

Original article

Evaluation of Ferritin Levels in Individuals with COVID-19: A Laboratory-Based Observational Research Investigation

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Abstract

COVID-19 has emerged as a major public health concern because of its rapid transmission and the high mortality risk associated with severe cases. Although considerable research has been conducted, the disease's pathophysiological processes and diagnostic indicators still require further investigation. Early detection, continuous patient monitoring, and appropriate therapeutic interventions are essential for improving clinical outcomes and reducing mortality. Serum ferritin has attracted attention as a potential indicator of inflammation and disease severity in patients with COVID-19. This study aimed to determine serum ferritin levels in patients with confirmed COVID-19 and explore their potential association with disease severity. A study was conducted at the Yafran Pathology Center and the Analysis Laboratory in the Andalusia District. We analyzed blood samples from patients with confirmed COVID-19 according to standard laboratory procedures. Serum ferritin concentrations were measured using the Integra 400 Plus analyzer. A total of 293 patients, including males and females, were enrolled in the study. Participants were classified into five age categories: 0–17 years, 18–34 years, 35–49 years, 50–64 years, and 65 years or older. Increased serum ferritin concentrations may be associated with greater severity of COVID-19. Ferritin could therefore be a useful potential biomarker for evaluating disease severity and supporting clinical decision-making. However, further statistical analysis is needed to determine the significance of this relationship and assess its predictive value.

Keywords. Ferritin Levels, COVID-19, A Laboratory Investigation.

Introduction

Ferritin is a widespread intracellular protein crucial for iron balance, acting as the main storage container for iron in a safe, bioavailable manner. Aside from its function in iron sequestration, ferritin acts as an important acute-phase reactant, with serum concentrations often utilized as a clinical marker for iron deficiency, overload, and systemic inflammation. Ferritin plays a crucial role in immune dysregulation, particularly during severe hyperferritinemia, by exerting direct immune-suppressive and pro-inflammatory effects, which aid in producing the cytokine storm [1]. Reports indicate that severe outcomes from COVID-19 are linked to cytokine storm syndrome [2], suggesting that the severity of the disease relies on this syndrome. Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus capable of inducing severe acute respiratory syndrome. The pathogen primarily targets the respiratory tract, with transmission occurring via infectious aerosols expelled during coughing or sneezing. The clinical presentation of the disease is highly variable; common symptoms include fever, rhinorrhea, nasal congestion, dyspnea, and headache. While a vast majority of cases present as a mild, influenza-like illness or remain entirely asymptomatic, a critical subset of patients experiences a more severe disease trajectory. This can culminate in severe pneumonia, acute respiratory distress syndrome (ARDS), and systemic multi-organ failure—frequently compromising the renal, hepatic, and cardiovascular systems.

Many diabetic patients show increased serum ferritin levels [3-5], and it is recognized that they have a greater risk of encountering severe complications from COVID-19 [6]. In light of this, we succinctly examine evidence backing the idea that ferritin levels could significantly impact the severity of COVID-19. The mechanisms linking hyperferritinemia to disease severity in COVID-19 patients remain uncertain, but there are several potential explanations for this occurrence. Firstly, pro-inflammatory cytokines like interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and IL-6 could enhance ferritin production [7]. Secondly, Inflammation-related cellular damage can lead to the release of intracellular ferritin, resulting in increased serum ferritin levels [8]. Thirdly, under acidosis, the microvascular environment and heightened reactive oxygen species (ROS) production may release iron from ferritin, and this free iron can engage in generating hydroxyl radicals, leading to additional cellular damage [8], aggravating tissue injury, thus establishing a destructive cycle of inflammation. This investigation may support and enhance other studies which point out that elevated serum ferritin levels may serve as an independent risk factor for the severity of COVID-19. Evaluating serum ferritin levels while hospitalized could be crucial for identifying high-risk patients with COVID-19.

