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**RESEARCH**

# Causes of hyperferritinemia: what has changed with the pandemic?

## Hiperferritineminin nedenleri: pandemi ile neler değişti?

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**Abstract**

**Purpose:** In this study, we aimed to analyze patients with ferritin levels of ≥ 1000 ng/mL based on diagnoses and the wards they received both before the COVID pandemic and during the pandemic periods.

**Materials and Methods:** This retrospective study evaluated the patients who applied to a tertiary hospital and had ferritin onset of the pandemic. The patients' demographic and clinical characteristics and ferritin levels were obtained from the hospital's medical records.

**Results:** There were 2022 patients, 635 (31.4%) female and 1387 (68.6%) male, with a median age of 62 (49-71) years. 554 patients (27.4%) before the pandemic, and 1468 patients (72.6%) during the pandemic had ferritin levels of ≥ 1000 ng/mL. Hyperferritinemia was detected more frequently in males during the pandemic ($p<0.001$). Before the pandemic, the most prevalent cause of hyperferritinemia was hematologic malignancies, while COVID-19 was the most common cause of hyperferritinemia during the pandemic. Hyperferritinemia was commonly detected in the hematology department before the pandemic, while it was frequently performed in COVID-19 clinics and intensive care units after the onset of the pandemic.

**Conclusion:** In the current study, the most prevalent cause of hyperferritinemia was hematological malignancies before the pandemic, and COVID-19 infection during the pandemic. Therefore, it is important to consider the most common conditions that match the patient's clinical condition when detecting extremely high ferritin values. Nevertheless, many other important clinical situations should also be kept in mind.

**Keywords:** COVID-19, hyperferritinemia, pandemic

**Öz**

**Amaç:** Çalışmanın amacı, ferritin düzeyi 1000 ng/mL ve üzeri olan hastaların, COVID-19 pandemi öncesi ve pandemi döneminde tanılarına ve takip oldukları servislere göre dağılımını değerlendirmektir.

**Gereç ve Yöntem:** Bu retrospektif çalışmada, pandemi öncesi 18 ay ile pandemi başlangıcından sonraki 18 ay arasında üçüncü basamak bir hastaneye başvuran ve ferritin düzeyleri 1000 ng/mL'nin üzerinde olan hastalar değerlendirilmiştir. Hastaların demografik ve klinik özellikleri ile ferritin düzeyleri hastanenin tıbbi kayıtlarından elde edilmiştir

**Tartışma:** Ortanca yaşı 62(49-71) olan 635'i (%31,4) kadın ve 1387'si (%68,6) erkek olmak üzere toplam 2022 hasta vardı. Pandemi öncesinde 554 hastanın (%27.4) ferritin düzeyi 1000 ng/mL ve üzeri, pandemi sırasında ise 1468 hastanın (%72,6) ferritin düzeyi 1000 ng/mL ve üzerindeydi. Pandemi döneminde erkeklerde hiperferritinemi daha sık saptandı($p<0,001$). Pandemi öncesinde en sık hiperferritinemi nedeni hematolojik maligniteler iken pandemi döneminde en sık COVID-19 yer almaktaydı. Takip oldukları servislere göre dağılımında ise pandemi öncesinde hematoloji bölümü, pandemi döneminde ise COVID-19 klinikleri hiperferritineminin en sık saptandığı bölümlerdi.

**Sonuç:** Bu çalışmada, hiperferritineminin en yaygın nedeninin pandemi öncesinde hematolojik maligniteler olduğu, pandemi döneminde ise COVİD-19 olduğu saptandı. Bu sebeple aşırı yüksek ferritin değerleri tespit edildiğinde önemli klinik durumlar akılda tutmak gerekse de ilk olarak hastanın klinik durumu ile uyumlu olabilecek en yaygın tabloları düşünmemiz gerektiği kanaatindeyiz.

