



## Ferritin Levels as Indicators of Severity and Mortality in COVID-19 Patients from Tripoli, Libya

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### Abstract

The rapid development of coronavirus disease nineteen (COVID-19) into a pandemic within months has posed significant risks, particularly for the elderly and individuals with underlying medical conditions. The primary driver of COVID-19 severity and mortality is the cytokine inflammatory storm. Elevated levels of ferritin, resulting from this storm and secondary hemophagocytic lymphohistiocytosis, have been observed in severe COVID-19 patients. The cytokine storm represents an uncontrolled and dysfunctional immune response within the pathogenic mechanism of COVID-19, leading to acute respiratory distress syndrome (ARDS) and systemic organ failure. Ferritin, an iron storage protein crucial for regulating cellular oxygen metabolism, shows a significant correlation with disease severity in COVID-19 patients. This study, conducted across three Libyan hospitals and two private laboratories from 2018 to 2022, targeted 500 cases to investigate ferritin's role in COVID-19. Polymerase Chain Reaction (PCR) tests confirmed COVID-19 positivity. Ferritin levels were measured using a fully automatic device, revealing high levels in almost all positive cases, with some experiencing levels as high as 4532 ng/ml. Analysis of 209 negative COVID-19 cases before and after the pandemic showed consistently low or normal ferritin levels. Among the positive cases, 250 were admitted to the ICU, with a significant proportion experiencing elevated ferritin levels, and 82 ICU patients succumbed to the disease. Gender and age did not seem to influence ferritin elevation in COVID-19 cases. In conclusion, increased ferritin levels may indicate worsening COVID-19 cases and could be associated with disease severity and mortality.

### 1. Introduction

In 2019, the coronavirus pandemic (COVID-19) spread worldwide, resulting in a significant number of positive COVID-19 cases [1]. Elderly individuals and those with underlying medical conditions such as diabetes, cancer, chronic respiratory disease, and cardiovascular disease are at high risk of experiencing serious complications and even death [2]. Despite initial reports about the disease in December 2019, many aspects of its pathophysiology remain unknown [3]. The primary initiating event associated with severity and mortality is the cytokine

inflammatory storm [4]. This storm is characterized by an uncontrolled and dysfunctional immune response, releasing inflammatory cytokines such as TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-1,2, and IL-8 in massive amounts during disease progression, which can lead to acute respiratory distress syndrome (ARDS) and systemic organ failure [2].

Ferritin, an iron storage protein, plays a crucial role in regulating cellular oxygen metabolism. It consists of two subunits, H and L, with previous studies suggesting that H-ferritin acts as an immunomodulatory molecule with both proinflammatory and immunosuppressive functions. Ferritin levels may indicate a strong inflammatory reaction triggered by viral introduction into the human body, impacting iron metabolism [5]. Elevated ferritin levels in serum have been significantly correlated with the severity of COVID-19 disease. A study revealed that severe cases of COVID-19 exhibited higher ferritin levels compared to moderate cases [5]. Reports also suggest that ferritin serves as an independent risk factor for the severity of COVID-19. Although the normal range of ferritin in most laboratories is 30 - 400 ng/ml, during infection, ferritin concentrations increase to sequester iron, reducing free iron available to pathogens. Increased ferritin synthesis during an acute phase response appears to be stimulated by cytokines independently of intracellular iron, leading to elevated serum ferritin levels [5].

A study conducted in China involving 20 cases of COVID-19 revealed a statistically significant difference in serum ferritin levels between individuals with severe and mild illnesses, with severe cases frequently experiencing increased ferritin levels. However, another study examining data from a significant multi-hospital health system in New York found serum ferritin to be ineffective at predicting mortality. Therefore, the association between ferritin and mortality and severity in COVID-19 patients remains unclear [4]. Similarly, another study reported high ferritin levels in patients who died from COVID-19 upon hospital admission and throughout their hospital stay, suggesting ferritin's potential role as a predictor for cytokine storm syndrome and progression to critical illness within the first seven days of hospitalization [18, 19]. Due to conflicting results from various studies regarding the association of ferritin with severity and mortality, further investigation into the relationship between iron metabolism and COVID-19 transmission is warranted.

The purpose of this study is to determine the role of ferritin in COVID-19 and investigate the relationship between iron metabolism and COVID-19 transmission. Additionally, it aims to determine whether ferritin levels are predictive of the severity of coronavirus disease 2019 (COVID-19).