Material and Methods

A study was conducted using blood samples obtained from patients diagnosed with COVID-19 at Yafrin Hospital (Western Mountain) and El-Andalus Laboratory (Tripoli). Data collected from patients were evaluated to determine Ferritin levels in blood samples. All samples were processed according to standard laboratory procedures, and Ferritin concentrations were measured using the Integra 400Plus system.

Results

The study cohort comprises a total of 293 patients, consisting of 136 males and 157 females, reflecting a slight female predominance overall.

Table 1. Number of patients by age group and sex (Ferritin)

Age group	Male, n	Female, n	Total, n
0–17 years	7	4	11
18–34 years	22	42	64
35–49 years	37	28	65
50–64 years	23	38	61
≥65 years	47	45	92

The ferritin profile for females shows a distinct pattern, which differs significantly from the general upward trend seen in males. There is a sharp decline in ferritin levels after childhood. The lowest levels are seen in the 18–34 years (23.9 ng/mL) and 35–49 years (17.1 ng/mL) age groups. This is a classic physiological pattern in women, primarily attributed to iron loss through menstruation and the high iron demands of pregnancy and breastfeeding. Levels begin to rise significantly in the 50–64 years group (80.0 ng/mL). This corresponds with the onset of menopause, where the cessation of monthly blood loss allows iron stores to begin rebuilding. The highest median ferritin level is found in the > 65 years group (177.0 ng/mL). By this age, women have typically been post-menopausal for over a decade, allowing ferritin levels to accumulate significantly, though they often remain lower than male peaks in the same age brackets. Interestingly, the 0–17 years group has a relatively high median (107.5 ng/mL). This may reflect the period before the onset of menstruation or high nutritional support during childhood. Overall, the graph highlights the significant impact of the female reproductive cycle on iron stores. Clinical interpretation of ferritin in women must be highly age-dependent, as levels considered "normal" for a 40-year-old would be considered very low for a 70-year-old or a child.

Table 2. The median concentration of ferritin

Age Group	Male Median (ng/mL)	Female Median (ng/mL)	The "Gap"
0–17 years	41.4	107.5	Females +66.1
18–34 years	100.2	23.9	Males +76.3
35–49 years	276.0	17.1	Males +258.9
50–64 years	564.0	80.0	Males +484.0
≥65 years	298.0	177.0	Males +121.0

The median values (ng/mL) were compared between males and females across five age groups (0–17, 18–34, 35–49, 50–64, and ≥65 years). In the 0–17 years age group, females demonstrated a higher median value (107.5 ng/mL) compared with males (41.4 ng/mL), indicating greater levels of the measured parameter among females during childhood and adolescence. In the 18–34 years age group, the trend reversed, with males showing a higher median value (100.2 ng/mL) compared with females (23.9 ng/mL). This difference suggests a possible age-related shift in the distribution of the measured variable between sexes. A substantial increase in the male median value was observed in the 35–49 years age group (276.0 ng/mL), whereas the female median remained low (17.1 ng/mL). This pattern continued in the 50–64 years group, where males reached the highest median value (564.0 ng/mL) across all categories, while females showed a moderate increase (80.0 ng/mL). In the ≥65 years age group, male median values decreased to 298.0 ng/mL compared with the previous age group, whereas female median values increased markedly to 177.0 ng/mL.

Consequently, the difference between males and females became less pronounced in older individuals. Overall, the results demonstrate a progressive increase in median values among males with advancing age, peaking at 50–64 years, followed by a slight decline in the elderly group. In contrast, females exhibited higher values during early life, a decline in young and middle adulthood, and a notable increase in older age. These findings suggest potential age, and sex-related physiological differences influencing the measured parameter. Ferritin can be considered as a marker for COVID-19 prognosis and disease severity. In addition to severe systemic inflammation caused by complex immunological changes, COVID-19 patients often present with a dysregulated coagulation cascade system, leading to further cardiovascular decompensation [9].