**Anahtar kelimeler**: COVD-19, hiperferritinemi, pandemi

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## INTRODUCTION

Ferritin indicates the total amount of body iron and is used as a clinical test since the late 1900s. Ferritin is crucial in iron metabolism by both transporting and storage. It stores iron in a biologically active and non-toxic form. It protects cellular molecules from the toxic effects of unstable iron[1–3]. Plasma ferritin levels usually represent the total iron storage. For example, 1 ng/ml ferritin level represents approximately 10 mg iron in the body. Ferritin values less than 15 ng/ml are specific for the diagnosis of iron deficiency, even ferritin levels vary depending on ethnicity, gender, age, and laboratory[4,5]. Normal levels of ferritin range between 15-300 ng/ml in males and 15-160 ng/mL in females. Although levels above 300 ng/mL in men and 200 ng/mL in women are entitled as hyperferritinemia, a ferritin level of 1000 ng/mL and above is considered as non-specific but more sensitive in predicting the presence of underlying inflammatory disease. Ferritin is a positive acute phase reactant and an indicator of inflammation, although it has limited value as an inflammatory marker[3,6]. However, ferritin can be used in the diagnosis of several clinical conditions. Hyperferritinemia is often difficult to interpret clinically[7]. Hyperferritinemia can stem from a variety of causes, encompassing liver, renal, and rheumatologic diseases, malignancies, chronic blood transfusions, HIV (human immunodeficiency virus) and other viral infections, diverse hematological disorders, chronic inflammation, or metabolic syndrome[1–3].

Hyperferritinemia is remarkably associated with mortality, regardless of underlying pathology[7]. In a prospective population-based study in Denmark, ferritin emerged as a robust predictor of premature death within the general population. The study also revealed a gradual escalation in the risk of premature death corresponding to incremental increases in ferritin levels, reaching the highest cumulative risk at levels equal to or exceeding 600 ng/mL[8]. A less common yet life-threatening condition associated with markedly elevated ferritin levels is hemophagocytic lymphohistiocytosis. In a mixed cohort study of critically ill patients, the maximum ferritin level that would differentiate hemophagocytic lymphohistiocytosis from other causes of hyperferritinemia was 9,083 ng/mL[9].

The novel Coronavirus disease 2019 (COVID-19) was detected in Wuhan, China, in December 2019 and became a pandemic rapidly. Excessive production of the pro-inflammatory cytokines may lead to a hyperinflammatory state in the course of COVID-19. Respiratory system involvement and severe hyperinflammation may cause a more severe clinic that may cause mortality and morbidity. Furthermore, recent clinical studies have investigated that high serum ferritin levels are associated with multiple organ dysfunction and death[4,10–14]. Macrophage activation syndrome, frequently leading to mortality in COVID-19 patients, is usually associated with extreme hyperferritinemia.

Serum ferritin is a critical biomarker whose importance was highlighted during the COVID-19 pandemic. Clinicians need to be able to predict and identify clinical conditions in which serum ferritin levels are significantly elevated. In this study, we aimed to evaluate the differences in the distribution of patients with serum ferritin levels of 1000 ng/mL and above according to their diagnoses and the wards in which they were hospitalized before and during the COVID-19 pandemic. We hypothesized that the diagnoses of hyperferritinemia with COVID-19 and the wards that followed them would differ. Our study makes a significant contribution to the validation of existing literature data. In addition, the impact of increased awareness of ferritin testing during the COVID-19 pandemic on the distribution of diagnosis has not yet been evaluated, although investigations into the causes of hyperferritinemia have been performed in various tertiary centers. Besides, other hyperferritinemia causes should not be overlooked even in the COVID-19 pandemic. Therefore, our study will provide important insights into this aspect of the literature.

## MATERIALS AND METHODS

### Sample

The sample size was determined by using the G. power 3.1 program, which indicated a minimum of 482 cases. The specified parameters for this calculation were an effect size of 0.300, an alpha error coefficient of 0.05, and a desired power of 95%. In this case, the actual power of the analysis method was 95%. There were no difficulties with the expected power.

