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Evaluation of hyperferritinemia causes in rheumatology practice: a retrospective, single-center experience

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Abstract

Hyperferritinemia may develop due to various reasons such as inflammation, infection, or malignancy. The purpose of the study to explore the prevalence and to figure out the causes of general hyperferritinemia and extreme hyperferritinemia as detected through the ferritin measurements requested by the rheumatology department. Adult patients at the age of 18 years and older with at least one serum ferritin level measurement at or above 500 ng/mL as requested by the rheumatology department between January 2010 and December 2019 were evaluated retrospectively. Hyperferritinemia was detected in 4.7% of 11,498 serum ferritin tests. The mean age of 242 patients found to have hyperferritinemia was 53.7 ± 17.1 years; of the patients, 63.2% were female, and the mean serum ferritin value was 2820 ± 5080 ng/mL. The most common cause of hyperferritinemia was rheumatological diseases with a ratio of 59.1%, which was followed by infections, iron overload, and solid malignancy. Among the rheumatologic diseases, adult-onset Still's disease (AOSD), rheumatoid arthritis, and vasculitis were the cause accounting for hyperferritinemia. Ferritin levels were significantly higher in the AOSD group compared to the other rheumatologic disease groups ($p < 0.0001$). While extreme hyperferritinemia (ferritin ≥ 10,000 ng/mL) rate in our cohort was 0.2%, the most common cause was AOSD (15/17). In patients with hyperferritinemia, 3 month mortality was found to be 8.7%. CRP level was identified as the only independent predictor for the 3 month mortality in all patients [OR 1.088 (95% CI 1.004–1.178), $p = 0.039$]. Although rheumatologic disease activation and infections are the most common causes, the other causes should also be considered for the differential diagnosis.

Keywords Ferritin · Hyperferritinemia · Rheumatologic diseases · Rheumatology

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Introduction

Ferritin is an acute-phase reactant and coordinates the cellular defense against oxidative stress and inflammation. As elevated free iron levels in hyperferritinemia increase inflammation and create a predisposition to coagulation, beyond being an acute-phase protein, ferritin holds a specific place in terms of inflammation-induced thrombosis [1–3]. Although ferritin is such a widely used test, there are not an adequate number of well-established recommendations regarding the terminology of hyperferritinemia. The term "elevated ferritin level" has been used for ferritin above normal limits; but there is no clear cut-off value specified for hyperferritinemia in the guideline published by the British Society of Hematology (BSH) in 2018 [4]. No standard upper limit has been established for hyperferritinemia. The upper limit has been accepted as 500 µg/L in some publications [5]. In a scarce number of studies in the literature, the definition "extreme hyperferritinemia" has been used

for extremely high serum ferritin values such as 3000 µg/L, 5000 µg/L, or 10,000 µg/L [6–8]. Excess iron, hematologic or solid malignancies, chronic inflammation, autoimmune diseases, and hepatic or renal diseases are the most commonly identified causes of hyperferritinemia. In particular, hemophagocytic lymphohistiocytosis (HLH, also known as macrophage activation syndrome (MAS), systemic-onset idiopathic arthritis, and other rheumatologic diseases, especially adult-onset Still's disease (AOSD), constitute the major etiologic causes of hyperferritinemia with levels above 5000 µg/L and 10,000 µg/L [4–11].

On the other hand, infectious diseases are also seen within the spectrum of hyperferritinemic syndromes. Severe COVID-19 infection is one of them. The elevation of ferritin during infectious diseases and malignancies and the clinical and laboratory simulation of rheumatic disorders by these diseases may create difficulties in differential diagnosis [12]. Even though ferritin was popular during the COVID-19 pandemic, we could not find any other study in the literature investigating the causes of hyperferritinemia in rheumatology practice and giving detailed laboratory and treatment data in the pre-COVID-19 periods. In this respect, it will be important to know how ferritin levels behave according to diseases in rheumatology practice.

The study aimed to identify the prevalence and causes of hyperferritinemia and extreme hyperferritinemia from the perspective of rheumatology in a tertiary-care unit within 10 years.

