

# dr. Diana Nur Asrini - Jurnal Rev 1

*by* Dr. Diana Nur Asrini

---

**Submission date:** 01-Jun-2023 07:30AM (UTC+0800)

**Submission ID:** 2106322678

**File name:** dr.\_Diana\_Nur\_Asrini\_-\_Jurnal\_Rev1.pdf (286.33K)

**Word count:** 6743

**Character count:** 33627



## ASSOCIATION BETWEEN FERRITIN LEVELS AND SEPSIS IN PATIENTS WITH COVID-19 AT DR M DJAMIL HOSPITAL

Diana Nur Asrini<sup>1</sup>, Oea Khairsya<sup>2</sup>, Afriani Afriani<sup>2</sup>

<sup>1</sup>Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Andalas, Padang, DR. M. Djamil General Hospital, Faculty of Medicine, <sup>2</sup>Department of Pulmonology and Respiratory Medicine, Dr. M. Djamil General Hospital, Padang

### Abstract

**Introduction:** 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 COVID-19 patient. 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  $\geq 500$  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  $\geq 500$  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 COVID-19 patients in patients with COVID-19 at DR M Djamil Hospital.

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

### Corresponding Author:

<sup>2</sup>  
Diana Nur Asrini | Department of Pulmonology and Respiration Medicine, Faculty of Medicine, Universitas Andalas, DR. M. Djamil General Hospital, Padang, Indonesia | nurasrini@yahoo.co.id

Submitted: Mei 30<sup>th</sup>, 2023

J Respirol Indones. 2023

### INTRODUCTION

COVID-19 is a disease caused by the SARS-CoV2 virus.<sup>1</sup> Coronavirus 2019 (COVID-19) virus is an enveloped positives single-stranded RNA virus. Coronavirus can cause respiratory, digestive, and nervous system disorders.<sup>2</sup> According to the Global Sepsis Alliance, SARS-CoV-2 can cause sepsis.<sup>3,4</sup>

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.<sup>5</sup> SARS-CoV-2 can induce cytokines storms in patients, resulting in high inflammatory mediators in patients with COVID-19, which is associated with severity and mortality.<sup>6,7</sup>

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, 254.5–1281 ng/mL) had a statistically significant association with SOFA score at hospital admission ( $p = 0.044$ ), and also there was a statistically significant association with another prognostic score, i.e. the Simplified Acute Physiology Score (SAPS II).<sup>5,8</sup>

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 was a predictor of 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.<sup>9,10</sup>

Abumayyaleh MS et al. in their 2021 cohort study of 624 COVID-19 patients with sepsis and, 5213 COVID-19 patients without sepsis found that there were increased ferritin values in 69.8% of COVID-19 patients with sepsis and 57.7% without sepsis. Univariate analysis revealed that increased ferritin was associated with sepsis (odds ratio (OR) = 1.88 (95% CI 1.59 - 2.24,  $p < 0.001$ ).<sup>11</sup>

In the study where the ferritin level cut-off value of  $\geq 300$  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  $\geq 300$  ng/ml (sensitivity of 60% and specificity of 70%). Meanwhile, in a study where the ferritin level cut-off value of  $\geq 600$  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  $\geq 600$  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.<sup>12</sup>

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.<sup>8,13</sup>

Ferritin, as a beneficial 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 the clinical grade, chest X-ray severity, and the need for oxygen support with High Flow Nasal Cannula (HFNC) and ventilator ( $p < 0.001$ ).<sup>14</sup> 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 ( $p = 0.0016$ ).<sup>15</sup>

A study by Ochoa et al. in Honduras in 2021 on 50 patients with COVID-19 stages II and III and 24 patients with bacterial sepsis showed that the mean ferritin value when the patient was admitted to the COVID-19 patient group was 1105 ng/ml, higher than the mean ferritin in the bacterial sepsis group, which was 525 ng/ml. Ferritin is an acute phase reactant that

is nonspecifically increased in acute and chronic inflammatory processes but is also increased in other diseases.<sup>16</sup> 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.<sup>16</sup>

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. Because there are still a few studies on the relationship between ferritin levels and sepsis incidence 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 relationship between the ferritin levels and the sepsis incidence in confirmed COVID-19 patients treated at 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.