The patients with a high serum ferritin level (1000 ng/mL and above) between the 18 months before and the first 18 months of the COVID-19 pandemic were included in the study. A list of all patients with

a ferritin level of 1000 ng/mL and above, who had applied to Gülhane Training and Research Hospital between September 2018 and September 2021, was compiled. Patient demographic and clinical characteristics and ferritin levels were obtained from hospital medical records. The general scan of the hospital was performed by the IT department after obtaining the necessary permissions. The patient list was reviewed by specialist doctors (Ö.K., M.K., E.Ç.G.) according to the inclusion criteria. There were 1170 serum ferritin tests before the pandemic and 5409 serum ferritin tests during the pandemic with 1000 ng/mL and above, corresponding to 2389 patients during the 36-month inclusion period. For patients who had multiple ferritin measurements, the highest value was utilized. Patients younger than 18 years and those with missing data were excluded. Before the pandemic, 117 patients and during the pandemic, 121 patients were determined to be younger than 18 years and were excluded from the study. Twelve patients before the pandemic and 17 patients during the pandemic were excluded from the study due to missing data. As a result, a total of 2022 patients were included in the study, 554 patients before the pandemic and 1468 patients during the pandemic.

## Procedure

The present study was approved by the Non-Interventional Research Ethics Committee of Gülhane University of Health Sciences and Research Hospital (date: 02.03.2022, decision number: 2022/22). All procedures were performed according to the Declaration of Helsinki. This retrospective study was conducted at Gulhane Training and Research Hospital between September 2018 and September 2021.

Hyperferritinemia was defined as a serum ferritin level of 1000 ng/mL and above [15]. Patients were further divided into two groups according to their ferritin levels; group 1 had ferritin levels between 1000 and 1500 ng/mL and group 2 had ferritin levels above 1500 ng/mL. In our center, high ferritin levels are often expressed as >1500 ng/mL. The groups were divided accordingly. The underlying causes of hyperferritinemia were determined by reviewing the patients' medical records. The causes of hyperferritinemia were classified as rheumatologic disorders, hematologic and solid organ malignancies, renal failure, infectious diseases, liver injury, and iron overload. Renal failure was defined as the need for renal replacement therapy or a glomerular filtration rate of less than 20 mL/min/1.73m$^2$ [1]. Liver injury was defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels greater than 500 U/L [1]. Iron overload was defined as patients receiving monthly erythrocyte suspension transfusions for at least six months, requiring chelation therapy, or iron overload as determined by a hematologist[16,17].

## Ferritin assay

Serum ferritin levels were measured by enzyme-linked immunosorbent assay (ELISA) using a Beckman Coulter device (UniCel DxI 800). Normal ferritin levels ranged from 11-306.8 ng/mL in female patients and 23.9-336.2 ng/mL in male patients.

## Outcome

The primary outcome of the study was to identify clinical conditions causing hyperferritinemia in the periods of 18 months before and during the first 18 months of the COVID-19 pandemic. The secondary outcome of the study was the distribution of hyperferritinemia by clinical ward.

## Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Compliance of variables with normal distribution was determined by Kolmogorov-Smirnov and Shapiro-Wilk tests, skewness and kurtosis values, and histogram graphs. The median (25%-75%) values of numerical variables that did not fit the normal distribution were reported. Categorical variables were expressed as numbers (percentage distributions). Comparative analyses were performed according to ferritin levels and pre-pandemic and pandemic periods. The Mann-Whitney U test was used to compare the median values of non-normally distributed numerical variables between these groups. Pearson chi-squared and Fisher's exact test were used to compare categorical variables between these groups. A p-value of $<0.05$ was considered statistically significant.

# RESULTS

There were 2022 patients (635 female and 1387 male) with a median age of 62 years (49-71 years). Hyperferritinemia was observed in 554 (27.4%) patients before the COVID-19 pandemic and in 1468

(72.6%) patients during the first 18 months of the pandemic. The most common cause of hyperferritinemia among all patients was COVID-19 infection (47.4%). Other causes of hyperferritinemia were hematologic malignancies (11.9%), other infectious diseases (11.2%), solid organ malignancies (11.2%), renal failure (7%), liver damage (5%), iron overload (4.4%), and rheumatologic diseases (1.8%) (Table 1).

