# Ferritin and High Sensitivity C-Reactive Protein (hs-CRP) may predict the COVID-19 patient's fate

Zahra A. Kheudhier[1,*], Alaa K. Mossa[2]

## Abstract

Objective: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has rapidly spread worldwide. Clinical outcomes and disease severity are still unknown and can be difficult to predict. In this study, we perform a cross-sectional observational study to investigate the clinical characteristics of ferritin and high sensitivity C-reactive protein status of patients infected with COVID-19 that may predict the COVID-19 patient's fate.

Methods: A total of 106 patients (56 males and 50 females, their ages ranging from 19 to 70 years) who were confirmed to have COVID-19 by real-time RT-PCR were recruited in this study. Blood samples were withdrawn, and biochemical tests (serum ferritin and C-reactive protein) were performed. The gained data were analyzed using GraphPad Prism software.

Results: Overall, the findings showed that ferritin and C-reactive protein were increased from day 1 to day 7 and then decreased on day 14 after diagnosis in patients who are released after full recovery. While they still dramatically increased from day 1 to day 7 to day 14 in those who moved to the intensive care unit or died by day 14 in those who moved to the intensive care unit or died by day 14. No gender-based differences were noted.

Conclusions: These findings suggest that the patient's fate and disease severity can be predicted at day 7 based on these two biomarkers.

## 1. Introduction

Coronavirus disease 2019 (COVID-19), the latest outbreak proclaimed a pandemic by the World Health Organization (WHO), is a diseased condition resulting from infection of the severe acute respiratory syndrome Coronavirus -2 (SARS-CoV-2) (Salman et al., 2020; Zhang et al., 2020). With the emergence, spread, and rapid evolution of the 2019 novel coronavirus (2019-nC0V), now it is named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recent public health crisis has been noticed and threatened the world. This is the result of an epidemic outbreak of the newly named (SARS-CoV-2) from its origin in Wuhan, China, to become a pandemic affecting more than 1 million individuals worldwide (Singhal, 2020).

The significant role of inflammation, which is resulted from infectious diseases in the development of various viral pneumonia, including SARS-CoV-2, has been recognized. A weakness in the adaptive immune response resulting from an imbalance of the immune response can be occurred by severe inflammatory responses (Yang et al., 2020). People with pre-existing comorbidities, including obese ones and those who are old age, are at higher risk of severe disease (Liu et al., 2020). However, the inflammatory cytokine storm, which is known as higher concen-

### Significance | Prediction of COVID-19 patient's fate

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**Table 1.** Characteristics and symptoms of study groups.
(* Data shown as the median and 95% CI, ICU= intensive care unit)

| | Male (n=56) | Female (n=50) | P |
|---|---|---|---|
| Age (years)* | 41(39.22-46.57) | 45.5(39.87-47.85) | 0.727 |
| **Patients n(%)** | | | |
| Improved | 33(58.92) | 38(76) | |
| ICU | 11(19.64) | 9(18) | |
| Died | 12(21.42) | 3(6) | |

| | **Symptoms** | | | |
|---|---|---|---|---|
| | Improved (n=71), n(%) | ICU (n=20), n(%) | Died (n=15), n(%) | Total (n=106), n(%) |
| **Diarrhea** | 3(4.2) | 2(10) | 2(13.3) | 7(6.6) |
| **Cough** | 59(83) | 18(90) | 13(86.6) | 90(84.9) |
| **Fever** | 71(100) | 20(100) | 15(100) | 106(100) |
| **Chest pain** | 2(2.8) | 3(15) | 6(40) | 11(10.3) |
| **Loss of taste** | 14(19.7) | 3(15) | 0 | 17(16) |
| **Loss of smell** | 5(7) | 2(10) | 0 | 7(6.6) |
| **Vomiting** | 3(4.2) | 2(10) | 0 | 5(4.7) |
| **Myalgia** | 6(8.4) | 7(35) | 1(6.6) | 14(13.2) |
| **Fatigue** | 16(22.5) | 3(15) | 3(20) | 22(20.7) |