The inclusion criteria for this study were confirmed COVID-19 patients from the SARS-CoV-2 RT PCR/TCM results, taken from nasal/nasopharyngeal swabs and they must be in the age group of  $> 18$  years. Exclusion criteria were patients with a confirmed mild clinical degree of COVID-19 and patients with a diagnosis of sepsis at initial admission. Data was collected based on the patient's medical record data. The data collected was analyzed statistically with SPSS version 21. Statistical tests were tested with 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 Padang Hospital. We obtained an initial sample of 612 patients with confirmed COVID-19, meanwhile, the number of samples that met the criteria was 474 patients.

Table 1. Characteristics of COVID-19 Patients treated at RSUP Dr. M. Djamil Padang

Characteristic	Number (%)
<b>Age (years)</b>	
18 – 49 years	183 (38.61)
50 – 59 years	112 (23.63)
60 – 69 years	106 (22.36)
≥ 70 years	73 (15.40)
<b>Gender</b>	
Male	209 (44.09)
Female	265 (55.91)
<b>Clinical Degree of Disease</b>	
Moderate	192 (40.50)
Severe	151 (31.86)
Critical	131 (27.64)
<b>Comorbidity</b>	
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)
<b>Length of treatment</b>	
<14 days	273 (57.60%)
≥14 days	201 (42.40%)
<b>End of treatment status</b>	
Survive	442 (93.25%)
Died	32 (6.75%)

Table 1 shows the characteristics of patients with COVID-19 at Dr. M. Djamil Padang Hospital. Most of the patients were in the age group of 18–49 years (38.61%) and female patients (55.91%). Most of the patients had moderate clinical degrees (40.5%), with obesity as the most common type of comorbid i.e. 37.97% of patients, followed by hypertension (18.14%), and diabetes mellitus (17.72%). The length of treatment was <14 days for most of the patients. The majority of patients survived (93.25%) at the end of treatment.

Table 2. The Ferritin Levels of COVID-19 Patients at Dr. M. Djamil 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 patients (45.78%) who had ferritin levels of less than 500 ng/ml and their median ferritin levels were 130.1 ng/ml, with a range of 1 to 493 ng/ml. Meanwhile, more than half of the total patients (54.22%) had ferritin levels of ≥ 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 Patients at Dr. M. Djamil Padang

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

Table 3. Shows the sepsis incidence was in 58 people (12.23%) and 418 people were not sepsis (87.76%).

Table 4 shows the results that the sepsis incidence in patients with COVID-19 who had ferritin levels of ≥500 ng/ml was 17.51%, which was higher than the sepsis incidence in patients who had ferritin levels below 500 ng/ml (5.99%), and the chi-square test showed a p-value of <0.001, indicated that there was a statistically significant association between ferritin levels and sepsis in patients with COVID-19 at Dr. M. Djamil Padang Hospital. The odds ratio (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.

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

Ferritin Levels	Incidence of Sepsis n (%)		Total n (%)	p-value	OR
	Sepsis	Not sepsis			
<500 ng/ml	13 (5.99)	204 (94.01)	217 (100.0)	< 0.001	3.331
≥500 ng/ml	45 (17.51)	212 (82.49)	257 (100.0)		
<b>Total</b>	58 (12.23)	416 (87.76)	474 (100.0)		