**Table 1. Demographic characteristics and diagnoses of patients with hyperferritinemia (n=2022)**

| Variable | value |
|---|---|
| Age * | 62 (49-71) |
| **Gender **** | |
| Male | 1387 (68.6) |
| Female | 635 (31.4) |
| **Diagnosis groups **** | |
| COVID-19 infection | 960 (47.5) |
| Non-COVID-19 infection | 227 (11.2) |
| Hematological Malignancy | 241 (11.9) |
| Iron overload | 89 (4.4) |
| Liver damage | 100 (5.0) |
| Kidney failure | 142 (7.0) |
| Solid Organ Malignancy | 226 (11.2) |
| Rheumatological diseases | 37 (1.8) |
| **Department followed **** | |
| COVID-19 clinics | 466 (23.1) |
| COVID-19 outpatient clinics | 49 (2.4) |
| COVID-19 intensive care | 389 (19.2) |
| Nephrology | 94 (4.7) |
| Hematology | 275 (13.6) |
| Oncology | 103 (5.1) |
| Infectious diseases | 17 (0.8) |
| Gastroenterology | 63 (3.1) |
| Rheumatology | 38 (1.9) |
| Internal medicine | 163 (8.1) |
| Emergency Service | 192 (9.5) |
| Other wards | 173 (8.6) |

COVID-19: Coronavirus Disease 2019, *median (25%-75%), **n (%)

The median age of patients was 57 years (39-69) before the pandemic and 63 years (52-72) during the pandemic ($p<0.001$). Hyperferritinemia was more common in male patients during the pandemic ($p<0.001$). Hematologic (29.6%) and solid organ malignancies (20%), infectious diseases (17.1%), and renal failure (13%) were the most common causes of hyperferritinemia before the pandemic. During the pandemic, the most common cause of hyperferritinemia was COVID-19 infection (65.3%). Non-COVID-19 infections (9.1%), solid organ malignancies (7.8%), and renal failure (4.8%) were less common. However, before the pandemic, the ferritin test was mainly performed in hematology (35.7%) and internal medicine (14.6%) clinics, whereas during the pandemic, the test was mainly analyzed in COVID-19 clinics (35.1%) and intensive care units (26%) (Table 2).

**Table 2. Distribution of patients with hyperferritinemia before and during the COVID-19 pandemic**

| Variable | Total (n=2022) | Pre-Pandemic (n=554) | Pandemic Period (n=1468) | p-value |
|---|---|---|---|---|
| Age* | 62 (49-71) | 57 (39-69) | 63 (52-72) | **<0.001**[1] |
| Gender** | | | | |
| Male | 1387 (68.6) | 334 (60.3) | 1053 (71.7) | **<0.001**[2] |
| Female | 635 (31.4) | 220 (39.7) | 415 (28.3) | |
| Diagnosis groups** | | | | |
| COVID-19 infection | 959 (47.4) | 0 | 959 (65.3) | **<0.001**[2] |
| Non-COVID-19 infection | 228 (11.3) | 95 (17.1) | 133 (9.1) | **<0.001**[2] |
| Hematologic malignancy | 241 (11.9) | 164 (29.6) | 77 (5.2) | **<0.001**[2] |
| Iron overload | 89 (4.4) | 52 (9.4) | 37 (2.5) | **<0.001**[2] |
| Liver damage | 100 (4.9) | 37 (6.7) | 63 (4.3) | **0.027**[2] |
| Renal failure | 142 (7.0) | 72 (13.0) | 70 (4.8) | **<0.001**[2] |
| Solid organ malignancy | 226 (11.2) | 111 (20.0) | 115 (7.8) | **<0.001**[2] |
| Rheumatological diseases | 37 (1.8) | 23 (4.2) | 14 (1.0) | **<0.001**[2] |
| Department followed** | | | | |
| COVID-19 clinics | 466 (23.3) | 0 | 466 (31.7) | **<0.001**[2] |
| COVID-19 outpatient clinics | 49 (2.4) | 0 | 49 (3.3) | **<0.001**[2] |
| COVID-19 intensive care | 389 (19.2) | 0 | 389 (26.5) | **<0.001**[2] |
| Nephrology | 94 (4.6) | 66 (11.9) | 28 (1.9) | **<0.001**[2] |
| Hematology | 275 (13.6) | 198 (35.7) | 77 (5.2) | **<0.001**[2] |
| Oncology | 103 (5.1) | 70 (12.6) | 33 (2.2) | **<0.001**[2] |
| Infectious diseases | 17 (0.8) | 16 (2.9) | 1 (0.1) | **<0.001**[3] |
| Gastroenterology | 63 (3.1) | 35 (6.3) | 28 (1.9) | **<0.001**[2] |
| Rheumatology | 38 (1.9) | 25 (4.5) | 13 (0.9) | **<0.001**[2] |
| Internal Medicine | 163 (8.1) | 81 (14.6) | 82 (5.6) | **<0.001**[2] |
| Emergency service | 192 (9.5) | 0 | 192 (13.1) | **<0.001**[2] |
| Other wards | 173 (8.6) | 63 (11.4) | 110 (7.5) | **0.005**[2] |
| Ferritin level[4] | | | | |
| 1000-1500** | 903 (44.7) | 262 (47.3) | 641 (43.7) | 0.143[2] |
| ≥1500** | 1119 (55.3) | 292 (52.7) | 827 (56.3) | |