**Table 2.** Serum ferritin and hsCRP concentrations of patients according to fate in a period of 14 days after entering hospital.

| | Day 1 mean±SD(95% CI) | Day 7 mean±SD(95% CI) | Day 14 mean±SD(95% CI) | P |
|---|---|---|---|---|
| | **Ferritin (ng/ml)** | | | |
| **Outcome** | | | | |
| Improved | 332.7±220.4(280.5-384.9) | 446.9±354.2(363.1-530.8) | 333.1±278.9(267.1-399.1) | <0.001* |
| ICU | 540.4±81.70(502.2-578.7) | 866.3±257.7(745.7-986.9) | 1025±256.6(905.0-1145) | <0.001* |
| Died | 567.5±334.5(382.3-752.7) | 846.9±333.2(662.4-1031) | 1060±310.2(888.4-1232) | <0.001* |
| **P** | <0.001† | <0.001† | <0.001† | |
| | **hsCRP (mg/ml)** | | | **P** |
| **Outcome** | | | | |
| Improved | 21.34±28.87(14.50-28.17) | 22.53±28.75(15.72-29.33) | 13.16±14.06(9.834-16.49) | <0.001* |
| ICU | 26.26±12.08(20.60-31.91) | 37.83±15.98(30.35-45.31) | 36.46±10.18(31.70-41.22) | 0.004* |
| Died | 45.57±37.69(24.70-66.44) | 46.47±25.30(32.46-60.48) | 69.12±57.98(37.01-101.2) | 0.002* |
| **P** | <0.001† | <0.001† | <0.001† | |

-trations and uncontrolled secretions of pro-inflammatory cytokines, has been identified as the main cause of death in critical SARS-CoV-2 infected cases admitted to ICUs (Velavan and Meyer, 2020). Inflammatory biomarkers can predict disease severity, such as ferritin and high sensitive CRP. This is because the level of these biomarkers was high among cases who needed admission to the hospital in comparison to not admitted patients. Also, throughout the clinical course of the disease, concentrations of both ferritin and hsCRP were at a lower level in survived patients than in non-survivors (Gómez-Pastora et al., 2020a; Yitbarek et al., 2021).

Thus, the significance of circulating biomarkers is an essential predictor for the prognosis of infected patients with COVID-19 as they can represent the severity of inflammation and immune status, especially in pandemic areas with a shortage of medical resources. Besides the role of several biomarkers that modulate the course of SARS-CoV-2, the focus will be on ferritin and C-reactive protein (CRP) (Yitbarek et al., 2021). Therefore, this study aims to investigate the data from 106 laboratory COVID-19 confirmed cases in an attempt to compare the effectiveness of ferritin and CRP as predictive biomarkers and select the most significant indicator between them in the early prediction of fatal cases.

## 2. Materials and methods

### 2.1. Study design

A cross-sectional study on patients hospitalized with confirmed COVID-19 (positive specific coronavirus PCR). A total of 106 patients (56 males and 50 females, age range 19-70 years) were confirmed to have COVID-19 by real-time RT-PCR and were admitted to Al-Sader Medical City from 30 November 2020 to 5 January 2021 were recruited in this study. The patients collected blood samples to assess the study's variables. Patients with a history of hematologic disease, autoimmune disease, or tumours were excluded from the study.

### 2.2. Biochemical analysis

CRP and serum ferritin were measured using latex-enhanced immunoturbidimetry (Cobas). All procedures were carried out according to the manufacturer's instructions.

### 2.3. Statistical analysis

Graph Pad Prism 8.0.1 (Graph Pad Software, CA, USA) was used to evaluate the findings' differences statistically. Statistical tests were applied to analyze data: Kruskal-Wallis test (or Friedman test), unpaired t-test (or Mann-Whitney U test), and Chi-square test. In addition, Dunn's posthoc test was also used for multiple comparisons. $P \leq 0.05$ was considered statistically significant, while $p < 0.01$ and $p < 0.001$ suggest a high and very high significant difference.