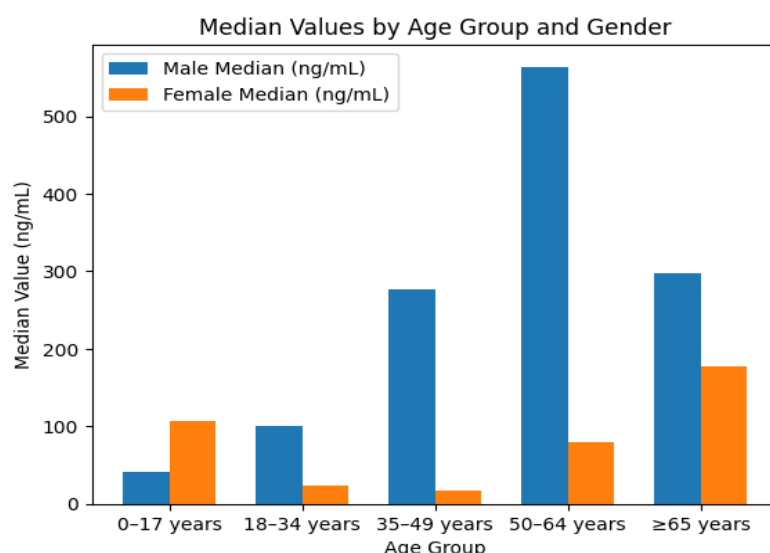


Figure 1. Comparison of Median Values by Age Group and Gender.

Discussion

This study highlights the importance of the use of inflammatory markers such as serum ferritin in predicting the outcome of COVID-19 subjects, as they have a strong relation with disease mortality, ICU admission, and need for mechanical ventilation, which helps in early detection of case risk of progression and consequently improving outcome. Ferritin can be considered as a marker for COVID-19 prognosis and disease severity. In addition to severe systemic inflammation caused by complex immunological changes, COVID-19 patients often present with a dysregulated coagulation cascade system leading to further cardiovascular decompensation [9]. Massive systemic release of pro-inflammatory mediators such as interleukin (IL)-1, IL-2, IL-6, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte colony-stimulating factor (G-CSF), etc., also known as cytokine storm [10] contributes to acute respiratory distress syndrome (ARDS) [11]. In addition, many of these patients present with hyperferritinemia, which may result from hemolysis caused by SARS-CoV-2-induced inflammation [12,13]. Considering the combined presence of excessive cytokine release and hyperferritinemia on many occasions, it was proposed that COVID-19 should be considered as a spectrum of hyperferritinemic syndromes [14-16]. Progressively high ferritin values, along with other inflammatory biomarkers, have been consistently reported to be associated with increased disease severity and mortality [17-19].

Recently, a scoring system for predicting disease severity, namely, the Severe COVID Prediction Estimate (SCOPE) score, has been developed, which is composed of circulating levels of ferritin, C-reactive protein, D-dimers, and IL-6. SCOPE score values of 6 or more predict the progression to severe respiratory failure or death within 2 weeks of hospital admission for pneumonia [20]. Also, serum ferritin levels dropped in patients treated with tocilizumab, an IL-6 receptor antibody [21]. Interestingly, a study reports that patients with higher ferritin levels (than the median value of 1419 $\mu\text{g/L}$) benefitted most from tocilizumab treatment [22]. Altogether, these results establish that ferritin assessment is a useful prognostic indicator that can be used as a screening test for the prediction of disease severity and mortality.

Regarding the data collected, the $\geq$ age 65 years category is the largest segment of the population, with a total of 92 patients. The 0-17 years category is the least represented (11 individuals), indicating that minors make up only a tiny fraction (less than 4%) of the total group. The adult groups (18-34, 35-49, and 50-64) are remarkably similar in total size, each containing between 61 and 65 individuals. Regarding gender configuration and differences, while the overall gender split is relatively balanced (53.6% female vs. 46.4% male), there are striking differences within specific age brackets; the young adults (18-34 years) show the most significant gender imbalance. There are nearly twice as many females (42) as males (22). However, in the case of Middle Age (35-49 years), the trend reverses, with males (37) outnumbering females (28). In Older Adults (50-64 years), the female population (38) is again notably higher than the male population (23). In the case of age greater than or equal to 65 years, the group is the most gender-balanced of the adult cohorts, with 47 males and 45 females.