COVID-19: Coronavirus Disease 2019, [1]Mann-Whitney U test, [2]Pearson Chi-square test, [3]Fisher's Exact test, [4]ng/mL, *median (%25-%75), **n (%)

Depending on the ferritin level, COVID-19 infection was the most common cause in group 1 (ferritin level 500-1000ng/mL). Besides COVID-19 infection, solid organ malignancies (12.2%), infectious diseases (11.8%), and hematologic malignancies (9.3%) were other causes of hyperferritinemia in group 1. Also, hematologic malignancies (14%), infectious diseases (10.7%), and solid organ malignancies (10.4%) were less frequently observed in group 2. Patients with hematologic malignancies were more likely to have ferritin levels >1500 ng/mL ($p<0.001$) (Table 3).

**Table 3. Diagnoses and follow-up departments of patients according to ferritin level**

| Variable | Total (n=2022) | Ferritin level - 1000-1500ng/mL Group 1 (n=903) | Ferritin level ≥1500ng/mL Group 2 (n=1119) | p-value |
|---|---|---|---|---|
| Age* | 62 (49-71) | 61 (48-70) | 62 (50-72) | 0.110[1] |
| Gender** | | | | |
| Male | 1387 (68.6) | 615 (68.1) | 772(69.0) | 0.670[2] |
| Female | 635 (31.4) | 288(31.9) | 347 (31.0) | |
| Diagnosis groups** | | | | |
| COVID-19 infection | 960 (47.5) | 411 (45.5) | 549 (49.1) | 0.112[2] |
| Non-COVID-19 infection | 227 (11.2) | 107 (11.8) | 120 (10.7) | 0.425[2] |
| Hematologic malignancy | 241 (11.9) | 84 (9.3) | 157 (14.0) | 0.001[2] |
| Iron overload | 89 (4.4) | 43 (4.8) | 46 (4.1) | 0.478[2] |
| Liver damage | 100 (4.9) | 51 (5.6) | 49 (4.4) | 0.191[2] |
| Renal failure | 142 (7.0) | 82 (9.1) | 60 (5.4) | 0.001[2] |
| Solid organ malignancy | 226 (11.2) | 110 (12.2) | 116 (10.4) | 0.198[2] |
| Rheumatological diseases | 37 (1.8) | 15 (1.7) | 22 (2.0) | 0.733[2] |
| Department followed** | | | | |
| COVID-19 clinics | 466 (23.3) | 248 (27.5) | 218 (19.5) | <0.001[2] |
| COVID-19 outpatient clinics | 49 (2.4) | 32 (3.5) | 17 (1.5) | 0.005[2] |
| COVID-19 intensive care | 389 (19.2) | 101 (11.2) | 288 (25.7) | <0.001[2] |
| Nephrology | 94 (4.6) | 65 (7.2) | 29 (2.6) | <0.001[2] |
| Hematology | 275 (13.6) | 109 (12.1) | 166 (14.8) | 0.071[2] |
| Oncology | 103 (5.1) | 46 (5.1) | 57 (5.1) | 0.997[2] |
| Infectious diseases | 17 (0.8) | 8 (0.9) | 9 (0.8) | 1.000[2] |
| Gastroenterology | 63 (3.1) | 36 (4.0) | 27 (2.4) | 0.043[2] |
| Rheumatology | 38 (1.9) | 16 (1.8) | 22 (2.0) | 0.877[2] |
| Internal Medicine | 163 (8.1) | 75 (8.3) | 88 (7.9) | 0.717[2] |
| Emergency service | 192 (9.5) | 83 (9.2) | 109 (9.7) | 0.675[2] |
| Other wards | 173 (8.6) | 84 (9.3) | 89 (8.0) | 0.281[2] |
| Period according to pandemic** | | | | |
| Pre-pandemic period | 554 (27.4) | 262 (29.0) | 292 (26.1) | 0.143[2] |
| Pandemic period | 1468 (72.6) | 641 (71.0) | 827 (73.9) | |

