



Comparison of Serum Ferritin Levels between Diabetic Patients with COVID-19 and Non-diabetic Patients with COVID-19 Based on Age Groups and Gender

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ABSTRACT

Aims Chronic diseases strongly affect the severity of infection and mortality in patients with COVID-19. High levels of ferritin also indicate the severity of the disease and may indicate the presence of secondary infections among patients. The aim of this study was to compare ferritin levels in diabetic patients with COVID-19 and non-diabetic patients with COVID-19 based on age and gender groups.

Instruments & Methods This descriptive cross-sectional study was conducted on 64 patients with COVID-19 and 26 people without COVID-19 referred to the Najaf Hospitals, Najaf, Iraq. Samples were selected by available sampling method. Clinical tests and laboratory diagnosis were used to investigate the subjects.

Findings In diabetic patients with COVID-19, the highest level of ferritin was in the age group of 51-65 years and the lowest level of ferritin was in the age group of ≤20 years. In non-diabetic patients with COVID-19, the highest level of ferritin was in the age group of 66-80 years and the lowest level was in the age group of ≤20 years. In diabetic patients with COVID-19, ferritin levels were higher in women than men. However, in non-diabetic patients with COVID-19, ferritin levels were higher in men than women. There was no significant difference between the disease groups in terms of ferritin production based on age groups and gender ($p>0.05$).

Conclusion Serum ferritin levels increase in diabetic patients with COVID infection than in non-diabetic COVID-19 patients, and the elderly produce higher levels of ferritin. Also, in diabetic patients ferritin levels increase in women more than men with COVID-19.

Keywords Ferritin; Hyperferritinemia; COVID-19; Diabetes Mellitus; Patients

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Introduction

On December 31, 2019, Chinese Health Authority informed the World Health Organization (WHO) of several cases of pneumonia of unknown cause in Wuhan City, Hubei Province, central China. Cases were reported on December 8, 2019, and several patients worked or resided near the local Huanan Seafood Wholesale Market, but other early cases had no connection to this market [1].

Eventually, a novel virus from the Coronaviridae family was detected by the Chinese centers for disease control and prevention from the throat culture of patients with influenza-like manifestations, which was subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. In March of 2020, WHO named this highly contagious disease COVID-19 (Coronavirus Disease 19) and declared the outbreak as a global pandemic [3].

Several risk factors, including individuals' underlying diseases, had been shown to be associated with higher vulnerability to get SARS-CoV-2 infection [4-6]. In this regard, Diabetes Mellitus (DM) is reported in a majority of studies to be among the most common comorbidities of patients with Coronavirus disease 2019 (COVID-19) [6]. According to the National Health Commission of China, as of February 4 the fatality rate among confirmed cases in China was 2.1 percent [7].

Based on the initial outbreak cases from China, researchers found a link between COVID-19 with comorbidities [8]. Deng and Peng reported that 25.1% had at least one underlying condition; concurrently hypertension (16.9%) and diabetes (8.2%) were two of the most prevalent comorbidities [9]. This correlated data between diabetes as a comorbidity for COVID-19 is concerning globally as diabetes has been considered the pandemic of the 21st century due to its escalation in the older population and adolescents [10].

Diabetes Mellitus (DM) is a well-known risk factor for worse clinical outcomes in patients with COVID-19. However, the relationship between these two entities seems to be bidirectional [11]. The ongoing pandemic of COVID-19 has significantly affected blood glucose control in patients with diabetes mellitus. The results of this effects can be classified into direct effects (those directly related to the viral infection) and indirect effects (those related to the impact of the pandemic on the management of blood glucose or the use of proposed treatments for the infection that also affect glucose homeostasis) [12].

In comparing COVID-19 patients with and without T2DM, the patients with T2DM tend to develop more severe forms of the disease and have a significant increase in inflammatory markers compared to non-diabetics (i.e., higher levels of C-reactive protein, procalcitonin, ferritin, lactate dehydrogenase, and d-

dimer) [13]. Furthermore, the prevalence of diabetes among the patients admitted to intensive care units for COVID-19 is two-to threefold higher, along with the mortality rate which is twice that of non-diabetic patients [14].