Materials and methods

Patient selection

The adult patients who were either followed up upon the diagnosis of a rheumatologic disease or experienced the signs or symptoms indicative of rheumatologic disease and were therefore examined as an outpatient or inpatient upon the pre-diagnosis of a rheumatologic disease in a tertiary-care rheumatology clinic between January 2010 and December 2019, and thus were determined to have a serum ferritin level of 500 ng/mL and above were included. The highest ferritin value was taken into consideration for the patients having more than one ferritin measurement of ≥ 500 ng/mL. For all patients, their demographics, detailed laboratory findings during the time of hyperferritinemia, bone marrow (BM) assessments, if any, and the mortality status were collected from medical records. Patients under 18 years of age were excluded. (The study covers the period before the emergence of the COVID-19 pandemic.)

Identification of the cause of hyperferritinemia

The cause of hyperferritinemia was identified case by a case basis by reviewing the individual clinical and laboratory findings. Accordingly, the patients were classified by their conditions causing hyperferritinemia into the groups of hyperferritinemia related to HLH, rheumatologic disease activation, hematologic or solid malignancy, renal failure, infection, hepatocellular damage, or iron overload.

The diagnosis of (primary) HLH was established according to HLH-2004 criteria [13]. Whether the patients were diagnosed with a rheumatologic disease before or after the diagnosis of hyperferritinemia was determined. It was also identified whether the inflammatory rheumatologic disease that causes hyperferritinemia was active along with the treatments given for primary diseases (steroids, immunosuppressive drugs, antibiotics, and anakinra). Renal failure was defined as the patients in need of renal replacement therapy or with a glomerular filtration rate of less than 20 mL/min/1.73 m^2 who had grade 4 or 5 chronic kidney disease and were receiving renal placement therapy. The patients were assigned to the cancer group if they had active or untreated cancer. Malignancies were divided into hematologic or solid tumors. The patients were classified in the infection group if they had a serious infection requiring antimicrobial/antifungal treatment during follow-up with a primary rheumatologic disease or if the patients were found to have a primary infection (septic arthritis, infective endocarditis, etc.) during evaluation due to a symptom or finding of rheumatologic disease. The focus of infection and culture results were also recorded. Next, hepatocellular damage was defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels typically above 500 U/L suggesting acute hepatic process or serious hepatic damage. Finally, iron overload was defined as the patients who had received monthly transfusions of erythrocyte suspensions for at least 6 months, required chelation therapy, or decided by a hematologist to have iron excess [5, 9, 10].

Written approval was obtained from the local ethics committee for the study.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) or median. Categorical data were presented in percentage (%). Shapiro–Wilk's test was used to figure out whether the data are normally distributed. In the comparison of the groups with normal distribution, independent samples *t* test analysis and one-way analysis of variance (One-Way ANOVA) were used in cases with two groups and

in cases with three or more groups, respectively. To compare the groups incompliant with normal distribution, the Mann–Whitney *U* test and Kruskal–Wallis *H* test were used in cases with two groups and in cases with three or more groups, respectively. Cross tabulation was implemented and analyzed using Pearson's Chi-Square, Pearson's Exact Chi-Square, and Fisher's Exact Chi-Square tests. Logistic Regression analysis was used to determine risk factors. ROC (Receiver-Operating Characteristics) analyses were used to determine the appropriate cut-off point for independent markers and to calculate sensitivity and specificity thereof. For the application of analyses, IBM SPSS Statistics 21.0 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used. A p value of <0.05 was considered statistically significant.

Results

Over the 10 years, a total of 11,498 serum ferritin were tested by the rheumatology department. Hyperferritinemia was detected in 4.7% of the tests. Based on our inclusion criteria, 242 patients had hyperferritinemia. The mean age of them was 53.7 ± 17.1 years, and 153 of the patients (63.2%) were female. In our cohort, the diagnosis of a rheumatologic disease was antecedent to the diagnosis of hyperferritinemia in 64.9% ($n=157$) of the patients for whom follow-up was ongoing; the remaining patients were those evaluated with a pre-diagnosis of a rheumatologic disease due to their symptoms and findings during hyperferritinemia, and 75% (64/85) of these patients were then diagnosed as a rheumatologic disease. Thus, the ratio of primary rheumatologic diseases was 91.3% ($n=221$) in the whole-study population. (The demographics of the patients are provided in Table 1.)