## 2. Theoretical Part

This study was conducted across three hospitals between April and September 2022: Tripoli Medical Centre Hospital (TMCH), Tripoli Eye Hospital, and Tripoli Central Hospital (TCH). Two private laboratories (Alaistisharii Laboratory and AL-mukhtar Laboratory) were used to assess ferritin levels in COVID-19 cases. A total of 500 cases (positive and negative COVID-19) from the period 2018-2022 were studied. Among these, 209 cases served as negative controls, collected before and after the coronavirus pandemic (105 cases before the pandemic (2018-2019) and 104 cases after the pandemic in 2022). 291 positive COVID-19 cases were studied, and ferritin levels were measured. Out of these 291 cases, 250 were admitted to the ICU (94 at Tripoli University Hospital, 123 at Tripoli Central Hospital, and 33 at Tripoli Eye Hospital), while 41 received care at home.

## 3. Experimental Procedure

COVID-19 diagnosis was confirmed through Polymerase Chain Reaction (PCR) examination using nasopharyngeal swab samples to detect the virus's genetic material. The severity of COVID-19 patients was categorized based on guidelines from the National Center for Disease Control - Libya, Tripoli branch. Data from 105 negative control cases (before the pandemic, 2018-2019) were collected from Alaistisharii Laboratory. 104 negative control cases (recovered from COVID-19 after the pandemic in 2022) were analyzed in AL-mukhtar Laboratory. Ferritin levels in the 104 blood samples were measured using chemiluminescence immunoassay technique. Results were reported in terms of ferritin nanograms (ng) per milliliter of serum (ng/ml).

### 3.1. Statistical Analysis

Prism 5 was used for statistical data analysis. Mean values were used to analyze the effects of age groups, gender, and ferritin levels.

4. Results and Discussion

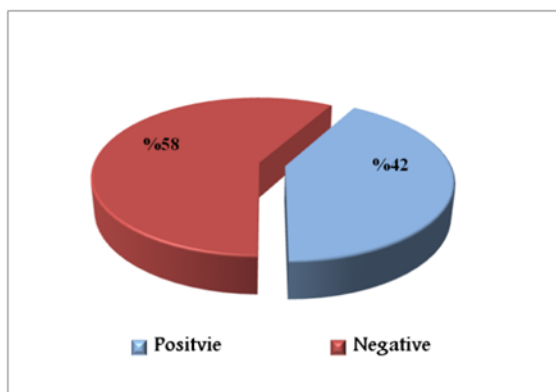
**Table (1):** Total distribution of patients.

1. Total patients (500)	
2. Negative COVID - 19	3. 209
4. Positive COVID - 19	5. 291
6.	
7. IUC	8. 250
9. Home care	10. 41
11. Died (ICU)	12. 82
13. Recovered (ICU)	14. 168

**Table (2):** Level of ferritin in died patients.

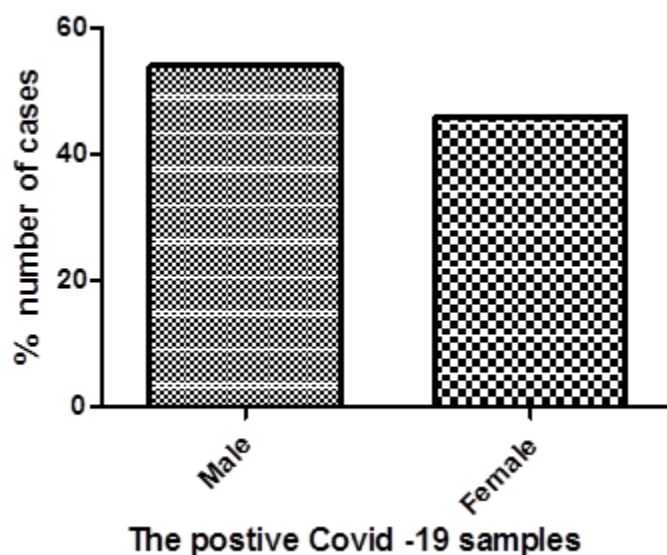
<b>1. Total patients died in ICU (82)</b>	
2. no of patients	3. Level of ferritin
4. 68	5. 4353ng/ml
6. 14	7. 30-400ng/ml

This study demonstrates that when comparing ferritin and CRP levels to ferritin and D-dimer levels, CRP shows a significant association with COVID-19.