## 3. Results

### 3.1. Patients outcome and symptoms

No significant difference in the age of patients has been observed between men and women, as shown in Table 1. Out of 106 patients (males=56 & females=50) covered in the current survey, about 67% were fully recovered and discharged from the hospital within 2 weeks; while the rest of them were either moved to ICU (18.8%) or died (14.1%) at the end of day 14. All the patients (100%), by referring to hospital records for symptoms, had a fever, and 84.9% had a dry cough. Chest pain, fatigue, loss of taste, myalgia, diarrhea, and other symptoms were also noted in included patients with various percentages.

To investigate how serum ferritin and high-sensitivity CRP (hsCRP) change during the infection period of 14 days after diagnosis, we analyzed laboratory-based data obtained on days 1, 7, and 14. Accordingly, serum ferritin and hsCRP levels were notably elevated in all patients (improved, ICU, and died) from day 1 to day 7. Day 14 findings showed that serum ferritin and hsCRP significantly dropped in patients who are improved. However, the results of other patients were still elevated at day 14, about 2-folds (Table 2). Detailed differences in serum ferritin and hsCRP concentrations among patients based on outcome and time point of testing are illustrated in Fig. 1.

We also analyzed serum ferritin and hsCRP concentrations based on gender during the infection period of 14 days after diagnosis. In male patients, improved patients' ferritin concentration was increased from day 1 to day 7 (381.8±219.9 vs 489.8±337.6), but it dropped then to 344.4±215.8 ng/ml. Serum ferritin of the rest of the patients was continually and significantly increased throughout the infection period. Ferritin results of females were similar to those of male patients. On the other hand, the hsCRP concentration of male patients who improved was markedly decreased through the infection period from day 1 to day 14.

Nevertheless, it increased notably in male patients who died or were moved to ICU. Apart from males, female patients who were improved and those who then moved to ICU had elevated levels of hsCRP from day 1 to day 7, but their hsCRP dropped again on day 14. In female patients who died, reduced levels of hsCRP were recorded on day 7, but they elevated again on day 14 significantly (Table 3). Detailed comparisons were entirely elucidated in Fig. 2 for males and Fig. 3 for females.

To explore a gender-based difference regarding the tested biomarkers, comparisons were conducted. Both ferritin and hsCRP showed no differences between males and females in almost all patients' categories through infection except on day 1 since men had significantly higher serum ferritin than women ($p < 0.05$).

