Association of Ferritin and HbA1c with Disease Severity in COVID-19 Patients

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Abstract

Space The World Health Organization (WHO) declared a new coronavirus infection brought on by the SARS-CoV-2 virus to be a pandemic on March 11, 2020, making it the eleventh pandemic in the previous century. To assess the clinical symptoms and laboratory data (Ferritin & HbA1c biomarkers' level), 150 patients diagnosed with COVID-19 pneumonia and 50 healthy controls were included in the study. The Real-Time RT-PCR Assay was used to diagnose every COVID-19 patient. According to data analysis, COVID-19 patients had significantly higher levels of D-dimer, Ferritin, and HbA1c at the time of admission ($P < 0.001$), and there was a strong correlation between D-dimer levels and HbA1c ($P \leq 0.001$). In conclusion, COVID-19 individuals who have persistently elevated ferritin and HbA1c levels are more likely to have a poor prognosis. To reduce their bad prognosis due to COVID-19, patients with ferritin and HbA1c readings over cutoff criteria should be properly controlled.

Keywords: COVID-19; Ferritin; HbA1c; RT-PCR

1. Introduction

Space coronaviruses (CoVs) are single-stranded positive-sense RNA viruses belonging to the order Nidovirales and family Coronaviridae (Chen et al., 2020; Yang et al., 2020). They are enveloped viruses with a non-segrnented genome that can cause respiratory illnesses of varying degrees of severity in both humans and animals (Subbarao, 2021). Alpha, Beta, Gamma, and Delta are the four genera to which they belong. Alpha and beta strain infections in humans (hCoVs) are included in the former (Zhu et al., 2020). Since December 2019, Wuhan, China, has experienced an outbreak of pneumonia cases with an unknown cause. The pathogen causing this pneumonia, known as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], causes a novel viral syndrome known as coronavirus disease 2019 (COVID-19), which is currently a pandemic (Gupta et al., 2020; Zhu et al., 2020). During the week of August 8-14, 2022, the number of new cases reported worldwide at all levels (national and sub-national) decreased by 24% compared to prior weeks, with over 5.4 million additional cases. Meanwhile, the number of new weekly deaths decreased by 6% during the same period, with over 15,000 new fatalities reported. As of August 14, 2022, there were 6.4 million recorded deaths and 587 million confirmed cases worldwide (WHO, 2022). COVID-19 can cause mild cases to severe acute respiratory failure with various organ dysfunctions. A sizable percentage of COVID-19 patients do not exhibit any symptoms. A positive COVID-19 test with no symptoms and normal imaging was considered asymptomatic. Patients may experience stomach symptoms and/or an acute upper respiratory tract infection in mild situations (Al-Jubury et al., 2025). Pneumonia without obvious hypoxemia or chest CT abnormalities was described in cases with milder histories (n = 3). Severe patients, on the other hand, have hypoxemia and pneumonia. Lastly, ARDS, shock, heart failure, encephalopathy, coagulation malfunction, myocardial injury, and acute renal injury are frequently present in severe COVID-19 cases (Yuki et al., 2020). According to Eljilany and Elzouki (2020), symptoms typically start on day 7 after infection, dyspnea on day 8, pneumonia by the end of day 9, and ARDS necessitating ICU hospitalization from day 10 to 11.

2. Material and Methods

Participants and study design Between January and May of 2022, this study was carried out at the Baghdad Medical City (BMC), a cluster of educational and medical facilities. The Mag-Bind® FFPE DNA/RNA 96 Kit from Germany was used in this investigation to detect the viral RNA in

patients who were admitted to Medical City Teaching Hospital, Baghdad (MCTH) and tested positive for COVID-19 by RT-PCR (ARCHITECT c4000). At the time of admission and during the hospital stay, samples were collected for laboratory testing. For a standard blood test using a hematology analyzer, peripheral venous blood samples were taken. At least two positive RT015 PCR test findings in MCTH and Central Laboratories confirmed COVID-19 (Al-Jubury et al., 2023). 150 positives (75 males and 75 women) and 50 negatives served as controls in our study. Three authors used the e-medical record systems in these two facilities to gather demographics and clinical features, such as medical history, underlying comorbidities, exposure history, signs and symptoms of disease, and laboratory examination results.

2.1. Study groups

Based on this outcome, groups were divided into:

• Group 1: 75 male COVID-19 patients.

• Group2: 75 female COVID-19 patients.

• Group3: 25 male negatives (control).

• Group3: 25 female negatives (control).

2.2. Statistical analysis

RStudio version 1.2.5033 was used for all meta-analyses, and significance was indicated by p-values less than 0.01. The T-test was used to compare means in a significant way. correlation coefficient between the parameters in the COVID group and patients that are part of this study.

2. Results and Discussion

Since this hospital was designated as a referral center for new coronavirus illness, every patient was tested using the PCR method upon admission. From January 22 to July 15, 2022, 189 cases were gathered; of these, 150 cases (75 males: Table 1 sex ratio of male/female = 1) were divided as indicated in Table 1. The age range of patients was 19 to 61. Fever and lower respiratory tract (LRT) symptoms, primarily dry cough, were the most prevalent presenting symptoms. Prior rates of fever, cough, and dyspnea were 67%, 33%, and 62%, respectively (Table 1).

Table 1. Clinical and demographic features of COVID-19 patients admitted to the study (n = 150).

Age (years)	**(n= 150)**
< 45	115 (76.6 %)
≥45	35 (23.3 %)
Mean ± SD	36.7 ± 9.1
Symptoms, n (%)	
Dyspnea	50 (33 %)
Cough	93 (62 %)
Fever	100 (67 %)

Mean ± SD = Mean ± standard deviation; % = Percentage.