Ferritin is a key mediator of immune dysregulation, especially under extreme hyperferritinemia, via direct immune-suppressive and pro-inflammatory effects, contributing to the cytokine storm [15]. It has been reported that fatal outcomes by COVID-19 are accompanied by cytokine storm syndrome, thereby it has been suggested that disease severity is dependent of the cytokine storm syndrome [16]. Many individuals with diabetes exhibit elevated serum ferritin levels [17-19], and it is known that they face a higher probability to experience serious complications from COVID-19 [20].

Hyperferritinemia is more prevalent in diabetic COVID-19 individuals. Serum ferritin can be considered as a valuable biomarker to screen the diabetic and non-diabetic for the presence of hyperinflammation and to predict severity of COVID-19 infection so that it will help the clinician for proper management [21].

In one study with 20 COVID-19 patients, it was found that individuals with severe and very severe COVID-19 exhibited increased serum ferritin level, being serum ferritin in the very severe COVID-19 group significantly higher than in the severe COVID-19 group [22]. In agreement with this, another study revealed that in patients who died by COVID-19, ferritin levels were high upon hospital admission and throughout the hospital stay. The median values of serum ferritin levels after day 16 of hospitalization exceeded the upper limit of detection in these patients, suggesting that ferritin levels increased non-stop [8]. Also, Chen *et al.* analyzed the clinical characteristics of 99 patients, in which 63 of them had serum ferritin way above of the normal range [23]. Elevated ferritin levels were found also in autopsies of 12 patients whose cause of death was SARS-CoV-2 infection [24]. An analysis of the peripheral blood of 69 patients with severe COVID-19 revealed elevated levels of ferritin compared with patients with non-severe disease. Therefore, it was concluded that serum ferritin levels were closely related to the severity of COVID-19 [25].

The aim of the present study was to compare ferritin levels in diabetic patients with COVID-19 and non-diabetic patients with COVID-19 based on age and gender groups.

Instruments and Methods

This descriptive cross-sectional study was conducted on 64 patients with COVID-19 and 26 people without COVID-19 (as a control group) referred to the Najaf Hospitals, Najaf, Iraq. Samples were selected by available sampling method.

Clinical tests and laboratory diagnosis were used to investigate the subjects. For this purpose, 5 CC of each person's venous blood was collected in a test tube and after centrifugation at 3500 rpm for 10 minutes, the serum was isolated. IgM and IgG of SARS-CoV-2 (COVID19) were measured using the VIDAS Kit (BioMérieux, France) and serum ferritin levels were measured using a kit (Boditech Med Inc.; South Korea); the test is designed to be used on I-chroma™ devices.

Data were analyzed by SPSS 28 software using Multivariate Analysis of Variance (MANOVA).

Findings

Of the 64 patients with COVID-19, 41 (64.1%) had diabetes and 23 (35.9%) had no diabetes. Also, 21 patients with COVID-19 was female and 43 was male (Table 1).

In diabetic patients with COVID-19, the highest level of ferritin was in the age group of 51-65 years (group D) and the lowest level of ferritin was in the age group of ≤ 20 years (group A). In non-diabetic patients with COVID-19, the highest level of ferritin was in the age group of 66-80 years (group E) and the lowest level was in the age group of ≤ 20 years (group A). There was no significant difference between the disease groups in terms of ferritin production based on age groups ($p > 0.05$; Table 2; Diagram 1).

In diabetic patients with COVID-19, ferritin levels were higher in women than men. However, in non-diabetic patients with COVID-19, ferritin levels were higher in men than women. There was no significant difference between the disease groups in terms of ferritin production based on gender ($p > 0.05$; Table 3; Diagram 2)

Table 1) Frequency distribution of subjects based on age group and gender

Age groups	Patients with Covid-19		Control	
	Diabetic	Non-diabetic	Positive	Negative
Age group				
A (≤ 20 years)	2	2	2	2
B (21-35 years)	2	4	2	3
C (36-50 years)	15	4	4	3
D (51-65 years)	13	10	4	2
E (66-80 years)	9	3	2	2
Gender				
Female	14	7	8	6
Male	27	16	6	6
Total	41	23	14	12

Table 2) The mean of serum ferritin levels (ng/ml) in different groups according to age