COVID-19: Coronavirus Disease 2019, [1]Mann-Whitney U test, [2]Pearson Chi-square test, *median (%25-%75), **n (%)

## DISCUSSION

Ferritin is a cellular iron storage protein that plays an essential role in iron metabolism. Ferritin synthesis increases in response to inflammation and oxidative stress[16,17]. Serum ferritin is one of the most commonly requested laboratory tests in day-to-day patient management. Ferritin levels below the optimal range indicate low iron stores in the body. However, there are many serious clinical pathologies in the differential diagnosis of high ferritin. Among these, in which the hyperferritinemia is associated with more severe clinical conditions, multiple organ involvement, and mortality, COVID-19 infection, as a biomarker, has recently been frequently requested by clinicians. In our study, the most common clinical condition causing hyperferritinemia before the COVID-19 pandemic was hematologic malignancies; during the pandemic period, COVID-19 infection took the first place. Considering the distribution according to the services followed up, the hematology department before the pandemic and the

COVID-19 clinics during the pandemic were the departments where hyperferritinemia was most frequently detected.

In addition, ferritin levels above 1000 ng/mL are more sensitive in predicting an inflammatory process, and patients should be evaluated for diseases such as systemic juvenile idiopathic arthritis, adult-onset Still's disease, systemic lupus erythematosus, infection, and malignancy. In the current study, COVID-19 infection was the most common cause of hyperferritinemia. Especially hematological and solid organ malignancies were the most prevalent causes of hyperferritinemia before the pandemic. Recent studies in the literature presented that the common causes of hyperferritinemia were malignancies as well as infections similar to our study[2,8,15,18]. Ellervik et al. presented a study that had a 23-year follow-up and investigated that higher ferritin levels were associated with an increased risk of mortality. Higher ferritin levels in patients with malignancy were associated with mortality[8].

Hyperferritinemia is often observed in diseases that can lead to systemic inflammation, such as COVID-19. In severe cases of COVID-19, the immune system can become overactive, and an extreme inflammatory response, called a "cytokine storm," can develop. Hyperferritinemia is at the center of this cytokine storm and associated with the disease. Therefore, hyperferritinemia may predict multiple organ failure and mortality during COVID-19[19,20]. Particularly, IL-6 plays a central role in the cytokine storm and is associated with hyperferritinemia as an acute phase response [21–24]. Keske et al. reported that severe lung and multiorgan involvements in COVID-19 are associated with high ferritin levels which are induced by pro-inflammatory cytokines, especially IL-6[25].