## DISCUSSION

### Characteristics of COVID-19 Patients treated at Dr. M. Djamil Hospital Padang

This study obtained 474 selected samples that fit the inclusion criteria for COVID-19 patients treated at Dr. M. Djamil Hospital Padang. The average age of COVID-19 patients ranged from 18–49 years for 183 people (38.61%) and >50 years for a total of 291 people (61.39%). This is in line with a study by Wuryantari et al. in 2022 which found samples aged over 40 years had a higher positive rate of COVID-19 than other age groups.<sup>17</sup> According to McLaughlin et al in 2020, age is another factor that needs to be considered in COVID-19.<sup>18</sup> Jing QL et al. in 2020 stated that the elderly is more susceptible to COVID-19 compared to the younger ones.<sup>19</sup>

Increasing age is related to physiological changes, the aging process here known as immunosenescence, results in a decrease in T cells and an accumulation memory T cells, which alters the recognition and elimination of pathogens, which causes a disparity in the functioning of many systems, i.e. the immune system, making them more susceptible to inflammatory processes and subsequently, death. Elderly patients have higher ACE2 expression (encoded by the ACE2 gene), and have other factors such as reduced immunity, poor organ function, or 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.<sup>20</sup>

Females were found to suffer from COVID-19 more often than males, i.e. 265 patients (55.91%), this is in line with a study by Chicamy et al. in 2021 which found that there were more females (55.6%) than males (44.4%).<sup>21</sup> A study by Wuryantari et al. in 2022 showed that 95.5% of the sample was in the age group of >18 years (n = 61,403) and 61.6% (n = 39,477) were females.<sup>17</sup> 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.<sup>22</sup> Moreover, a study by Chen et al. Stated that ACE2 expression was increased by up to 100% in adrenal glands, esophagus, lungs,

adipose tissue, heart, blood vessels, and colon in Asian women.<sup>23</sup>

Data from The Chinese National Reporting System in 2020 and the results of Lino K 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.<sup>24</sup>

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 L et al. in 2020 which showed that COVID-19 patients who have one or more comorbidities show a poor prognosis.<sup>26</sup> The most common type of comorbid found in this study was obesity, i.e. 180 patients (37.97%). Cheng L et al.'s study obtained different results, where the most comorbidities were hypertension (18.14%), followed by diabetes mellitus (17.58%).<sup>26</sup> Meanwhile, a study Lino K et al. in 2021 found 38.6% (27/43) of COVID-19 patients had diabetes.<sup>24</sup> 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 patients.<sup>21</sup>

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 in February 2022 on 96 patients in the intensive care unit at M Djamil Hospital, Padang found that there was a statistically significant association between obesity and mortality in COVID-19 patients (p-value <0.05) with OR = 2.84 (95% CI: 1.12- 7.18), there was also a statistically significant correlation to the length of conversion of COVID-19 patients (p-value <0.05) with OR = 30.00 (95% CI: 2.85-31.61) and there was a statistically significant relationship to the length of stay of COVID-19 patients (p<0.05) with OR = 3.67 (95% CI 1.09-12.35).<sup>27</sup> Patients with obesity and overweight tend to have comorbid diseases, i.e. metabolic diseases and cardiovascular diseases.<sup>28</sup> Bello-Chavola et al in a cross-sectional study of 8,261 COVID-19 patients

showed that obese patients (body mass index, BMI >30 kg/m<sup>2</sup>) had a higher mortality rate of 13.6% compared to non-obese patients of 7.1%.<sup>29</sup> 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.<sup>30</sup>

This study showed that most patients (57.60%) were treated for 14 days or more. The results of Surendra et al.'s study stated that the median length of stay of patients was 24 days, with a range of 13–36 days. Meanwhile, the median length of stay in the study by Sanyaolu et al. was around 12 days.<sup>31,32</sup> The majority of patients 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.'s showed that the mortality rate (3.34%) was lower than the recovery rate (78.98%). Furthermore, Guan et al.'s showed a mortality rate of around 3.1%.<sup>26</sup>