## 4. Discussion

Since the COVID-19 pandemic infection emerged, the main cause of morbidity and mortality was due to the effect of cytokine storms. The hyper-inflammatory state accompanying the illness
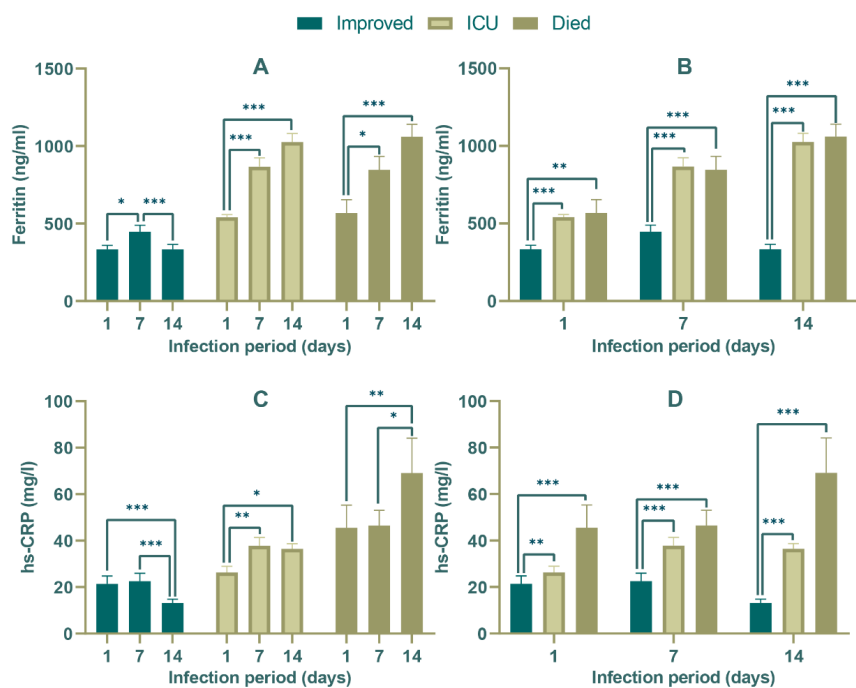
**Figure 1.** Serum ferritin and hsCRP concentrations of patients according to the patient's fate in a period of 14 days after entering the hospital. A) Changes of ferritin concentration during the infection period, at different time points, within the same group. B) Changes of ferritin concentration at the same time point, of infection period, among the three groups. C) Changes of hsCRP concentration during the infection period, at different time points, within the same group. D) Changes of hsCRP concentration at the same time point, of infection period, among the three groups. Mean and SEM are used to present the data.
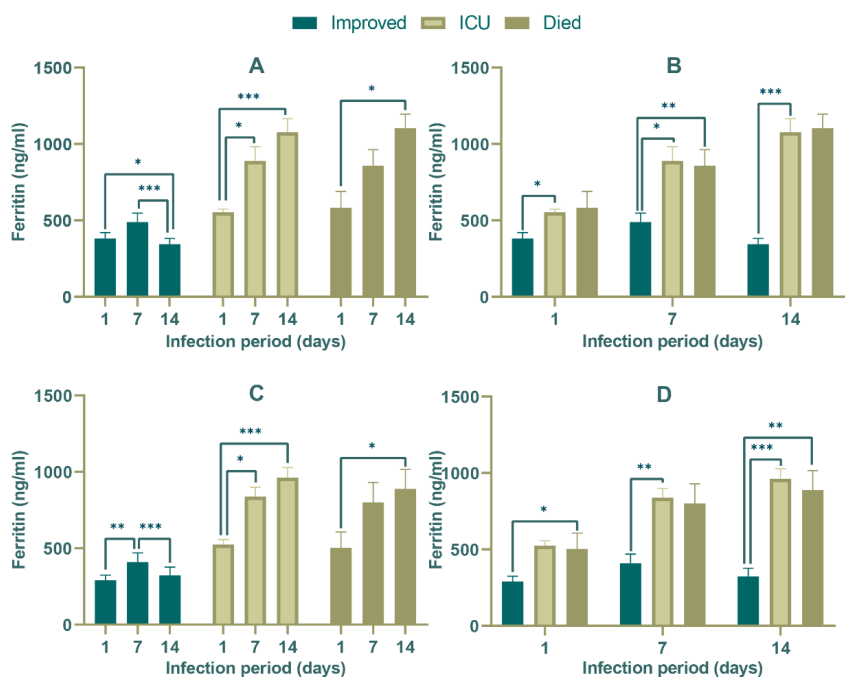


**Figure 2:** Serum ferritin and hsCRP concentrations of male patients according to the patient's fate in a period of 14 days after entering the hospital. A) Changes of ferritin concentration during the infection period, at different time points, within the same group. B) Changes of ferritin concentration at the same time point, of infection period, among the three groups. C) Changes of hsCRP concentration during the infection period, at different time points, within the same group. D) Changes of hsCRP concentration at the same time point, of infection period, among the three groups. Mean and SEM are used to present the data.

