected by clinicians. SARS-CoV-2 can cause sepsis in any way, either secondary due to bacterial or fungal infection or not.[39]

A study by Patil et al in 2021, showed that the virus itself plausibly causes septic syndrome as a result of several mechanisms, i.e. immune dysregulation, respiratory disturbance which leads to hypoxia, and metabolic acidosis caused by circulatory dysfunction. The circulatory impairment caused by hypoxia and microvascular dysfunction might end with multi-organ failure seen in COVID-19 patients.[40]

Shappell et al in their study on 200 patients treated for COVID-19 in Massachusetts, United States of America in March 2020-March 2021 found a higher incidence of sepsis, this occurred in 65 people (32.5%), with 70.8% of all sepsis episodes caused by SARS-CoV-2 alone and 26.2% by both SARS-CoV-2 and non-SARS-CoV-2 infections was 3.1% were due to isolated bacterial infections.[41] It was hypothesized that the differences in the incidence of sepsis in this study were due to the different timing of the COVID-19 pandemic under study.

COVID-19 patients with ferritin levels ≥500 ng/ml had a higher incidence of sepsis, namely 17.51%. In this study, a chi-square test was performed, yielding a value of $P<0.001$. There is a statistically significant association between ferritin levels and sepsis, with patients in the group with ferritin levels ≥500 ng/mL having a 3.331-fold higher risk of developing sepsis. This is consistent with a study by Abumayyaleh et al with larger sample size in 2021 i.e. 624 COVID-19 patients with sepsis and 5,213 COVID-19 patients without sepsis. Their study showed that COVID-19 patients with sepsis had a 69.8% increase in ferritin levels, while those without sepsis had a 57.7% increase in ferritin levels. A univariate analysis in their study found that elevated ferritin levels were associated with the incidence of sepsis in patients with COVID-19 ($P<0.001$; OR=1.88; 95% CI=1.59–2.24),

which also means elevated ferritin levels. This level has a cause of 1.88 times more likely to have sepsis.[11]

Several similar studies related to ferritin levels, the sepsis incidences, and COVID-19 include a study conducted by Chen et al in 2022 in their study involving 71 COVID-19 patients with sepsis and 85 COVID-19 patients without sepsis which obtained an average ferritin level in COVID-19 patients with sepsis of 752.4 ng/mL, this value was much higher than COVID-19 patients without sepsis, i.e. 493.63 ng/mL and there was a statistically significant difference in mean ferritin levels in patients with COVID-19 and sepsis compared to those without sepsis ($P=0.006$).[42]

Lino et al in Brazil in 2020 conducted a study on 97 COVID-19 patients and found that an increased ferritin value with a cut-off of 1.873 ng/mL could predict mortality in hospital COVID-19 patients (AUC=0.79; $P<0.001$), sensitivity 68.4% and specificity 79.3%)).[24] A study by Rajanna et al in India in 2021 on 1,977 patients with COVID-19 showed a significant difference in the average serum ferritin levels of patients who died compared to those who recovered, i.e. 1,225.6±2,502.91 ng/ml and 285.71±391.99 ng/ml, respectively. Significant increases in serum ferritin levels in COVID-19 patients who did not survive compared to those who eventually recovered from infection assess the severity and prognosis of COVID-19 proved to be a useful marker for.[43]

Fang et al conducted an analysis of 2,451 sepsis patients from the Intensive Care Medical Information Mart (MIMIC)-IV database in 2022 and found serum ferritin concentrations, elevated SOFA scores, in-hospital mortality, and inter-mortality rates. found that there is a positive linear correlation between ICU, 28-day mortality, 90-day mortality, longer hospital stay, longer ICU stay (all value of $P<0.001$), higher rates of vasopressor use in the first 24 hours of sepsis diagnosis ($P<0.021$). Receiver Operating Characteristic (ROC) analysis concluded that ferritin is an independent prognostic predictor for predicting mortality in patients with sepsis, moderate predictive value (AUC=0.651) with a primary cutoff of 591.5 ng/mL ($P<0.001$; OR=2.29; 95% CI=1.83–2.87), 119% lower risk of in-hospital mortality.[44]

