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The role of serum ferritin level and disease severity in COVID-19 with type 2 diabetes mellitus patients

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ABSTRACT

Introduction: The disease progression of coronavirus disease 2019 (COVID-19) in individuals with comorbidities, such as type 2 diabetes mellitus (T2DM) in particular, has been associated with the occurrence of the cytokine storm. Ferritin, an acute-phase protein indicating inflammation, has been linked to T2DM and the severity of COVID-19. Our study aimed to investigate the association between the level of ferritin and the severity of COVID-19 in T2DM patients.

Methods: A cross-sectional study was conducted among COVID-19 patients admitted at Dr. Soetomo General Hospital, Surabaya, from April to September 2020. The patients who met the inclusion criteria were enrolled in the study. The data used in this study was secondary data obtained from the medical records at Dr. Soetomo General Hospital, which consisted of serum ferritin levels, the severity of COVID-19, the results of blood analysis, and other demographic and clinical characteristics (age, gender, hypertension, the number of complaints, and vital signs). Data analysis was performed using SPSS software and presented in percentage (%), mean ± standard deviation (SD), or median (min-max). A chi-square test was carried out to identify the association between serum ferritin level and the severity of COVID-19 in T2DM patients at α=0.05.

Results: Of the total 159 patients were included and 80.8% of them had moderate severity of COVID-19, whereas the rest (19.5%) had severe COVID-19. Out of total patients, 78.6% had ferritin levels of ≥400 mg/dL, suggesting hyperferritinemia syndrome (mean ± SD: 1177.21 ± 1275.90 mg/dL). The Chi-squared analysis revealed a significant association between serum ferritin levels with the severity of COVID-19 in T2DM patients (p=0.024).

Conclusion: There was a significant relationship between serum ferritin levels and the severity of COVID-19 in T2DM patients and further study with a bigger sample size is needed to confirm this finding.

Keywords: Serum ferritin; COVID-19; disease severity; type 2 diabetes mellitus, Indonesia.
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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a lung infection caused by SARS-CoV-2 and has disturbed many community aspects.[1] The disease manifestations vary among infected individuals, depending on the body response to the infections and their effect on healthy body tissues. Symptoms might start from fever, dry cough, to shortness of breath. Other symptoms include headache, dizziness, weakness, vomiting, and diarrhea. In the case of acute respiratory distress syndrome (ARDS), mild to significant functional impairments may occur owing to hypoxia.[2-4] Some factors such as old age and certain comorbidities, including cardiovascular disease (10.5%), diabetes mellitus (7.3%), chronic respiratory disease (6.3%), hypertension (6%), and cancer (5, 3%) can worsen the progression of COVID-19 and have been reportedly associated with a high rate of morbidity and mortality.[3-10] COVID-19 is also associated with significant long-term symptoms.[11,12]

Approximately 5%-31% prevalence of DM in COVID-19 has been reported worldwide.[9,13-16] Type 2 diabetes mellitus (T2DM) is associated with the critical condition of COVID-19.[17-19] A recent study involving 1099 COVID-19 patients found that 16.2% of patients with severe degree had diabetes.[20] Another study among 52 critically ill adult patients admitted to the Intensive Care Unit revealed that 22% of non-survivors also had diabetes.[20] T2DM has also been associated with a high probability of developing ARDS, septic shock, and death among pneumonia COVID-19 patients.[18,21,22] In Indonesia, the prevalence of DM was approximately 8.5 % in 2018, affecting around 20.4 million people according to the data of Basic Health Research (Riskesdas) and 10.6 million people in 2019 according to the International Diabetes Federation 2019.[23]