Age groups	Patients with Covid-19		Control	
	Diabetic	Non-diabetic	Positive	Negative
A (≤ 20 years)	214.50 \pm 23.33	102.00 \pm 25.46	369.00 \pm 114.55	141.50 \pm 51.62
B (21-35 years)	365.50 \pm 173.24	359.80 \pm 339.12	154.00 \pm 125.87	194.79 \pm 109.07
C (36-50 years)	250.79 \pm 163.03	639.65 \pm 711.44	222.62 \pm 125.39	265.00 \pm 35.51
D (51-65 years)	647.73 \pm 310.73	331.89 \pm 214.69	190.41 \pm 160.71	74.50 \pm 67.18
E (66-80 years)	550.67 \pm 260.57	860.00 \pm 496.62	273.00 \pm 84.85	94.16 \pm 103.25

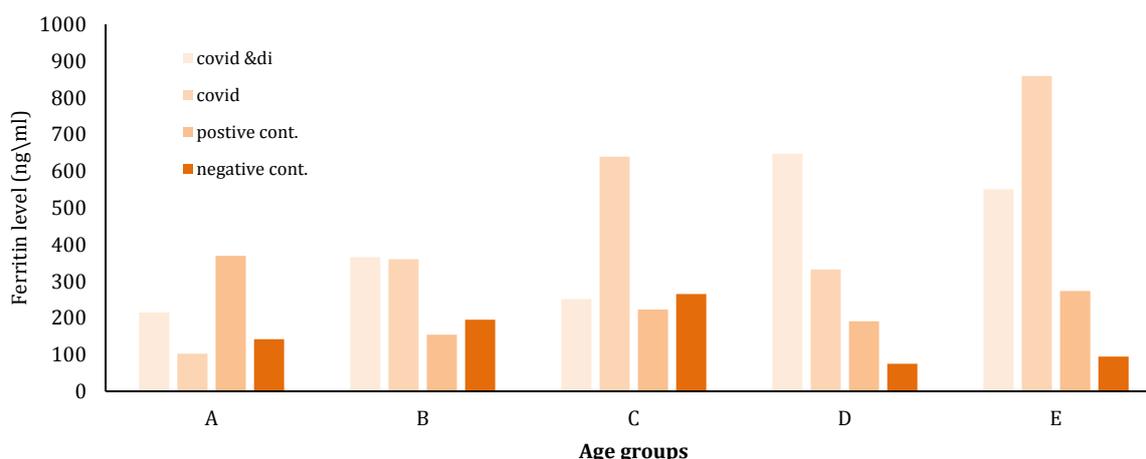


Diagram 1) Comparison of serum ferritin levels (ng/ml) in different groups based on age groups; Group A: ≤ 20 years; Group B: 21-35 years; Group C: 36-50 years; Group D: 51-65 years; Group E: 66-80 years

Table 3) The mean of serum ferritin levels (ng/ml) in different groups according to gender

Gender	Diabetic patients with COVID-19	Non-diabetic patients with COVID-19	Positive control	Negative control
Female	477.42 \pm 272.75	236.65 \pm 306.21	206.6 \pm 158.76	145.7 \pm 127.66
Male	459.45 \pm 287.6	535.14 \pm 415.77	234.41 \pm 149.65	197.08 \pm 93.32

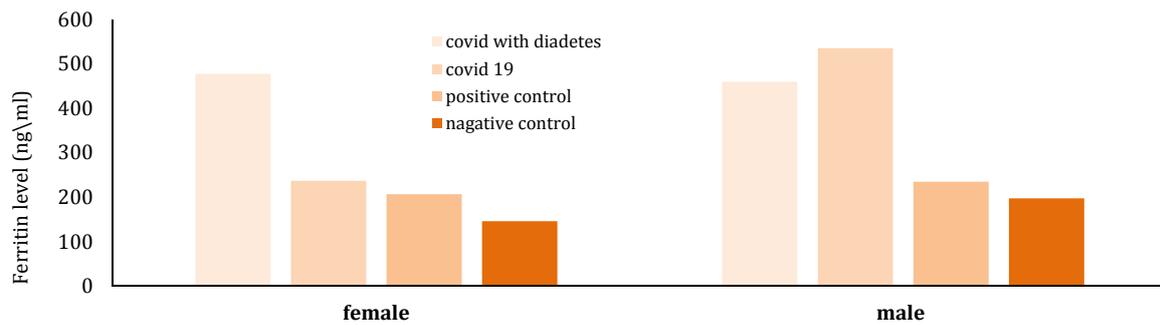


Diagram 2) Comparison of serum ferritin levels (ng/ml) in different groups based on gender

Discussion

The emerging COVID-19 virus (SARS COV 2) is believed to affect most people with chronic diseases, including diabetics.