**Table 3.** Serum ferritin and hsCRP concentrations of patients according to gender and fate in a period of 14 days after entering hospital.

| | Day 1 mean±SD(95% CI) | Day 7 mean±SD(95% CI) | Day 14 mean±SD(95% CI) | P |
|---|---|---|---|---|
| | Ferritin (ng/ml) | | | |
| **Male** | 381.8±219.9(303.8-459.8) | 489.8±337.6(370.1-609.5) | 344.4±215.8(267.8-420.9) | <0.001[*] |
| **Improved** | 553.3±69.45(506.6-600.0) | 889.0±313.1(678.6-1099) | | <0.001[*] |
| **ICU** | 583.5±367.6(.3500-817.1) | .8585±362.7(.6281-1089) | 1077±295.4(878.4-1275) | <0.001[*] |
| **Died** | | | 1103±321.6(.8991-1308) | |
| **P** | 0.005[†] | <0.001[†] | <0.001[†] | |
| **Female** | | 409.7±368.4(.2886-530.8) | 323.3±326.5(216.0-430.7) | |
| **Improved** | 290.1±214.6(219.6-360.6) | 838.7±183.3(697.8-979.6) | 961.8±197.9(809.6-1114) | <0.001[*] |
| **ICU** | 524.7±96.53(450.5-598.9) | .8003±222.9(246.7-1354) | .8877±221.5(337.4-1438) | <0.001[*] |
| **Died** | 503.3±180.1(55.83-950.8) | | | 0.028[*] |
| **P** | 0.004[†] | 0.003[†] | <0.001[†] | |
| | hsCRP (mg/ml) | | | **P** |
| **Male** | 25.41±33.47(13.54-37.28) | 22.90±25.78(13.75-32.04) | 15.01±14.64(9.823-20.20) | 0.002[*] |
| **Improved** | 27.35±12.51(18.95-35.76) | 36.56±15.87(25.89-47.22) | 36.36±12.21(28.16-44.57) | 0.038[*] |
| **ICU** | 45.97±42.14(19.19-72.74) | 47.37±27.79(29.72-65.03) | 72.37±64.68(31.28-113.5) | 0.013[*] |
| **Died** | | | | |
| **P** | 0.013[†] | <0.001[†] | <0.001[†] | |
| **Female** | 17.80±24.10(9.876-25.72) | 22.21±31.44(11.87-32.54) | 11.56±13.53(7.107-16.00) | <0.001[*] |
| **Improved** | 24.91±12.14(15.58-34.24) | 39.38±16.94(26.36-52.40) | 36.58±7.724(30.64-42.52) | NS |
| **ICU** | 44.00±13.08(11.52-76.48) | 42.85±14.39(7.097-78.60) | 56.10±14.26(20.69-91.51) | NS |
| **Died** | | | | |
| **P** | 0.003[†] | 0.003[†] | <0.001[†] | |
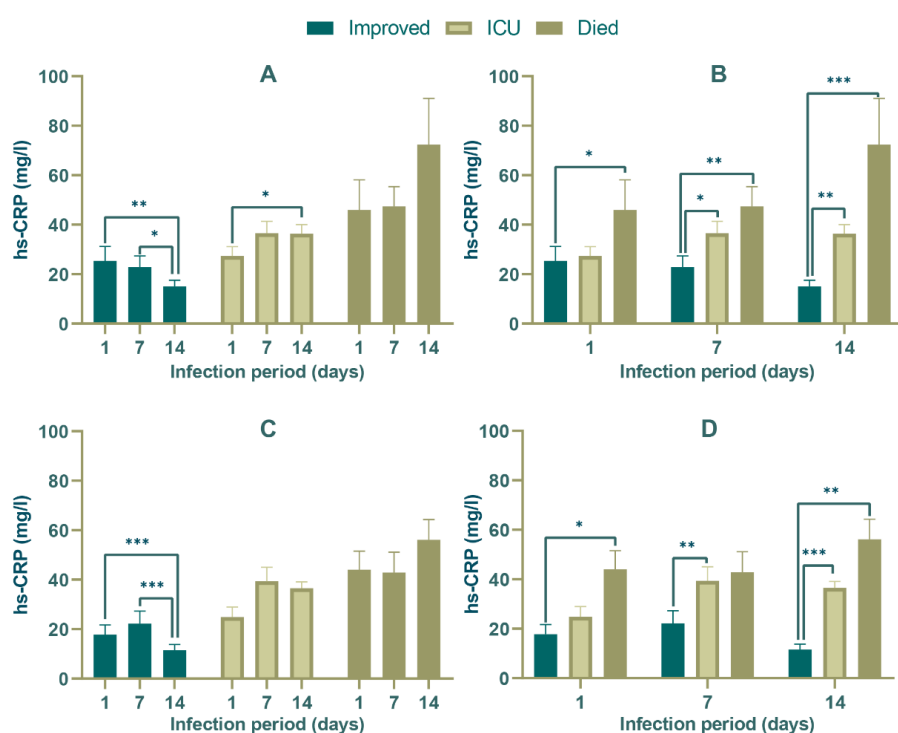