Table 1 Demographics of the whole-study group with hyperferritinemia

N	242
Age, mean ± SD, years	53.7 ± 17.1
< 50 years old, *n*, %	90 (37.2%)
≥ 50 years old, *n*, %	152 (62.8%)
Gender, female, *n*, %	153 (63.2%)
Clinical findings, *n*, %	214 (88.4%)
Fever, *n*, %	93 (38.4%)
Skin eruption, *n*, %	55 (22.7%)
Others, *n*, %	170 (70.2%)
Splenomegaly, *n*, %	16 (6.6%)
Hepatomegaly, *n*, %	91 (37.6%)
Presence of rheumatological disease before hyperferritinemia is detected, *n*, %	157 (64.9%)
Frequency of cytopenia, *n*, %	200 (82.6%)
Frequency of anemia, *n*, %	195 (80.6%)
Frequency of leukopenia, *n*, %	39 (16.1%)
Frequency of thrombocytopenia, *n*, %	38 (15.7%)
Number of patients with BM analysis, *n*, %	73 (30.2%)
Presence of hemophagocytosis in BM analysis, *n*, %	8 (3.3%)
Causes of hyperferritinemia	
Rheumatological diseases, *n*, %	143 (59.1%)
Infections, *n*, %	66 (27.3%)
Iron overload, *n*, %	8 (3.3%)
Solid tumor, *n*, %	7 (2.9%)
Hematological malignancy, *n*, %	6 (2.5%)
Renal insufficiency, *n*, %	6 (2.5%)
Hepatocellular damage, *n*, %	4 (1.7%)
HLH, *n*, %	2 (0.8%)

BM bone marrow, *HLH* hemaphagocytic lymphohistiocytosis, *SD* standard deviation

Laboratory results

The patients had the following mean laboratory values: hemoglobin (Hb) 10.4 ± 2.01 gr/dL, white blood cell (WBC) 9710 ± 6440 **/µL**, platelets (PLT) 271,000 ± 159,000 **/µL**, and C-reactive protein (CRP) (normal range 0–5 mg/L) 9.92 ± 8.42 mg/dL. The detailed hematologic and biochemical results of the patients are provided in Table 2.

Causes of hyperferritinemia

In our study group, the most common cause of hyperferritinemia was rheumatologic diseases encountered in 59.1% ($n=143$) and infections were in the second place with a ratio of 27.3% ($n=66$). These were followed by iron overload, solid malignancy, hematologic malignancy, renal failure, hepatocellular damage, and HLH. When listed in descending order of frequency, the top 3 rheumatologic diseases causing hyperferritinemia and their respective ratios were AOSD: 29.4% ($n=42$), rheumatoid arthritis (RA): 25.6% ($n=37$), and vasculitis: 12.6% ($n=18$). Among the patients with hyperferritinemia due to infection, the most common focus of infection was pneumonia with a ratio of 42.8%. (The details on the rheumatologic diseases, infections, and malignancies causing hyperferritinemia are provided in Table 3.)

Analysis of rheumatologic diseases

AOSD was the most common rheumatologic disease-causing hyperferritinemia. Ferritin levels were significantly higher in AOSD compared to the other rheumatologic disease groups ($p<0.0001$). There was no statistical difference among the other groups. (Mean ferritin levels by rheumatologic diseases are provided in Table 4.)

Table 2 Laboratory findings of the whole-study group with hyperferritinemia

Hemoglobin level, mean ± SD, gr/dL	10.4 ± 2.01
MCV, mean ± SD, U/L	84.5 ± 9.32
White blood cell, mean ± SD, /μL	9710 ± 6440
Absolute neutrophil count, mean ± SD, /μL	7400 ± 5760
Absolute lymphocyte count, mean ± SD, /μL	1410 ± 931
Platelet count, mean ± SD, /μL	271,000 ± 159,000
MPV, mean ± SD, fL	8.81 ± 1.44
Fibrinogen, mean ± SD, mg/dL	512 ± 214
AST, mean ± SD, U/L	44.3 ± 86.8
ALT, mean ± SD, U/L	38.5 ± 61.1
ALP, mean ± SD, U/L	173 ± 168
LDH, mean ± SD, U/L	570 ± 565
Triglycerides, mean ± SD, mg/dL	164 ± 113
Total protein, mean ± SD, g/dL	6.51 ± 1.02
Albumin, mean ± SD, g/dL	3.37 ± 0.661
CRP, mean ± SD, mg/dL	9.92 ± 8.42
ESR, mean ± SD, mm/h	76.6 ± 32.3
BUN, mean ± SD, mg/dL	24.9 ± 19.2
Cr, mean ± SD, mg/dL	1.32 ± 1.35
Ferritin, mean ± SD, ng/mL	2820 ± 5080
Fe, mean ± SD, ug/dL	58.3 ± 38.9
TIBC, mean ± SD, ug/dL	200 ± 63.1
Sat, mean ± SD, %	30.4 ± 21.4