This study examined some parameters of immunity in patients with COVID-19 and compared the results of patients with COVID19 and diabetes according to age groups and gender.

No significant difference was observed in the disease groups in terms of the rate of ferritin production in the blood, as there is a relationship between the age of ferritin overproduction and age among COVID-19 patients.

The highest rate among non-diabetic COVID patients was in the age group of 66-80 years compared to other disease and age groups in which ferritin production was 860.00 ± 496.62 and based on this, we examine the data supporting this concept that the ferritin levels may be a major component of the severity of COVID-19 disease.

Perhaps the high ferritin in COVID patients is a result of the good nutrition that is recommended for COVID-19 patients, as this nutrition depends on foods that increase the percentage of iron in the blood, which leads to a high concentration of ferritin and this may lead to serious complications.

As shown by one study, high levels of blood ferritin are attributed to inflammatory disease pathways, and ferritin synthesis actively occurs at the site of infection by various inflammatory stimuli such as cytokines [26]. On the other hand, increased ferritin levels may be the result of a subsequent bacterial infection and be associated with poor clinical outcomes [27].

Many people infected with COVID-19 have elevated ferritin levels in their blood and have been shown to be at risk for significant COVID-19 consequences [28]. A study by Italian scientists showed that ferritin is able to activate macrophages (macrococytes), a type of white blood cell in the immune system, when they are activated, they begin to secrete cytokines. This is a class of signaling molecules that mediate and regulate immunity. When it is secreted in low concentrations, it is considered safe for the body and helps protect it from viruses and bacteria. When it is secreted in high concentrations, a so-called "cytokine storm" develops, which can be fatal for

half of patients, especially the elderly. These findings are consistent with the results of our study [29].

The results of our study also showed that COVID patients with diabetes have higher levels of ferritin production in the blood, which is higher in the age group of 51 to 65 years (647.73 ± 310.73), and that the percentage of ferritin in non-infected COVID patients with diabetes is higher than COVID-19 patients. For diabetes, in general, the level of ferritin in patients with COVID is higher than in healthy people. This is because ferritin is high in diabetics, as iron stores levels of abnormal glucose metabolism, which makes the surrounding cells less sensitive to insulin, as high ferritin concentrations indicate the secretion of free radicals that destroy beta cells in the liver [30].

The results of our study showed higher levels of ferritin in men than in women, where the mean ferritin in men was 535.14 ± 415.77 , but these differences were not statistically significant ($p > 0.05$).

This suggests that men are more likely to develop severe disease and liver damage than women, and this may be partly due to the increased expression of Angiotensin-Converting Enzyme-2 (ACE-2), a cell-associated receptor for SARS-CoV-2 that mediates virus entry. The lungs of men are more than that of women. High levels of ferritin indicate liver damage and serious disease, and this was confirmed by a study [31].

Rane & Bhadade in their study showed that high levels of ferritin in the blood lead to weak liver activity or as a result of metabolic syndrome [32].

The cause of death may be acute inflammation of the virus, which is associated with high levels of ferritin. However, blood ferritin levels can not only show a strong phase reaction, but also play an important role in inflammation [33].

The results of our study agreed with Perricone *et al.* [34], as well as with Hussein *et al.* [35] and Lau *et al.* [36] which showed that ferritin concentration increases more in men than women.

Conclusion

Chronic diseases, including diabetes, greatly affect the susceptibility to infection with the COVID virus, and blood ferritin levels increase significantly in

diabetic patients with COVID infection than in non-diabetic COVID-19 patients, and the elderly produce higher levels of ferritin. In addition, ferritin levels increase in women more than men with COVID-19.

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