Regarding key demographic "Shapes", the male population shows a steady increase as age increases, peaking sharply at the senior level $\geq$ age 65). The female population, on the other hand, shows a "bimodal" or two-peak distribution, with high representation in the young adult (18-34) and senior $\geq$ age 65 categories, and a dip in the 35-49 range. In conclusion, the data describe a population that is skewed toward older age groups, particularly those over 65. While the total gender ratio is close to equal, the significant fluctuations in gender balance across different life stages (e.g., the female majority in young adulthood vs. the male majority in middle age) may be an important factor to consider as this data is used for medical research. In the case of median concentration regarding males, Direct Correlation with Age (Up to 64 Years): There is a clear and steady increase in median ferritin levels from childhood (0-17 years) through middle age (50-64 years). This suggests that ferritin, which reflects the body's iron stores, naturally accumulates over time. The highest median ferritin level is observed in the 50-64 years age group (564.0 ng/mL). This concentration is more than double that

of the preceding group (35–49 years). Interestingly, after the peak in the 50–64 group, there is a substantial decline in the ≥ 65 years group, where the level drops to 298.0 ng/mL. Despite this drop, it remains significantly higher than the levels seen in younger adults (under 35). The youngest group (0–17 years) has the lowest median ferritin at 41.4 ng/mL, which is typical as iron requirements are high during growth and development.

Concerning the comparative Analysis of Ferritin by gender, the most striking finding is the divergent "shape" of iron storage over time for men versus women. Male ferritin levels show a linear increase that peaks in the 50–64 age group (564.0 ng/mL). This suggests a steady lifetime accumulation of iron. The subsequent drop in the ≥ 65 group (298.0 ng/mL) may be related to age-associated chronic conditions or changes in dietary intake/absorption. On the other hand, female data show a "U-shaped" curve. High childhood levels (107.5 ng/mL) plummet during the reproductive years (ages 18–49), reaching a nadir of 17.1 ng/mL. This is maybe a clear physiological marker of menstruation and pregnancy, which deplete iron stores. After age 50 (the post-menopausal convergence, female levels begin to climb again, peaking at ≥ 65 (177.0 ng/mL). While women's iron stores "recover" after menopause, their median levels never reach the high peaks seen in the male cohort. The demographic table provides essential context for how much weight we should give to these ferritin medians. High Confidence in Senior Data: The ≥ 65 group is the most robustly sampled ($n=92$), meaning the ferritin medians of 298.0 (M) and 177.0 (F) are likely the most stable and representative figures in the set.

Conclusion

This retrospective investigation highlights the utility of serum ferritin as an independent risk factor for determining COVID-19 severity, demonstrating that elevated ferritin levels at hospital admission can play a crucial role in early risk assessment, clinical management, and identifying high-risk patients. Overall, the findings indicate that older individuals and male patients face a significantly higher risk of developing severe or critical forms of the disease compared to younger or female counterparts. Beyond its relationship to COVID-19 severity, the cohort's baseline ferritin profiles reflect key biological and demographic patterns across age groups. Data for the pediatric cohort (0–17 years) remain limited due to a small sample size of just 11 participants (7 males, 4 females), meaning median ferritin values of 41.4 ng/mL for males and 107.5 ng/mL for females should be interpreted with caution due to susceptibility to outliers. In contrast, the 18–34 age bracket features nearly double the number of females compared to males (42 vs. 22), providing a strong statistical sample that reinforces the reliable observation of low ferritin in young women. Sex-specific differences become particularly pronounced in middle adulthood. Women aged 35–49 exhibit a low median ferritin level of 17.1 ng/mL, placing more than half of the females in this bracket near or below standard clinical thresholds for iron deficiency (<15 to <30 ng/mL). Conversely, middle-aged men display a remarkably high median ferritin level of 564.0 ng/mL, warranting clinical investigation into potential iron overload risks or contributing demographic factors such as high red meat intake and alcohol consumption.

Conflict of interest. Nil

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