The progression of the COVID-19 severity in patients is closely associated with the cytokine storm, showing an exaggerated immune response to viral infection. Various acute-phase proteins indicating inflammation have been known and used for the determination of infections and cell damage, including C-reactive protein and ferritin. Ferritin is an iron (Fe)-binding protein in cells responsible for maintaining Fe metabolism and balance.[24] Elevated ferritin in the blood circulation due to massive cell damage during the acute inflammatory process will result in hyperferritinemia syndrome,[25,26] thereby making it an important inflammatory disease marker.[27] Several studies reported that ferritin

levels affect the risks for infectious and inflammatory diseases including COVID-19.[28] In addition, ferritin has also been reportedly increased in DM patients and is considered as one of the predictors of T2DM.[22] However, to the best of our knowledge, studies regarding the relationship between the level of ferritin and comorbidity-associated predictors aggravating the condition of COVID-19 patients such as T2DM in particular, are still limited in Indonesia. Therefore, the aim of this study was to evaluate the association between serum ferritin levels and the severity of COVID-19 in patients with T2DM.[21]

METHODS

Study design and sample collection

A cross-sectional study was carried out among COVID-19 patients admitted to Dr. Soetomo General Hospital from April to September 2020. Patients ≥ 18 years of age, diagnosed with T2DM prior to or after being admitted to the hospital, diagnosed with COVID-19, and had a medical record of serum ferritin during the first 10 days of hospitalization were enrolled in the study after being previously informed about the study and provided written consent. On the other hand, patients with incomplete medical records; having other comorbidities increasing the level of ferritin; having chronic kidney disease, liver disease, cardiovascular disease, thalassemia, anemia, and malignancy; and those who were pregnant, smokers, and obese were excluded.

Study variables and data collection

The data used in this study was secondary data obtained from the medical records at Dr. Soetomo General Hospital, Surabaya. It included the patients' serum ferritin level as a dependent variable, the severity of COVID-19 as an independent variable, and the results of blood glucose analysis for the determination of T2DM: the levels of random blood glucose (RBG), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), and 2-hour postprandial blood glucose (2hPPBG). Other demographic and clinical characteristics such as age, gender, hypertension, number of complaints, C-reactive protein (CRP), and vital signs were also collected.

Serum ferritin analysis (collected from the patient's venous blood) was performed during the first 10 days of hospitalization and classified into two categories: normal (≤400 mg/dL) and hyperferritinemia syndrome (≥400 mg/dL). COVID-19 was determined at admission based on the World Health Organization (WHO) criteria for COVID-19. Further, the severity of COVID-19 was decided based on the guidelines for the management of COVID-19 in Indonesia and classified as moderate (with complaints of pneumonia, fever, cough, dyspnea, rapid breathing, and SpO2 of ≥93%) and severe (with pneumonia symptoms, fever, cough, dyspnea, rapid breathing, respiratory rate of >30x/minute, ARDS, and SpO2 of <93%.[29] Blood glucose test was also performed to support the diagnosis of T2DM.

Statistical analysis

The collected data were analyzed using SPSS software. Univariate analysis was conducted to provide the distribution of frequency of the tested variables. Numerical variables such as age, HbA1c, RBG, FBG, and 2hPPBG were presented in percentage (%), mean ± standard deviation (SD), and median (min-max). Bivariate analysis using the chi-square test was carried out to identify the association between serum ferritin level and the severity of COVID-19 in T2DM patients. A p of ≤0.05 was considered statistically significant.

RESULTS

A total of 159 COVID-19 patients with T2DM were enrolled in this study. The patient's demographics and clinical characteristics are summarized in Table 1. The mean age of the patients was 55.89 years (median: 56 years; range: 29-83 years). More than half of the patients were female (57.2%), have hypertension (55.3%), and possessed more than one clinical complaint (84.3%). The majority of the patients (74.3%) showed rapid breathing (respiratory rate median: 22x/minute) but normal saturated oxygen in general (mean ± SD: 96.84 ± 3.24). In terms of T2DM, 59.1% of the patients had high

Table 1. Distribution of demographic and clinical characteristics of the COVID-19 patients with T2DM.