ALT alanine aminotransferase, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CRP* C-reactive protein, *Cr* creatinine, *ESR* erythrocyte sedimentation rate, *Fe* iron, *LDH* lactate dehydrogenase, *MCV* mean erythrocyte volume, *MPV* mean platelet volume, *TIBC* total iron-binding capacity, *Sat* Saturation

The ferritin level of > 1757 ng/mL had 85.71% sensitivity and 81% specificity for the diagnosis of AOSD (95% CI 0.868–0.944, $p < 0.0001$) (shown in Fig. 1).

Analysis of ferritin results

In the entire set of 242 patients, the mean ferritin level was 2820 ± 5080 ng/mL. The ferritin levels of the patients were at the level of 500 to < 1000 ng/mL in 45.5% ($n = 110$) (Group 1), 1000 to < 5000 ng/mL in 43% ($n = 104$) (Group 2), 5000 to 10,000 ng/mL in 4.5% ($n = 11$) (Group 3) and above ≥ 10,000 ng/mL in 7% ($n = 17$) of the patients (Group 4). When etiologies were examined in these ferritin level-based groups, rheumatologic diseases constituted the most common etiologic cause in all groups; and the second most common cause was an infection in groups 1 and 2, and iron overload in group 3. (The comparison of ferritin levels by the cause of hyperferritinemia is provided in Table 5.)

Characteristics of the patients with ferritin ≥ 10,000 ng/mL

A ferritin level of ≥ 10,000 ng/mL was detected in 17 patients. The mean age of the patients was 46.5 ± 14.2 years and 15 of them were females. The patients had a mean CRP level of 17.8 ± 8.88 mg/dL, mean ESR of 75.5 ± 39.7 mm/h, and mean ferritin level of 18,800 ± 7930 ng/mL. Of them, 88.2% ($n = 15$) had fever and 64.7% ($n = 11$) had rash. Hyperferritinemia was due to primary HLH in 1 patient, AOSD in 15 patients, and infection in 1 patient. Hemophagocytosis was identified in 6 of 10 patients who underwent BM

Table 3 Data on rheumatologic diseases, infections, and malignancies causing hyperferritinemia

Rheumatological diseases ($n = 143$)	*n* (%)	Infections ($n = 66$)	*n* (%)	Solid malignancy ($n = 7$)	*n* (%)	Hematological malignancy ($n = 6$)	*n* (%)
AOSD	42 (29.4%)	Pneumonia	34 (51.5%)	Prostat ca	2 (28.6%)	MDS	3 (50%)
RA	37 (25.6%)	Urinary infection	12 (18.2%)	Kolon ca	2 (28.6%)	Lymphoma	2 (33.3%)
Vasculitis	18 (12.6%)	Septic arthritis	6 (9.1%)	Akciğer ca	1 (14.3%)	ALL	1 (16.7%)
SLE	18 (12.6%)	Infective endocarditis	5 (7.6%)	Meme ca	1 (14.3%)		
Behçet's disease	8 (5.6%)	Wound infection	4 (6.1%)	Malignant melanoma	1 (14.3%)		
Scleroderma	4 (2.8%)	Catheter infection	2 (3%)				
Gout disease	3 (2.1%)	Tuberculosis	2 (3%)				
PMR	3 (2.1%)	Dental abscess	1 (1.5%)				
Psoriatic arthritis	3 (2.1%)						
Ankylosing spondylitis	3 (2.1%)						
Temporal arteritis	2 (1.4%)						
Dermatomyositis	2 (1.4%)						
Retroperitoneal fibrosis	1 (0.7%)						