**Figure 3:** Serum ferritin and hsCRP concentrations of female patients according to the patient's fate in a period of 14 days after entering the hospital. A) Changes of ferritin concentration during the infection period, at different time points, within the same group. B) Changes of ferritin concentration at the same time point, of infection period, among the three groups. C) Changes of hsCRP concentration during the infection period, at different time points, within the same group. D) Changes of hsCRP concentration at the same time point, of infection period, among the three groups. Mean and SEM are used to present the data.
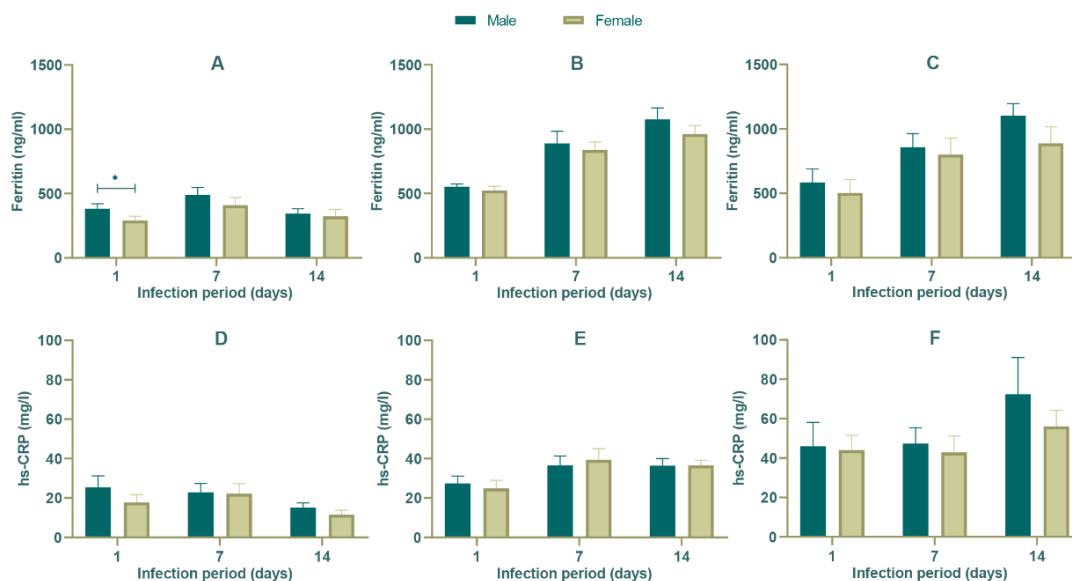
**Figure 4.** Serum ferritin and hsCRP concentrations of patients according to the gender in a period of 14 days after entering the hospital. A) Difference in ferritin concentrations during the infection period, at the same time points, between males and females in patients who improved after 14 days. B) Difference in ferritin concentrations during the infection period, at the same time points, between males and females in patients who became at ICU after 14 days. C) Difference in ferritin concentrations during the infection period, at the same time points, between males and females in patients who died after 14 days. D) Difference in hsCRP concentrations during the infection period, at the same time points, between males and females in patients who improved after 14 days. E) Difference in hsCRP concentrations during the infection period, at the same time points, between males and females in patients who became at ICU after 14 days. C) Difference in hsCRP concentrations during the infection period, at the same time points, between males and females in patients who died after 14 days.