## Ferritin Levels of COVID-19 Patients at Dr. M. Djamil Padang

Most of the patients (54.22%) in our study had ferritin levels of  $\geq 500$  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 EP et al. in 2021 at M Djamil Hospital, Padang, in which most of their patients (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 EP et al. involved a relatively large sample of clinically mild COVID-19 patients, i.e. 45.25%.<sup>14</sup>

Karanvir Kaushal et al found higher ferritin levels in patients with COVID-19 [SMD 0.889 (95% C.I. 1.201, 0.577),  $I^2 = 85\%$ ]. Severe to critical COVID-19 patients showed higher ferritin levels compared to the mild and moderate COVID-19 patients [SMD 0.882 (0.738, 1.026),  $I^2 = 85\%$ ], whereby the patients who died had higher serum ferritin levels than with survived patients

[SMD 0.992 (0.672, 1.172),  $I^2 = 92.33\%$ ]. Patients requiring ICU [SMD 0.674 (0.515 to 0.833),  $I^2 = 80\%$ ] and mechanical ventilation [SMD 0.430 (0.258, 0.602),  $I^2 = 32\%$ ] had higher serum ferritin levels compared to those who did not. This means that serum ferritin levels can be used as an important biomarker that can assist in the management of COVID-19.<sup>33</sup>

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. The results of a study by Komariah et al. in 2022 showed that there was a relationship between ferritin levels and disease severity in COVID-19 patients.<sup>34</sup> Ferritin levels show a positive correlation with disease severity where ferritin levels increased along with the increase in disease severity.<sup>35,36</sup> 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. Since cytokines can induce ferritin expression, but ferritin can also induce pro- and anti-inflammatory cytokines expression, a complicated feedback mechanism between ferritin and cytokines controlling pro- and anti-inflammatory mediators may exist.<sup>37</sup>

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.<sup>35</sup> Many in-hospital patients with elevated serum ferritin levels (>300 g/L) have a much higher mortality rate.<sup>7,38</sup>

## Sepsis Incidence in COVID-19 Patients at Dr. M. Djamil Hospital Padang

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 was conducted using The International Health Outcome Predictive Evaluation (HOPE) Sepsis Score which consists of nine factors useful in assessing patients with COVID-19 at high risk for developing sepsis, grouping patients into three risk groups, i.e., the low-risk group (probability of sepsis 3.1-11.8%); medium risk (24.8-53.8%); and high risk (58.3-100%), and it was concluded that sepsis in COVID-19 is associated with a high mortality rate.<sup>11</sup>

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.<sup>39</sup>

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.<sup>39</sup>

Shappell CN 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, which occurred in 65 people (32.5%), of which 70.8% of the total episodes of sepsis were caused by SARS-CoV-2 alone, 26.2% were caused by both SARS-CoV-2 and non-SARS-CoV-2 infection, and 3.1% were caused by isolated bacterial infection.<sup>40</sup> The difference in the sepsis incidence in this study was thought due to the difference in the time of the COVID-19 pandemic during the study.

### Association between Ferritin Levels and Sepsis in Patients with COVID-19 at Dr. M. Djamil Padang

There were more sepsis incidences in Covid-19 patients who had ferritin levels  $\geq 500$  ng/ml, i.e. 17.51%. The chi-square test was carried out in this study and a p-value of  $<0.001$  was obtained which indicated that there was a statistically significant association between ferritin levels and sepsis in patients with COVID-19 at Dr. M. Djamil Hospital Padang and the patients in the ferritin level group of  $\geq 500$  ng/ml have a 3.331 times higher chance of developing sepsis. This is in line with a study by Abumayyaleh MS et al. in 2021 with a larger sample size, i.e. 624 COVID-19 patients with sepsis and 5,213 COVID-19 patients without sepsis. Their study showed that there was an increase in ferritin levels in COVID-19 patients with sepsis i.e. 69.8 %, meanwhile, it was 57.7% in patients without sepsis. The univariate analysis in their study stated that increased ferritin was associated with the sepsis incidence in patients with COVID-19 (odds ratio (OR) = 1.88 (95% CI 1.59 - 2.24,  $p < 0.001$ ) which also meant that increased ferritin had a probability of 1, 88 times higher to be sepsis.<sup>11</sup>