After the onset of the pandemic, hyperferritinemia was frequently detected in COVID-19 clinics and ICUs because healthcare resources were generally devoted to these patients' care during the pandemic. However, before the pandemic, hyperferritinemia was most commonly detected in hematology and internal medicine clinics, in accordance with the diagnosis of the diseases. Araç et al. reported that the cause of hyperferritinemia was end-stage renal disease and was mainly performed in a nephrology clinic, which was different from our study[18]. These differences may be related to the different patient populations in the studies.

Before the pandemic, the emergency department was not included in the ward distribution; it was included after the pandemic. We attribute the current situation to the increased awareness of ferritin after the COVID-19 pandemic and to the fact that COVID-19 infection has become a differential diagnosis for emergency physicians due to its wide range of symptoms.

Ferritin has recently emerged as a good biomarker for COVID-19. Older age and male sex are associated with more severe COVID-19[4,10]. In our study, the mean age of patients with ferritin levels ≥1500 μg/L was higher; most of them were men. The most common underlying cause of hyperferritinemia in these patients was COVID-19 infection, followed by hematologic malignancy. The majority of patients in the COVID-19 ICU had ferritin levels ≥1500 μg/L. In conclusion, high serum ferritin in COVID-19 is associated with more severe disease and longer ICU stay.

Our study has revealed that individuals with hyperferritinemia during the pandemic tend to be of advanced age. The outcomes of this investigation underscore the significance of close clinical surveillance of this group of patients. Given that the pandemic has considerably impacted the health of the elderly population, this research offers valuable insights to healthcare providers who seek to improve their clinical practices.

Our study showed that individuals with hyperferritinemia during the pandemic tended to be of advanced age. The results of this investigation underscore the importance of close clinical monitoring of this patient population. Given that the pandemic has had a significant impact on the health of the elderly population, this research offers valuable insights for healthcare providers seeking to improve their clinical practice.

The present study provides valuable insights into the significance of hyperferritinemia in a clinical context, both before and during the pandemic. It provides a comprehensive understanding of the impact of the pandemic on the clinical relevance of hyperferritinemia. However, it is important to acknowledge the limitations of the study in order to avoid erroneous conclusions. Therefore, the results of the study should be interpreted within the limitations to better understand the issue.

The retrospective design of the study was a major limitation. Ferritin levels are not reported as titers in our laboratory, especially values above 1500 ng/mL.

This may be a disadvantage in clinical situations where ferritin levels need to be monitored. Hyperferritinemia may result from multiple overlapping diagnoses. In such patients, it may be difficult to determine the underlying cause if the historical ferritin level is unknown. We believe we have minimized this limitation in our study by confirming the diagnosis at hospital admission according to the criteria described in the procedure section.

In summary, ferritin is a valuable tool in the evaluation of anemia due to iron deficiency. It indicates the total iron stored in the body and is useful in the differential diagnosis as an acute phase reactant in infectious, inflammatory, and malignant conditions. Ferritin levels above 1000 ng/mL are particularly useful, as they help to make more specific diagnoses. In hyperinflammatory conditions initiated by COVID-19 infection, ferritin is often requested as a diagnostic and follow-up parameter in pulmonary and multi-organ involvement. However, the clinical significance of elevated ferritin levels should be evaluated in the context of the patient's medical history and current clinical condition. It is important to note that very high ferritin levels may indicate underlying pathologies and should be interpreted with caution. Therefore, the patient's medical history and current clinical condition should be considered when interpreting ferritin levels. Undoubtedly, improving our understanding of these aspects of ferritin will greatly contribute to the treatment and prevention of complications. In addition, sequential monitoring of serum ferritin levels may provide an opportunity to consider possible complications of new diseases. Finally, there is a need for more comprehensive studies using other markers of inflammation, expressing ferritin levels as titers, and examining their association with mortality.