can cause severe damage to many organs, including lung parenchyma. This is mainly due to the secretion of specific biomarkers, such as ferritin and CRP, that can increase the state of inflamed tissue by some mechanisms. For example, a cytokine storm can stimulate the macrophage to increase ferritin secretion. Subsequent hyperferritinemia can lead to immune activations by increased secretion of IL-1β and immune suppressions by releasing IL-10 (Gómez-Pastora et al., 2020b). Also, Ali (2020) has explained that although CRP can bind phosphocholine presented strongly on the surface of damaged cells, causing the modulation of phagocytic activity by activating the classical complement pathway of the coagulation with subsequent removal of damaged cells from the organisms, the hyperactive immune system with overproduction of inflammatory cytokines can cause a very high level of CRP with damaged lung tissue.

As shown in Table 1, the current study found no significant difference between male and female patients' ages; most cases were middle-aged and elderly patients. However, Luo et al. (2020) have explained that more than twice the percentage of elderly patients who were critically ill with severe disease in comparison to middle-aged patients with only a few percentages of young patients who had severe disease. Santesmasses et al. (2020) identified the age-related appearance of SARS-COV-2 based on some facts, for example, an expanding growth of the disease fatality rate with age, its tremendous combination with preceding diseases related to age, including hypertension, obesity, and chronic lung diseases, and an interrelated rise in the expression of the SARS-COV-2 mRNA receptor in the lungs of non-ventilator aged individuals. There were no huge gender disparities among patients infected with COVID-19, with only 56(53%) male and 50(47%) female in the current study. However, more cases with serve disease either admitted to the ICU (20%) or died (21%) were male, compared to 18% of female cases with critical illness were admitted to the ICU, and only 6% died Table 1. Variation in the immune system responses could be a primary factor contributing to delay viral clearance in males, higher disease severity, and fatality in males than in women, together with other possible mechanisms. However, the infection rate between men and women seems to be the same (Gagliardi et al., 2020; Pradhan and Olsson, 2020). Previous clinical studies have identified such mechanisms despite the actual mechanism of gender variations in COVID-19 stays unknown. The less susceptible females to be virally infected are by their greater innate immune response with higher production of immunosuppressive molecules to decrease systemic inflammation than males (Kopel et al., 2020). Also, since estrogen has immunoenhancing results, whereas testosterone has immunosuppressive roles, such variations in sex hormones may be a cause of viral infections (Haitao et al., 2020; Pradhan and Olsson, 2020).

Interestingly, testing and quarantining suspected infected patients with SARS-COV-2 depend on common initial symptoms. Both fever and cough account for the highest prevalent symptoms of adults infected by COVID-19 (Grant et al., 2020). In the present study, the same predominant prevalent symptoms are fever (100%) and cough (85%) in all infected patients with COVID-19, whether they were improved, admitted to the ICU, or died. Fatigue, myalgia, and chest pain were common among improved, ICU admitted, and dead patients. Also, more improved patients presented with two additional symptoms, including loss of smell or taste, than patients admitted to the ICU. Ibekwe et al. (2020) explained that healthcare providers and clinicians must be aware of these symptoms since the sudden loss may be the isolated features in asymptomatic recently COVID-19 infected patients and may additionally be early symptoms of the disease. Thus, it has been suggested by the 'American Academy of Otolaryngology-Head and Neck surgery' that infected patients with SARS-COV-2 could be presented with only a sudden loss of smell and taste in the absence of other respiratory symptoms. Thus, the suggestion was to self-isolate those patients for 14 days to reduce the possibility of disseminating the infection by hidden carriers. Table 1 shows the baseline characteristics and clinical symptoms of these patients.