Several similar studies related to ferritin levels, the sepsis incidences, and COVID-19 include a study conducted by Chen HY 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 between the average ferritin value in patients COVID-19 with sepsis compared to those without sepsis ( $p=0.006$ ).<sup>41</sup>

Lino K 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%).<sup>24</sup> 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.  $1,225.6 \pm 2,502.91$  ng/ml and  $285.71 \pm 391.99$  ng/ml, respectively. A significantly increased serum ferritin level in COVID-19 patients who did not survive compared to those who eventually recovered from infection proved it to be a beneficial marker for estimating the severity and prognosis of COVID-19.<sup>27</sup>

Fang YP et al. in 2022 conducted an analysis of 2,451 patients with sepsis from the Medical Information Mart for Intensive Care (MIMIC)-IV database and found that there was a positive linear association between the serum ferritin level, increased SOFA score, hospital mortality, ICU mortality, 28 days mortality, 90 days mortality, longer duration of hospital stay, longer duration of ICU stay (all with a p-value of  $<0.001$ ), a higher percentage of vasopressor use during 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 591.5 ng/ml as a prime cut-off value (OR 2.29, 95% CI, 1.83-2.87 and  $p < 0.001$ ), and the risk of death in hospital by 119%.<sup>43</sup>

Samuel MS et al. in India in 2021 showed different results, in which they stated that ferritin has low sensitivity as a biomarker in sepsis patients. The study was conducted on 40 patients with sepsis and 20 patients without sepsis, and they obtained a cut-off value of  $\geq 300$  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).<sup>5</sup> Moreover, while the cut-off value of ferritin levels  $\geq 600$  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  $\geq 600$  ng/ml (35% sensitivity and 90% specificity). This difference in results is likely due to the smaller number of study samples and involving different subjects, i.e. patients without COVID-19.<sup>12</sup>

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.<sup>37</sup> Blood 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.<sup>10,33</sup> The primary modulator of ferritin levels is iron availability, but many different inflammatory cytokines, such as IL-1 $\beta$  and IL-6 can also regulate them. Up-regulation of hepcidin also affects the production of serum ferritin, in which hepcidin is stimulated by pro-inflammatory cytokines, especially IL-6.<sup>44-45</sup>

Hyperferritinemia has an immunomodulatory effect, i.e. in the form of the release of IL-10 and IL-1 $\beta$  cytokines which have immune activation and immunosuppression effects that later return to inflammatory effects. Hyperferritinemia also stimulates inflammation.<sup>46</sup> Inflammation will cause activated macrophages, monocytes, and neutrophils and release inflammatory mediators or proinflammatory cytokines such as TNF  $\alpha$  and IL-1 $\beta$ , 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.<sup>47</sup>

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.<sup>48</sup>

Our study has the advantage of taking total sampling with a large sample size and obtaining a

statistically significant relationship between ferritin levels and the sepsis incidence in COVID-19 patients at RSUP Dr. M. Djamil 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

<sup>16</sup> The majority of patients with COVID-19 in our study 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 <sup>1</sup> <14 days and survived at the end of treatment. Most of the COVID-19 patients at Dr. M. Djamil Padang were in the ferritin levels group of  $\geq 500$  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.