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**Ethical Approval:** This study was approved by the Ethics Committee of Health Sciences University, Gulhane Training and Research Hospital under the Declaration of Helsinki (Date: 02.03.2022 Decision No: 2022/22).
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**Conflict of Interest:** Authors declared no conflict of interest.
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## REFERENCES

1. Senjo H, Higuchi T, Okada S, Takahashi O. Hyperferritinemia: causes and significance in a general hospital. Hematology. 2018;23:817-22.
2. Goldhaber G, Segal G, Dagan A. Hyperferritinemia in the elderly can differentiate the bad from the worst. Medicine (Baltimore). 2020;99:e21419.
3. Fauter M, Mainbourg S, El Jammal T, Guerber A, Zaepfel S, Henry T et al. Extreme hyperferritinemia: Causes and prognosis.J Clin Med. 2022;11:5438.
4. Ruan Q, Yang K, Wang W, Jiang L, Song J. Correction to clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020;46:1294-97.
5. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124-31.
6. Sandnes M, Ulvik RJ, Vorland M, Reikvam H. Hyperferritinemia- a clinical overview. J Clin Med. 2021;10:2008.
7. VasanthiDharmalingam P, Karuppagounder V, Watanabe K et al. SARS–CoV-2 Mediated hyperferritinemia and cardiac arrest: Preliminary ınsights. Drug Discov Today. 2021;26:1265-74.
8. Ellervik C, Marott JL, Tybjærg-Hansen A, Schnohr P, Nordestgaard BG. Total and cause-specific mortality by moderately and markedly increased ferritin concentrations: General population study and meta-analysis. Clin Chem. 2014;60:1419-28.
9. Lachmann G, Knaak C, Vorderwülbecke G, Rosee P, Balzer F, Schenk T et al. Hyperferritinemia in critically Ill patients. Crit Care Med. 2020;48:459-65.
10. Li Y, Hu Y, Yu J, Ma T. Retrospective analysis of laboratory testing in 54 patients with severe or critical type 2019 novel coronavirus pneumonia. Lab Invest. 2019;100:794-800.
11. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N et al. Complex ımmune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27:992-1000.e3.
12. Feld J, Tremblay D, Thibaud S, Kessler A, Naymagon L. Ferritin levels in patients with COVID-19: A poor predictor of mortality and hemophagocytic lymphohistiocytosis. Int J Lab Hematol. 2020;42:773-79.
13. Kaya MN. Mental status of healthcare professionals according to the level of exposure to COVID-19 patients during the pandemic. J Health Sci Med. 2022;5:1081-85.
14. Gómez-Pastora J, Weigand M, Kim J, Wu X, Strayer J, Palmer AF et al. Hyperferritinemia in critically ill COVID-19 patients – Is ferritin the product of inflammation or a pathogenic mediator? Clin Chim Acta. 2020;509:249-51.

15. Moore C, Ormseth M, Fuchs H. Causes and significance of markedly elevated serum ferritin levels in an academic medical center. J Clin Rheumatol. 2013;19:324-8.
16. Üsküdar Cansu D, Üsküdar Teke H, Cansu GB, Korkmaz C. Evaluation of hyperferritinemia causes in rheumatology practice: a retrospective, single-center experience. Rheumatol Int. 2021;41:1617-24.
17. Wang W, Knovich MA, Coffman LG, Torti FM, Torti S V. Serum ferritin: Past, present and future. Biochim Biophys Acta. 2010;1800:760-69.
18. Araç E, Solmaz İ. Bir eğitim ve araştırma hastanesinde hiperferritinemi hastalarının analizi. STED. 2020;29:435-38.
19. Canna SW, Behrens EM. Making Sense of the Cytokine Storm: A conceptual framework for understanding, diagnosing, and treating hemophagocytic syndromes. Pediatr Clin North Am. 2012;59:329-44.
20. Behrens EM, Koretzky GA. Review: Cytokine storm syndrome: Looking toward the precision Medicine Era. Arthritis Rheumatol. 2017;69:1135-43.
21. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015;16:448-57.
22. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single-center experience. J Med Virol. 2020;92:814-18.
23. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117:10970-75.
24. Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020;38:529-32.
25. Keske Ş, Tekin S, Sait B, İrkören P, Kapmaz M, Çimen C. et al. Appropriate use of tocilizumab in COVID-19 infection. Int J Infect Dis. 2020;99:338-43.