Characteristics	n	Frequency
Age (year)	159	
Mean ± SD		55.89 ± 10.84
Median (min-max)		56 (29-83)
Gender	159	
Male		68 (42.8%)
Female		91 (57.2%)
Hypertension	159	
Yes		88 (55.3%)
No		71 (44.7%)
Complaints	159	
< 1		25 (16.3%)
> 1		134 (84.3%)
Heart rate (beats/minute)	154	
Mean ± SD		94.48 ± 14.20
Median (min-max)		95 (57-133)
Temperature (°C)	154	
36-37.5		138 (86.8%)
>37.5		16 (10.1%)
Respiratory rate (breaths/minute)	152	
Mean ± SD		22.92 ± 2.75
Median (min-max)		22 (18-37)
<12		0
12-20		39 (25.7%)
>20		113 (74.3%)

level of RBG (mean ± SD: 251.52 ± 125.24 mg/dL), 79.8% had elevated FBG (mean ± SD: 209.92 ± 92.39 mg/dL), and 61.6% had increased HbA1c (mean ± SD: 10.24 ± 3.21%). Furthermore, the vast majority of the patients (91.8%) had a significant rise in CRP (≥0.3 mg/dL; total mean ± SD: 10.10 ± 9.26 mg/L), whereas 78.6% showed hyperferritinemia (serum ferritin of ≥400 mg/dL). Moderate pneumonia severity was observed in 80.5% of the patients, whereas the rest (19.5%) were notably in severe condition.

Table 2 presented the association of ferritin level with the severity of COVID-19 in T2DM. Diabetic COVID-19 patients with either moderate or severe pneumonia tended to possess abnormal or significantly high values of serum ferritin (≥400 mg/dL). The result of the chi-square analysis suggested a significant association between the level of ferritin and the severity of COVID-19 among patients with T2DM (p=0.024).

In order to address any possible risk factor for hyperferritinemia syndrome, we also evaluated the relationship between the patients characteristics (age, gender, hypertension, number of complaints, T2DM parameters, and other vital signs) with the level of serum ferritin. Our chi-square analysis suggested that there was no significant association between the patients' characteristics and serum ferritin level (Table 3).

Characteristics	n	Frequency
SpO2 (%)	159	
Mean ± SD		96.84 ± 3.24
Median (min-max)		97 (67-100)
<91		3 (1.9%)
91-95		17 (10,7%)
>95		138(86.8%)
RBG (mg/dL)	159	
Mean ± SD		251.52 ± 125.24
Median (min-max)		225 (27-683)
<140		29 (18.2%)
140-199		36 (22.6%)
≥200		94 (59.1%)
FBG (mg/dL)	119	
Mean ± SD		209.92 ± 92.39
Median (min-max)		201 (58-503)
<100		11 (9.2%)
100-125		13 (10.9%)
≥126		95 (79.8%)
2hPPBG (mg/dL)	28	
Mean ± SD		250 ± 116.45
Median (min-max)		219 (89-535)
<140		6 (21.4%)
140-199		5 (17.9%)
≥200		17 (60.7%)
HbA1C (%)	112	
Mean ± SD		10.242 ± 3.21
Median (min-max)		9.80 (5.30-19.70)
<7.5		28 (25.0%)
7.5-9		15 (13.4%)
≥9		69 (61.6%)
CRP (mg/dL)	159	
Mean ± SD		10.10 ± 9.26
Median (min-max)		7.80 (0.10-40)
<0.3		13 (8.2%)
≥0.3		146 (91.8%)
Ferritin (ng/dL)	159	
Mean ± SD		1177.21 ± 1275.90
Median (min-max)		775.7 (9.50-7978.0)
<400 (normal)		34 (21.4%)
≥400 (hyperferritinemia syndrome)		125 (78.6%)
The severity of COVID-19	159	
Moderate		128 (80.5%)
Severe		31 (19.5%)

SD: Standard deviation

Table 2. Association between the ferritin level with the severity of COVID-19 in patients with T2DM.