## REFERENCES

- Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J*. 2020;55:9–11.
- Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. Vol. 83, *Journal of the Chinese Medical Association*. Wolters Kluwer Health; 2020. p. 217–20.
- Global Sepsis Alliance. COVID-19/CORONA VIRUS/SARS-COV-2. Global Sepsis Alliance. 2020. p. 1–14.
- da Silva Ramos FJ, de Freitas FGR, Machado FR. Sepsis in patients hospitalized with coronavirus disease 2019: how often and how severe? *Curr Opin Crit Care*. 2021 Oct;27(5):474–9.
- Brandtner A, Tymoszyk P, Nairz M, Lehner GF, Fritsche G, Vales A, et al. Linkage of alterations in systemic iron homeostasis to patients' outcome in sepsis: A prospective study. *J Intensive Care*. 2020;8(1):1–13.
- Beltrán-garcía J, Osca-verdegel R, Pallardó F V, Ferreres J, Rodríguez M, Mulet S, et al. Sepsis and Coronavirus Disease 2019: Common Features and Anti-Inflammatory Therapeutic Approaches. *Soc Crit Care Med Wolters Kluwer Heal*. 2020;(19):1–4.
- 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 (London, England)*. 2020 Mar;395(10229):1054–62.
- Banchini F, Cattaneo GM, Capelli P. Serum ferritin levels in inflammation: a retrospective comparative analysis between COVID-19 and emergency surgical non- COVID-19 patients. *world J Emerg Surg*. 2021;3:3–9.
- Carcillo JA, Kernan KK, Horvat CM. Why and How Is Hyperferritinemic Sepsis Different From Sepsis Without Hyperferritinemia? *Pediatr Crit Care Med*. 2020;21(5):509–12.
- Garcia PCR, Longhi F, Branco RG, Piva JP, Lacks D, Tasker RC. Ferritin levels in children with severe sepsis and septic shock. *Acta Paediatr*. 2007 Dec;96(12):1829–31.
- Abumayyaleh M, Nuñez-Gil JJ, El-Battrawy I, Estrada V, Becerra-Muñoz VM, Uribarri A, et al. Sepsis of Patients Infected by SARS-CoV-2: Real-World Experience From the International HOPE-COVID-19-Registry and Validation of HOPE Sepsis Score. *Front Med*. 2021;8(October):1–10.
- Samuel MS, Latha R, Kavitha K, Sivasubramanian V. A study on biomarkers of sepsis and potential role of procalcitonin and ferritin marker in diagnosis, prognosis and treatment. *J Fam Med Prim care*. 2022/06/30. 2022 Jun;11(6):2608–12.
- Kell DB, Pretorius E. Serum ferritin is an important inflammatory disease marker, as it is mainly a leakage product from damaged cells. *Metallomics*. 2014;6(4):748–73.
- Sari EP, Medison I, Sari EP. Association Between Ferritin Levels and Severity of COVID-19 in RSUP Dr. M. Djamil. *J Respirologi Indones*. 2022;42:237–43.
- Qin L, Li X, Shi J, Yu M, Wang K, Tao Y, et al. Gendered effects on inflammation reaction and outcome of COVID-19 patients in Wuhan. *J Med Virol*. 2020 Nov;92(11):2684–92.
- Linarez Ochoa NE, Rodríguez G, Reyes ID, Rico Rivas KM, Ramírez C, Durón RM. Differences in inflammatory markers between coronavirus disease 2019 and sepsis in hospitalised patients. *Clin Epidemiol Glob Heal*. 2022;15:101059.
- Setiadi W, Rozi IE, Safari D, Daningrat WOD, Johar E, Yohan B, et al. Prevalence and epidemiological characteristics of COVID-19 after one year of pandemic in Jakarta and neighbouring areas, Indonesia: A single center study. *PLoS One*. 2022;17(5 May):1–9.
- McLaughlin KM, Bechtel M, Bojkova D, Münch C, Ciesek S, Wass MN, et al. COVID-19-