ALL acute lymphoblastic leukemia, *AOSD* adult-onset Still's disease, *ca* cancer, *MDS* myelodysplastic syndrome, *PMR* polymyalgia rheumatica, *RA* Rheumatoid arthritis, *SLE* systemic lupus erythematosus

Table 4 Mean ferritin levels by the rheumatologic disease subgroups causing hyperferritinemia

Rheumatological diseases	*n* (%)	Ferritin, mean±SD, ng/mL	*P* value
AOSD	42 (29.4%)	9075±9191	<0.0001
RA	37 (25.6%)	946±505	
Vasculitis	18 (12.6%)	1042±547	
SLE	18 (12.6%)	1165±704	
Behçet's disease	8 (5.6%)	745±300	
Scleroderma	4 (2.8%)	873±201	
Gout disease	3 (2.1%)	1150±183	
PMR	3 (2.1%)	732±138	
Psoriatic arthritis	3 (2.1%)	611±46	
Ankylosing spondylitis	2 (1.4%)	682±1419	
Temporal arteritis	2 (1.4%)	1692±1409	
Dermatomyositis	2 (1.4%)	630±4384	
Retroperitoneal fibrosis	1 (0.7%)	1651	

AOSD adult-onset Still's disease, *PMR* polymyalgia rheumatica, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

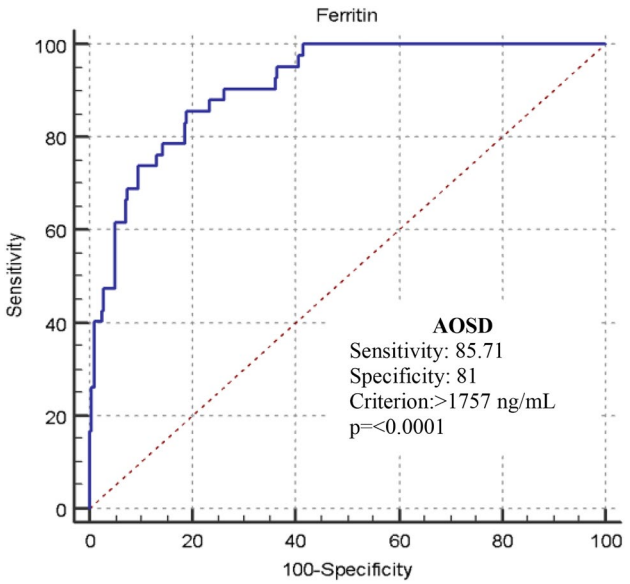

Fig. 1 ROC analysis result of ferritin levels for adult-onset Still's disease

examination. As a treatment, 16 patients had received steroids, 10 patients received additional immunosuppressive agents, 3 patients received intravenous immunoglobulin (IVIG), and 5 patients received anakinra. During their follow-up, 2 patients had died: one at month 1 (AOSD patient) and another at month 8 (HLH patient).

Table 5 Comparison of ferritin levels by the causes of hyperferritinemia

	Rheumatological diseases	Infections	Iron overload	Solid tumor	Hematological malignancy	Renal insufficiency	Hepatocellular damage	HLH	*P* value
n (%)	143 (59.1%)	66 (27.3%)	8 (3.3%)	7 (2.9%)	6 (2.5%)	6 (2.5%)	4 (1.7%)	2 (0.85%)	
Ferritin, mean ± SD, ng/mL	3360 ± 6190	1650 ± 2420	3320 ± 2380	2600 ± 2400	2410 ± 2260	1600 ± 1130	1190 ± 829	10,400 ± 3960	0.09
Median (Q1 – Q3)	1040 (691 – 2380)	1110 (650 – 1730)	2830 (1430 – 4900)	1490 (730 – 4000)	1770 (1190 – 2070)	1350 (807 – 1830)	851 (791 – 1250)	10,400 (8970 – 11800)	

HLH hemaphagocytic lymphohistiocytosis, *SD* standard deviation

Comparison of the rheumatologic diseases group and the infection group

We have also compared the rheumatologic diseases group with the infection group, i.e., the first 2 groups of hyperferritinemia causes. Accordingly, the patients in the rheumatologic diseases group were younger compared to the patients in the infection group (51.6 ± 16.6 years vs 58.1 ± 17.0 years, $p = 0.010$), and had higher WBC (10,900 ± 6230 /μL vs 7650 ± 6470 /μL, $p = < 0.001$) and PLT counts (298,000 ± 153,000 /μL vs 245,000 ± 185,000 /μL, $p = 0.004$). There was no difference between the two groups in terms of other laboratory parameters.