Samuel et al in India in 2021 showed different results, they said the sensitivity of ferritin as a biomarker in sepsis patients is low. The study was conducted in 40 patients with sepsis and 20 without sepsis, with a cut-off value of ≥300 ng/mL. In their study, 60% of patients with sepsis had increased ferritin levels, but 30% of patients without sepsis also revealed ferritin levels >300 ng/ml (60% sensitivity and 70% specificity). Moreover, while the cut-off value of ferritin levels ≥600 ng/ml as a useful marker of sepsis, 27.5% of patients with sepsis had increased ferritin levels, but 10% of patients without sepsis also showed ferritin levels ≥ 600 ng/ml (35% sensitivity and 90% specificity). This difference in results is probably due to the small number of study samples and the inclusion of diverse subjects, i.e. patients who are not infected with COVID-19.[12]

The role of ferritin is to bind the molecules of iron and store them in a bioavailable form for important cellular processes while also preserving proteins, lipids and DNA from the potential harmful and toxic effects of this metallic element. Ferritin is composed of two isoforms, H- and L-, and are differentially expressed in different tissues and have different effects on the inflammatory process.[37] Serum ferritin levels increase rapidly as part of the normal systemic reaction to inflammatory processes, thus a hyperferritinemia is associated with significantly increased mortality and morbidity in patients with sepsis.[10,45] The main regulator of ferritin levels is iron availability, but many different inflammatory cytokines such as IL-1β and IL-6 also regulate iron availability. Up-regulation of hepcidin also affects the production of serum ferritin, in which hepcidin is stimulated by pro-inflammatory cytokines, especially IL-6.[10,33]

Hyperferritinemia has an immunomodulatory effect, i.e. in the form of the release of IL-10 and IL-1β cytokines which have immune activation and immunosuppression effects that later return to inflammatory effects. Hyperferritinemia also stimulates inflammation.[46] Inflammation activates macrophages, monocytes, and neutrophils, releasing inflammatory mediators or proinflammatory cytokines such as TNFα, IL-1β, IL-2, IL-6, interferon-gamma and platelet-activating factor (PAF). These cytokines will affect several organs and cells. Hypotension can occur due to the influence of inflammatory mediators on the walls of blood vessels by inducing the synthesis of nitric oxide (NO). The impact of this excess NO is vasodilatation and capillary plasma leakage, long-lasting hypoxia-related cells organ dysfunction occurs and this usually occurs in septic shock that is not handled properly.[47]

Cytokine exposure also causes endothelial damage which has the effect of increasing capillary permeability, resulting in hypoperfusion and multi-organ ischemia. Inflammatory cytokines circulating systemically will trigger the coagulation cascade, which has an effect on thrombus formation. Thrombus will have the effect of capillary blockage, microvascular occlusion, tissue hypoperfusion, and hypoxia, which may end with multi-organ damage and subsequently, death.[48]

LIMITATIONS

Our study has the advantage of taking total sampling with a large sample size and obtaining a statistically significant association between ferritin levels and in patients with COVID-19 at Dr. M. Djamil Hospital, Padang. The limitation of this study is that there are other factors that also influence the increase in ferritin levels and increased ferritin levels also occur in certain disorders including ARDS, atherosclerosis, cancer, cirrhosis of the liver, CAD, diabetes mellitus, hypertension, metabolic syndrome, multiple sclerosis, myocardial infarction, NAFLD, preeclampsia, RA, sepsis, stroke, and SLE.

CONCLUSION

The majority of COVID-19 patients treated at Dr. M. Djamil Hospital, Padang were in the age group of 18–49 years, female, moderate clinical degree, had 1 comorbidity, with obesity as the most common comorbid, had a length of treatment of <14 days and survived at the end of treatment. Most of the COVID-19 patients at Dr. M. Djamil Hospital, Padang belonged to the group with ferritin levels group of ≥500 ng/ml. There are fewer cases of sepsis than those without sepsis. There are statistically significant association

between the ferritin levels and sepsis in patients with COVID-19 at Dr. M. Djamil Hospital, Padang.

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CONFLICT OF INTEREST

None.

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