Table 2. Changes in the levels of biochemical parameters in the patients during the acute and recovery phases.

Parameter	**Acute phase (Mean ± SD)**	**Recovery phase (Mean ± SD)**	***P-value***
RBS (mg/dL)	290.6 ± 154	140 ± 63.8	*< 0.001
B. Urea (mg/dL)	33.8 ± 12.9	28.5 ± 5.3	*< 0.001
S. Creatine (mg/dL)	0.8 ± 0.3	0.7 ± 0.3	**0.670
Uric acid (mg/dL)	5.6 ± 1.2	6 ± 1.2	*0.010
S. Iron (µg/dL)	67.9 ± 18.6	47.6 ± 16.7	*< 0.001
S. Ferritin (ng/mL)	563.1 ± 307.9	218.6 ± 124.1	*< 0.001
S. LDH (U/L)	639.8 ± 315.5	283.5 ± 182.1	*< 0.001
HbA1c	6.61 ±0.28	5.027 ±0.17	*< 0.001

Mean ± SD = Mean ± standard deviation; n = 150; $p < 0.001$ was considered significant. * Significant; ** Non-significant; RBS = Random blood sugar; S. LDH = Lactate dehydrogenase; HbA1c = Hemoglobin A1c, glycated hemoglobin.

There were notable biochemical differences between the acute and recovery stages. HbA1c and random blood sugar (RBS) levels were considerably lower after recovery (both $p < 0.001$) and

significantly higher during the acute phase, suggesting inadequate glycemic management during the acute phase with later improvement (Table 2). The acute phase had significantly higher serum ferritin levels (563.1 ± 307.9 ng/mL) than the recovery period (218.6 ± 124.1 ng/mL), with a very significant difference ($p < 0.001$). Interestingly, ferritin and HbA1c were both markedly elevated during the acute phase and concurrently declined following recovery (Table 3).

In summary, these findings show that elevated HbA1c levels are linked to hyperferritinemia during the acute phase, and both values significantly return to normal during recovery, suggesting a possible connection between dysglycemia and the amount of inflammation.

Table 3: Comparison of HbA1c and S.Ferritin levels in COVID-19 patients and controls.

Group	Means ± SE	
	HbA1c (%)	**S. Ferritin (ng/ml)**
Patients	6.61± 0.28	477.94 ± 52.19
Control	5.027 ± 0.17	182.33 ± 24.85
T-test	1.028*	144.957**
P-value	0.03187	0.0062

*** (p≤0.05), ** (p≤0.0).**

4. Discussion

Serum ferritin and HbA1c levels were significantly higher in the acute stage of COVID-19 compared to the recovery phase and control group in the study described here. These findings show a strong correlation between dysglycemia and inflammatory load in individuals infected with SARS-CoV-2. Ferritin is a recognized acute-phase reactant and a sign of bodily inflammation. Significantly elevated ferritin levels during the acute phase of COVID-19 are consistent with past research on hyperferritinemia as a hallmark of severe COVID-19 infection. The key pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which are both mainstays in the cytokine storm linked to severe disease course and disease outcome, mediate dysregulated immune activation and macrophage stimulation, which is reflected in elevated ferritin (Qi et al., 2021; Vargas-Vargas & Cortés-Rojo, 2020). On the other hand, HbA1c was also markedly higher during the acute phase compared to the convalescent phase, indicating that COVID-19 patients had aberrant glycemic control. Chronic hyperglycemia causes elevated

HbA1c, which is linked to immunological dysregulation, oxidative stress, and endothelial damage. Numerous mechanisms, including stress-induced insulin resistance, direct viral damage to pancreatic β-cells, and the systemic inflammatory response linked to SARS-CoV-2 infection, can account for this observation (Apicella et al., 2020; Rubino et al., 2020). It should be mentioned that a simultaneous rise in ferritin and HbA1c during the acute phase, followed by a fall following recovery, suggests a parallel between inflammation and metabolic disruption. Chronic hyperglycemia may exacerbate an inflammatory surge because it can trigger cytokines, react with scaffolding oxygen species, and undermine innate immunity, resulting in elevated ferritin levels. However, through cytokine-induced insulin resistance, increased inflammation might worsen glycemic control, potentially creating a vicious cycle that increases the severity of the disease (Codo et al., 2020). This relationship is further supported by the association between infected and non-infected patients, where ferritin and HbA1c were considerably greater in the former. These findings imply that patients who have poor basal glycemic control or undetected dysglycemia are more likely to experience severe inflammation after contracting SARS-CoV-2. Increased risk for severe COVID-19, ICU admission, ARDS, and mortality is frequently linked to higher HbA1c levels (Zhu et al., 2020; Williamson et al., 2020). Additionally, hyperferritinemia has been shown to be an independent predictor of both death and the development of severe COVID-19 (Gallo Marin et al., 2021). In addition to being a marker of inflammation, ferritin may directly contribute to immunological dysregulation and coagulopathy, which are frequently seen in severe instances (Cheng et al., 2020).

5. Conclusion

There is a strong correlation between inflammation and poor glycemic control, as seen by the significantly higher serum ferritin and HbA1c levels during the acute phase of COVID-19 and the lower levels post recovery. Increased disease severity was linked to elevated levels of these biomarkers. Early management of inflammation and blood glucose may improve the clinical prognosis in COVID-19 patients, and routine evaluation of ferritin and HbA1c may assist identify individuals at higher risk of poor outcomes.

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