- Related Coagulopathy-Is Transferrin a Missing Link? *Diagnostics* (Basel, Switzerland). 2020 Jul;10(8).
19. Goldstein E, Lipsitch M, Cevik M. On the Effect of Age on the Transmission of SARS-CoV-2 in Households, Schools, and the Community. *J Infect Dis*. 2021 Feb;223(3):362–9.
20. Indriyani N, Sabri Y, Afriani A. Association Between Comorbidities and Outcome of COVID-19 Patients at dr. M. Djamil General Hospital Padang. *Respir Sci*. 2022;3(1):38–50.
21. 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. 2022;10:1056–61.
22. Liu T, Zhang J, Yang Y, Ma H, Li Z, Zhang J, et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. *EMBO Mol Med*. 2020;12(7):1–12.
23. Chicamy Y, Safitri A, Nindrea R. Serum Ferritin Levels for the Prediction of Mortality among COVID-19 Patients in an Indonesia ' s National Referral Hospital. 2022;10:1056–61.
24. Lino K, Macedo G, Guimarães C, Santos L, Caroline A, Faustino R, et al. Serum ferritin at admission in hospitalized COVID-19 patients as a predictor of mortality. *Soc Bras Infectol*. 2021;5(2):1–6.
25. Krishnan A, Hamilton J, Alqahtani S, Woreta T. A narrative review of coronavirus disease 2019 (COVID-19): clinical, epidemiological characteristics, and systemic manifestations. *Intern Emerg Med*. 2021;16(4):815–30.
26. 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 Oct;34(10):e23618.
27. T Liu T, J Zhang J, Y Yang Y, H Ma H, Z Li Z J, Zhang J et al. The role of interleukin-6 in monitoring severe case of coronavirus disease 2019. *EMBO Mol Med*. 2020;12(7):1–12.
28. K-M McLaughlin, M Bechtel M, D Bojkova D, C Münch C, S Ciesek S, WN Wass MN et al. COVID-19-Related Coagulopathy-Is Transferrin a Missing Link? *Diagnostics*. (Basel, Switzerland). 10(8).
29. Hippchen T, Altamura S, Muckenthaler M, Merle U. Hypoferremia is Associated With Increased Hospitalization and Oxygen Demand in COVID-19 Patients. *HemaSphere*. 2020;4(6):1–9.
30. Sawadogo W, M MT, A AG, Adera T. Overweight and obesity as risk factors for COVID-19-associated hospitalisations and death: systematic review and meta-analysis. *BMJ Nutr Prev Heal*. 5(1):10–8.
31. Tojo K, Sugawara Y, Oi Y, Ogawa F, Higurashi T, Y YY. The U-shaped association of serum iron level with disease severity in adult hospitalized patients with COVID-19. *Sci Reports*. 2021;11(1):1–7.
32. Sonnweber T, Boehm A, Sahanic S, Pizzini A, Aichner M, Sonnweber B. Persisting alterations of iron homeostasis in COVID-19 are associated with non-resolving lung pathologies and poor patients' performance: a prospective observational cohort study. *Respir Res*. 21(1):1–9.
33. Kaushal K, Kaur H, Sarma P, Bhattacharyya A, Sharma DJ, Prajapat M, et al. Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis. *J Crit Care*. 2022 Feb;67:172–81.
34. Rajanna A, Krishnegowda, Govindaiah R. To Correlate Serum Ferritin Levels with Clinical Outcome in Covid-19 Patients. *Asian J Med Sci*. 2021;12(5):25–9.
35. J S, Ye G, Shi K, Wan Y, Luo C, Aihara H. Structural basis of receptor recognition by SARS-CoV-2. *Nature* [Internet]. 2020;581(7808):1–18.
36. Wern N, Tipih T, Makoah N, Vermeulen J, Goedhals D, Sempa J. Comorbidities in SARS-CoV-2 patients: A systematic review and meta-analysis. *MBio*. 2021;12(1):1–12.
37. 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.
38. Suriawinata E, Mehta KJ. Iron and iron-related proteins in COVID-19. *Clin Exp Med*. 2022;(0123456789).
39. Tufan Z, Kayaaslan B, MeR M. COVID-19 and Sepsis. *Turkish Journal of Medical Sciences*. 51(7):3301–11.
40. Shappell C, Klompas M, Kanjilal S, Chan C, Rhee C. Prevalence, clinical characteristics and outcomes of sepsis caused by severe acute respiratory syndrome coronavirus 2 versus other pathogens in hospitalized patients with COVID-19. *Critical care explorations*. 4(5):1–8.
41. L LC, Li H, Li L, Liu C, Yan S, Chen H. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Lab Anal*. 34(10):1–18.
42. 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):25–9.
43. Fang Y, Zhang, Z G, Ren C, Zhang Y, Liu Q. Effect of Serum Ferritin on the Prognosis of Patients with Sepsis: Data from the MIMIC-IV Database. *Emerg Med Int*. 2022;1–10.
44. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y. Risk factors for severity and mortality in adult