	Severity, n (%)		Total, n (%)	p-value	Contingency coefficient
	Moderate	Severe			
Ferritin levels, n (%)					
<400	32 (94.1)	2 (5.9)	34 (21.4)	0.024	1.176
≥400	96 (76.8)	29 (23.2)	125 (78.6)		
Total	128 (80.5)	31 (19.5)	159 (100)		

DISCUSSION

Diabetes mellitus (DM) has been considered as one of the comorbidities conferring worse prognosis and increasing the mortality rate in COVID-19 patients.[13,17,21,30-33] It is often associated with severe conditions of COVID-19 patients that require intensive care.[9,34] An increase in the expression of ACE-2, furin, type-1 membrane protease responsible for virus replication contributes to the severity of COVID-19 in T2DM patients. In addition, impaired immune function, hyperglycemia, and vascular complications are also associated with the disease aggravation owing to the cytokine storm, leading to a higher severity and fatality rate among COVID-19 patients.[35-38] Furthermore, insulin resistance and hyperglycemia, when co-

Table 3. Association between the patients' characteristics with the ferritin level.

Characteristics	Ferritin levels, n (%)		Total, n (%)	p-value
	<400	≥400		
Gender				
Male	10 (14.7)	58 (85.3)	68 (42.5)	0.076
Female	24 (26.9)	67 (73.6)	91 (57.2)	
Total	34 (21.4)	125 (78.6)	159 (100)	
Hypertension				
Yes	13 (18.3)	58 (81.7)	71 (44.7)	0.396
No	21 (23.9)	67 (76.1)	88 (55.3)	
Total	34 (21.4)	125 (78.6)	159 (100)	
Complaints				
1 <	5 (20.0)	20 (80.0)	25 (15.7)	0.854
> 1	29 (21.6)	105 (78.4)	134 (84.3)	
Total	34 (21.4)	125 (78.6)	159 (100)	
RBG				
<140	8 (27.6)	21 (72.4)	29 (18.2)	0.460
140-199	9 (25.0)	27 (75.0)	36 (22.6)	
200 >	17 (18.1)	77 (81.9)	94 (59.1)	
Total	34 (21.4)	125 (78.6)	159 (100)	
FBG				
<100	2 (18.2)	9 (81.8)	11 (9.2)	0.100
100 - 125	6 (46.2)	7 (53.8)	13 (10.9)	
126 >	19 (20.0)	76 (80.0)	95 (79.8)	
Total	27 (22.7)	92 (77.3)	119 (100)	
2hPPBG				
<140	1 (16.7)	5 (83.3)	6 (21.4)	0.936
140-199	1 (16,7)	4 (80.0)	5 (17.9)	
200 >	4 (23.5)	13 (76.5)	17 (60.7)	
Total	6 (21.4)	22 (78.6)	28 (100)	
HbA1C				
<7,5	3 (10.7)	25 (89.3)	28 (25.0)	0.201
7,5 - 9	5 (33.3)	10 (66.7)	15 (13.4)	
>9	14 (29.3)	55 (79.7)	69 (61.6)	
Total	22 (19.6)	90 (80.4)	112 (100)	
CRP				
<0,3	4 (30.8)	9 (69.2)	13 (8.2)	0.478
>0,3	30 (20.5)	116 (79.5)	146 (91.8)	
Total	34 (21.4)	125 (78.6)	159 (100)	
SpO2				
<91	1 (33.3)	2 (66.7)	3 (1.96)	0.818
91-95	3 (17.6)	14 (82.4)	17 (10.8)	
>95	30 (21.7)	108 (78.3)	138 (87.3)	
Total	34 (21.5)	124 (78.5)	158 (100)	

occurring with COVID-19, will increase the risk of vascular endothelial damage, which in turn, gives rise to an increased blood viscosity aggravating the severity of the disease.[22] It has been suggested that T2DM patients with COVID-19 had a significantly 1.55 times higher risk of severe illness (p=0.04),37 and 1.65 times higher risk of mortality than those without DM.[39] However, the present study revealed that most of the patients with T2DM (80.5%) experienced moderate pneumonia, and only 19,5% of them experienced severe conditions (Table 1).