It is important to note from table 2 and figure 1 that serum ferritin and hs-CRP slightly increased from day 1 to day 7 of illness, with a decline in their levels at the end of day 14 in improved patients. Regarding infected patients with COVID-19 who were either admitted to the ICU or died, there was a continuous increase in levels of both biomarkers throughout the 14 days of illness. Significant increase in serum ferritin and hsCRP from day 7 of illness in ICU admitted patients or those who died as compared to a slight rise in both levels of these biomarkers in the improved patients. Similarly, Bozkurt, et al. demonstrated the tremendous role of both serum ferritin and CRP as inflammatory biomarkers in the early prediction of disease severity where their levels were high in infected patients with COVID-19 who either died or were admitted to the ICU in comparison to survived cases (Bozkurt et al., 2021).

Studies have identified the paramount value of these biomarkers in predicting poor outcomes of patients infected with COVID-19 (Velavan and Meyer, 2020; Wang, 2020). An acute-phase inflammatory protein 'CRP', produced from the liver, could also have a role in monitoring the progression and the improvement of infected patients with SARS-COV-2. In this study (table 2), CRP levels were (31.7-41.22) and (37.01-101.2) in patients who were admitted to the ICU and those who died, respectively. Whereas, CRP level in improved patients was (9.834-16.49). Similarly, (Huang et al., 2020a) has demonstrated that CRP can be used as an early prediction of disease severity with an increase in CRP

associated with the critical disease; however, this may depend on the cutoff of the serum level of CRP.

Ferritin may have a better value in predicting the mortality of COVID-19 cases than CRP (Huang et al., 2020b). In our study, in patients who died from SARS-COV-2, serum ferritin levels (Figure 1A) was significantly and continuously increased on day 1, 7, and 14. In contrast, there was no significant change in the CRP on day 1 and 7 before reaching a high level on day 14 (Figure 1C). As a result, serum ferritin may help detect the case fatality of COVID19 infected patients early. Hyperferritinemia may be due to the role of this viral infection in triggering secondary hemophagocytic lymphohistiocytosis. This syndrome can cause multi-organ failure by eliciting hyper inflammation characterized by a cytokine storm. (Huang et al., 2020b; Velavan and Meyer, 2020) Such a notion may support the finding that SARS-COV-2 is an infection that can cause a condition of hyper inflammation with subsequent damage to many organs. This current study is subject to some limitations. These limitations are the small sample size and limited age groups. Further clinical studies with larger sample sizes are required from different regions worldwide.

## 5. Conclusions

Determining the severity of COVID is crucial and should be of great interest to clinicians and healthcare providers to monitor and carefully manage severe cases. In clinical settings, predicting the severity of COVID in a patient is still not accessible to healthcare professionals. However, biomarkers may assist in such an issue. Therefore, this study assesses serum ferritin levels and high sensitivity CRP levels in COVID patients over 14 days. Results showed that both biomarkers are increased from day 1 to day 7 and returned to be declined in patients who fully recovered and released by day 14. In contrast, they increased dramatically from day 1 to day 14 in patients who moved to the intensive care unit or died. These findings suggest that both biomarkers can assist in predicting the overall severity and possible outcome.

### Author Contributions

ZA researched literature and wrote the manuscript's first draft. AK collected the samples, patients' clinical case history, follow up the patient's status in the Al-Sader Medical City. All authors have read and approved the final version of the manuscript.

### Competing financial interests

The authors have no conflict of interest

### Ethics

The current study was approved by Najaf Health Directorate (No:25/11/2020-29016) and the Al-sader Medical City ethics committee (No. 10675 in 30/11/2020) in Iraq, and inform consent was obtained from each patient who had been recruited.

### Data Availability

The authors have their own repository for any additional data availability.

### Abbreviations

COVID-19, Coronavirus disease 2019; hs-CRP, High-sensitivity C-reactive Protein; ICU, intensive care unit; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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