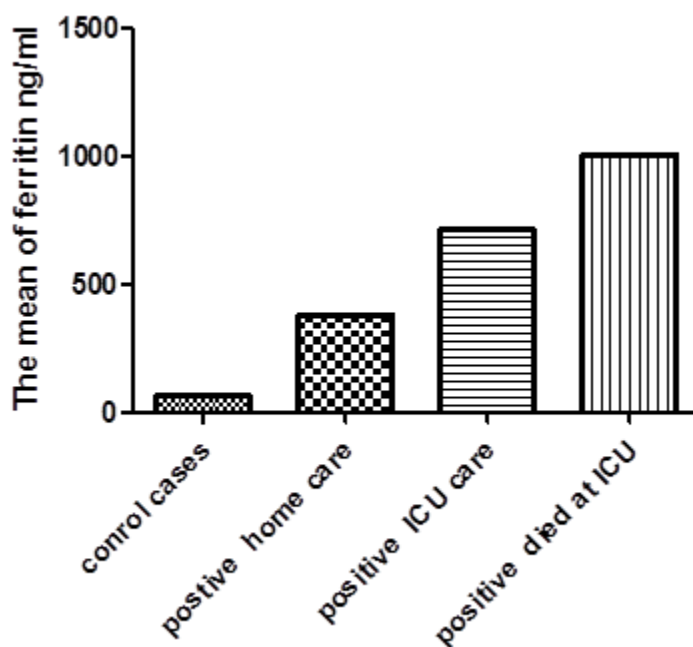
**Figure (1):** The study's sample by pathological condition.

In this study (Table 1), a total of 500 (100%) cases were targeted. Among these, 209 (41.8%) cases were utilized as negative COVID-19 controls, while 291 (58.2%) cases were classified as positive COVID-19 cases (Figure 1). Among the 291 positive COVID-19 cases, 156 (54%) were males and 135 (46%) were females (Figure 2).



**Figure (2):** The positive COVID -19 sample classification by gender.

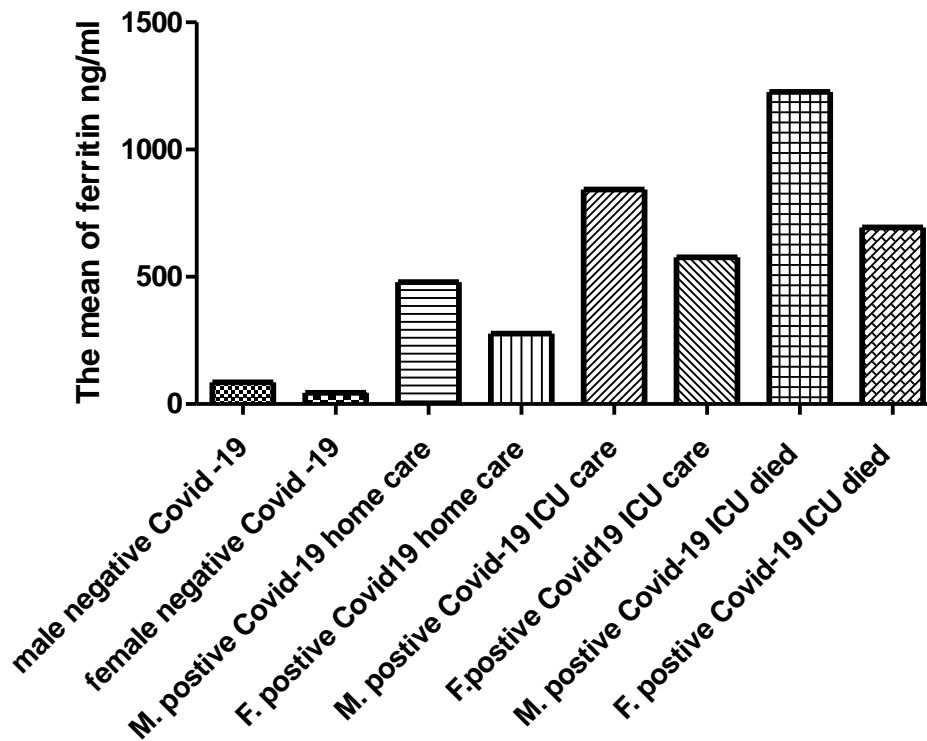
Out of the 500 cases, the average ferritin levels were as follows: 63.65 ng/ml for the 209 negative COVID-19 cases, 380.6 ng/ml for the 41 positive COVID-19 cases that received care at home, 714.26 ng/ml for the 168 cases admitted to the ICU and recovered, and 1005.8 ng/ml for the 82 cases that were admitted to the ICU and died (Figure 3).