SARS-CoV-2 infection in T2DM patients has been linked to severe inflammation and pneumonia, subsequently leading to worse clinical outcomes.[16] Therefore, study regarding various inflammatory markers including ferritin have been widely carried out. Ferritin level plays an important role in the prognosis of COVID-19. Individuals with high ferritin level have been reportedly more susceptible to either mild or severe COVID-19 illness. Elevated ferritin is considered as a sign of an aggravated progression of COVID-19 and has been related to a poor prognosis or clinical outcomes of COVID-19 patients.[7,9,40] Hence, monitoring patients' ferritin levels for the prediction of COVID-19 severity and mortality is prominent. In terms of ferritin level in T2DM patients with COVID-19, our data exhibited that the vast majority (78.6%) of the patients showed significant increase in ferritin level (≥400 ng/dL) (Table 1). Previous studies also reported significantly higher ferritin levels in patients with comorbidities such as T2DM compared to those without DM ($p<0.05$).[41,42] They also suggested that ferritin levels were significantly greater in patients with severe pneumonia compared to those with mild or moderate severity, which was contrary to our finding indicating that T2DM patient with hyperferritinemia (≥400 mg/dL) were mostly (80.5%) found in moderate severity of pneumonia. However, our chi-square analysis suggested that there was statistically significant association between the ferritin level and the severity of COVID-19 in patients with T2DM ($p\leq0.05$) (Table 2).

A study also suggested a positive correlation between HbA1c and serum ferritin ($r=0.55$, $p<0.05$) among diabetic COVID-19 patients.[41] Ferritin level was higher in the patients with HbA1c of >7.0% compared to those with HbA1c of 7.0% ($p=0.011$). High HbA1c was associated with decreased SpO2 ($r=-0.78$) and increased lung damage ($r-0.66$), ferritin ($r=0.79$), CRP ($r=0.67$), and D-dimer ($r=0.60$).[43] In accordance with the previous report, the majority of the patients in the current investigation also had a high concentration of HbA1c (> 9.0%). However, our data suggested no significant association between HbA1c and other T2DM parameters (RBG, FBG, and 2hPPBG) with the level of serum ferritin and the severity of COVID-19 patients ($p=0.201$).

This study possessed several limitations

that should be addressed. The study was performed only among T2DM patients treated in the isolation unit of the Internal Medicine and thereby the data might not represent all the COVID-19 patients undergoing inpatient treatment at Dr. Soetomo General Hospital. In addition, our investigation was based on the secondary data obtained from the patients' medical records, thus the availability of some required information might not be sufficient. Hence, a prospective cohort study should be conducted assessing a more accurate causal relationship between serum ferritin level and the severity of COVID-19 in T2DM patients. Further longitudinal investigation involving vaccination status and other inflammatory markers among T2DM patients with COVID-19 is also suggested.

CONCLUSIONS

We conducted a cross-sectional study among COVID-9 with T2DM patients admitted at Dr Soetomo General Hospital to evaluate the association between the level of ferritin with the severity of COVID-19 in patients with T2DM. Of 159 participants, 80.8% had moderate pneumonia, whereas the rest (19.5%) showed severe conditions. In terms of serum ferritin, 78.6% had ferritin ≥400 ng/dL, suggesting hyperferritinemia syndrome (mean ± SD: 1177.21 ± 1275.90 ng/dL). The chi-square analysis revealed a significant association between serum ferritin level with the severity of COVID-19 in T2DM patients at Dr. Soetomo General Hospital (p= 0.024).

ETHICAL APPROVAL

Ethical approval was obtained from the Research Ethics Committee of Dr. Soetomo General Hospital (Ref. No. 0880/LOE/301.4.2/IV/2022). The patient provided the signed informed consent prior to the study inclusion.

AUTHOR CONTRIBUTION

All authors had contributed in manuscript writing and agreed for the final version of manuscript for publication.

COMPETING INTERESTS

The authors declare no competing interest.

GRANT INFORMATION

None.

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