- COVID-19 inpatients in Wuhan. *J Allergy Clin Immunol.* 2020;146(1):110–8.
45. Langford B, So M, Raybardha S, Leung V, Westwood D, MacFadden D. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect.* 2020;26(12):1622–9.
46. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. *Int Immunol.* 2017 Nov;29(9):401–9.
47. Irvan I, Febyan F, Suparto S. Sepsis dan Tata Laksana Berdasar Guideline Terbaru. *JAI (Jurnal Anestesiologi Indones.* 2018;10(1):62.
48. S SR, Brito-zerón P, Sisó-almirall. Haemophagocytic syndrome and COVID-19. *ARheumatology, Clin.* 40(4):1233–44.

ORIGINALITY REPORT

---

19%

SIMILARITY INDEX

19%

INTERNET SOURCES

14%

PUBLICATIONS

6%

STUDENT PAPERS

---

PRIMARY SOURCES

---

1	jurnalrespirologi.org Internet Source	5%
2	bioscmed.com Internet Source	2%
3	Submitted to Surabaya University Student Paper	2%
4	www.jurnalrespirologi.org Internet Source	1%
5	journals.lww.com Internet Source	1%
6	Karanvir Kaushal, Hardeep Kaur, Phulen Sarma, Anusuya Bhattacharyya et al. "Serum ferritin as a predictive biomarker in COVID-19. A systematic review, meta-analysis and meta-regression analysis", Journal of Critical Care, 2022 Publication	1%
7	cegh.net Internet Source	1%

---

8	<a href="https://e-tarjome.com">e-tarjome.com</a> Internet Source	1 %
9	<a href="https://journals.plos.org">journals.plos.org</a> Internet Source	1 %
10	<a href="https://www.researchgate.net">www.researchgate.net</a> Internet Source	1 %
11	"Lung Inflammation in Health and Disease, Volume II", Springer Science and Business Media LLC, 2021 Publication	1 %
12	Submitted to Badan PPSDM Kesehatan Kementerian Kesehatan Student Paper	1 %
13	Akhilesh Mahajan, Jonathan Moore, Anup K Singh, Margarita Oks. "Impact of Timing of Tocilizumab Use in Hospitalized Patients With SARS-CoV-2 Infection", Respiratory Care, 2022 Publication	1 %
14	<a href="https://www.frontiersin.org">www.frontiersin.org</a> Internet Source	1 %
15	<a href="https://jurnal.poltekeskupang.ac.id">jurnal.poltekeskupang.ac.id</a> Internet Source	1 %
16	<a href="https://mdpi-res.com">mdpi-res.com</a> Internet Source	1 %

17

Anna Brandtner, Piotr Tymoszek, Manfred Nairz, Georg F. Lehner et al. "Linkage of alterations in systemic iron homeostasis to patients' outcome in sepsis: a prospective study", *Journal of Intensive Care*, 2020

Publication

1 %

18

Carlo Perricone, Elena Bartoloni, Roberto Bursi, Giacomo Cafaro, Giacomo Maria Guidelli, Yehuda Shoenfeld, Roberto Gerli. "COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy", *Immunologic Research*, 2020

Publication

1 %

Exclude quotes On

Exclude matches < 1%

Exclude bibliography On