**Figure (3):** The mean of ferritin level for all positive (COVID-19) cases.

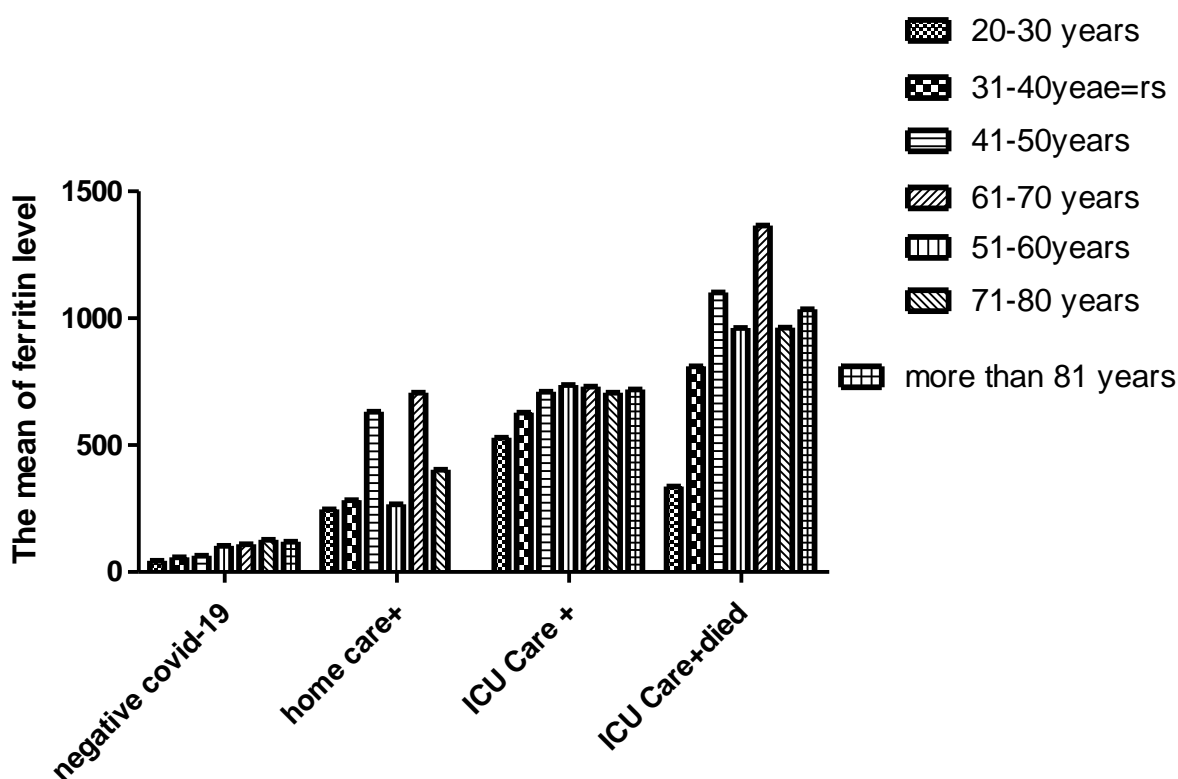
The mean level of ferritin for males in the negative control group for COVID-19 was 85.31 ng/ml, while for females, it was 43.75 ng/ml (Figure 4). Among the positive COVID-19 cases receiving home care, the mean ferritin level was 479.64 ng/ml for males and 276.6 ng/ml for females (Figure 4).

For COVID-19 positive cases admitted to the ICU and subsequently recovered, the mean ferritin level was 842.6 ng/ml for males and 576.43 ng/ml for females (Figure 4). In contrast, for COVID-19 positive cases admitted to the ICU who later died, the mean ferritin level was 1226.59 ng/ml for males and 694.1 ng/ml for females (Figure 4).



**Figure (4):** The mean level of ferritin fo male and female.

Comparison between the mean level of ferritin and the ages of patients is depicted in Figure 5. For individuals aged 20 to 30 years old, the mean ferritin levels were as follows: 44.98 ng/ml for negative control COVID-19 cases, 247.03 ng/ml for positive COVID-19 cases receiving care at home, 529.99 ng/ml for positive COVID-19 cases admitted to the ICU and recovered, and 337.1 ng/ml for positive COVID-19 cases admitted to the ICU and subsequently died.



**Figure (5):** The level of ferritin in the patients according to the age.

The mean level of ferritin for the age group 31 to 40 years old was 58.65 ng/ml for negative control COVID-19 cases, 283.17 ng/ml for positive COVID-19 cases receiving home care, 628.45 ng/ml for COVID-19 patients recovered from the ICU, and 810.7 ng/ml for COVID-19 patients who died in the ICU. For the age group 41 to 50 years old, the mean ferritin level was 64.36 ng/ml for negative control COVID-19 cases, 632.28 ng/ml for positive COVID-19 cases receiving home care, 710.67 ng/ml for COVID-19 patients recovered from the ICU, and 1101.52 ng/ml for COVID-19 patients who died in the ICU. Among individuals aged 51 to 60 years old, the mean ferritin level was 102.54 ng/ml for negative control COVID-19 cases, 266.29 ng/ml for positive COVID-19 cases receiving home care, 736.39 ng/ml for COVID-19 patients recovered from the ICU, and 961.98 ng/ml for COVID-19 patients who died in the ICU. For the age group 61 to 70 years old, the mean ferritin level was 108.77 ng/ml for negative control COVID-19 cases, 706.61 ng/ml for positive COVID-19 cases receiving home care, 730.42 ng/ml for COVID-19 patients recovered from the ICU, and 1365.57 ng/ml for COVID-19 patients who died in the ICU. In addition, for individuals aged 71 to 80 years old, the mean ferritin level was 126.49 ng/ml for negative control COVID-19 cases, 403.38 ng/ml for positive COVID-19 cases receiving home care, 706.43 ng/ml for COVID-19 patients recovered from the ICU, and 962.5 ng/ml for COVID-19 patients who died in the ICU. For those aged 81 years old and over, the mean ferritin level was 119.11 ng/ml for negative control COVID-19 cases, 719.28 ng/ml for COVID-19 patients recovered from the ICU, and 1035.98 ng/ml for COVID-19 patients who died in the ICU; no cases in this age group received care at home for positive COVID-19. The main finding of our study is that higher ferritin levels were observed among COVID-19 patients compared to (negative) controls, and elderly patients with elevated ferritin showed higher mortality rates than those with lower ferritin levels. Serum ferritin has recently been identified as one of the predictors of death in COVID-19 patients.

In positive COVID-19 cases, the mean ferritin level was twice as high in males than in females (911.9 ng/ml in males and 516.6 ng/ml in females). The mean age of 65 years with predominantly male COVID-19 control cases had higher ferritin levels than females; generally, males are at a higher risk of severe COVID-19 than females. The possible reasons for the gender discrepancy could include differences in social habits, comorbid conditions, and psychological and social characteristics.

This study also shows that the average ferritin level in positive COVID-19 cases admitted to the ICU and died was higher than in positive COVID-19 cases admitted to the ICU who recovered and those who received home care, respectively. This study is consistent with a previous study that also reported elevated ferritin levels in non-survivors. Furthermore, Zhou et al. revealed that the hospital death rate was higher in patients with serum ferritin levels  $>300$  ng/mL than in patients with serum ferritin levels  $\leq 300$  ng/mL. The high level of ferritin in positive COVID-19 cases admitted to the ICU and died may have contributed to the mortality of COVID-19 cases. Therefore, the ferritin test may be a useful biomarker for predicting mortality in the ICU. Our findings are supported by the studies conducted by Zhou et al. (2020) in China and Ahmed et al. (2021) in Egypt, where increased CRP, ferritin, and D-dimer levels occurred in all patients, with a significantly higher value in the severe COVID-19 group. The present study also found that elderly COVID-19 patients in their 50s and 60s tended to have more severe disease than younger patients. Liu and their colleagues (2020) found that elderly patients with COVID-19 had more severe disease compared to younger patients. The higher mortality rate in the elderly population might be explained by an increase in comorbidities with advancing age. In conclusion, we advise researchers in the future to track cases and record ferritin levels from the beginning of COVID-19 infection to the stage of recovery or death. We also recommend ferritin as a biomarker for COVID-19 patients in determining the severity of inflammation, and we advise future researchers to extend the geographical range of research to all cities of Libya.

## 5. Conclusions

The study conclusively demonstrates that elevated ferritin levels are a significant indicator of COVID-19 severity, with the highest levels observed in ICU patients, particularly those who succumbed to the disease, suggesting its potential as a biomarker for predicting mortality. Gender did not markedly affect ferritin elevation, but age did, with elderly patients showing higher levels, correlating with increased severity and mortality rates. These findings emphasize the importance of monitoring ferritin levels for better management of COVID-19 patients and suggest the need for expanded research across different geographic and demographic groups to further understand the implications of ferritin in COVID-19 progression and outcomes.

**Conflict of Interest:** The authors declare that there are no conflicts of interest associated with this research project. We have no financial or personal relationships that could potentially bias our work or influence the interpretation of the results.

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