Treatment

In the current study, 69% patients ($n = 167$) had received steroids, 50.4% ($n = 122$) immunosuppressive therapy, 3.7% ($n = 9$) IVIG, and 2.9% ($n = 7$) anakinra. Taking into account the underlying diseases, steroids were used as monotherapy in 32% ($n = 55$) of the patients and in combination with immunosuppressives/immunomodulatory drugs in 68% ($n = 112$). IVIG was used as monotherapy in 4 of 9 patients (44%) and combined with steroids in 5 patients (66%). Anakinra was given to 7 (5 AOSD, 1 gout arthritis, 1 HLH) patients who were unresponsive to steroid and/or IVIG treatment.

Mortality

For all patients with hyperferritinemia, 3 month mortality was calculated, and 21 (8.7%) patients were lost in 1.5 ± 0.67 months (1–3) on average. In the logistic regression analysis performed to determine the independent risk factors for the 3 month mortality in all patients, CRP level was identified as the only independent predictor [OR 1.088 (95% CI 1.004–1.178), $p = 0.039$]. A CRP level > 7.15 mg/dL in all patients had 80.95% sensitivity and 50.68% specificity to identify the 3 month mortality (95% CI 0.603–0.727, $p = 0.002$).

Discussion

Our study is the first study in the literature to reveal the prevalence and causes of hyperferritinemia in detail by evaluating the data obtained from a rheumatology center.

It is difficult to conclude a definite prevalence or incidence rate of hyperferritinemia, since different levels for the description of hyperferritinemia have been used in the previous studies [5–11]. The prevalence and causes of hyperferritinemia vary according to ethnic differences, gender-age, outpatient or inpatient of the study population, adult or pediatric age group, whether it was done in a general hospital or not, and the cut-off value for ferritin [14]. In a study evaluating patients with serum ferritin levels greater than 3000 μg/L in Canada over 1 year (from general + hematology + malignancy database), hyperferritinemia was identified in 141 of 25,600 ferritin measurements [7]. In another study, 65,536 measurements were made and 269 measurements of 86 patients had ferritin levels above 10,000 μg/L**.** The ratio of extreme hyperferritinemia was 0.4% [6]. In another study conducted in the UK, all ferritin measurements run at a laboratory over 1 year were evaluated; and out of 53,815 measurements, 41 samples of 23 patients with ferritin levels of ≥ 10,000 μg/L were identified, thus yielding extreme hyperferritinemia ratio of 0.08% [8]. Our study, on the other hand, does not cover all ferritin measurements studied in our tertiary hospital, but only those requested by the rheumatology department were evaluated. In 542 measurements from 242 patients, we identified the rate of hyperferritinemia (≥ 500 ng/mL) as 4.7%, and the rate of extreme hyperferritinemia (≥ 10,000 ng/mL) as 0.2%, that is, in line with the literature. The ferritin cut-off value that we took as ≥ 500 ng/mL might have been the reason why our overall rate was higher.

In the literature, there are very few studies on hyperferritinemia, except for the studies elucidating the causes of extreme hyperferritinemia. In a study including general patients and evaluating 1394 patients for which ferritin cut-off value was taken as ≥ 500 μg/L, the most common causes were non-HIV infections, solid tumors, liver diseases, and renal failure. In the same study, the rheumatologic/inflammatory disease ratio was 6.3% only. While the median ferritin level was 1024 μg/L in the entire group in that study, it was 872 μg/L in the infection group and 1142 μg/L in the group of rheumatologic diseases [5]. The lower rate of rheumatologic diseases in this study might be due to being analyzed all ferritin levels in the hospital. In another study evaluating 627 patients for whom ferritin ≥ 1000 μg/L was taken as hyperferritinemia, the most common cause of hyperferritinemia was malignancies, which was followed by iron overload. It was stated that only 6 of these patients had HLH or AOSD. While the mean ferritin level was 2647 μg/L across the whole group, it was 2849 μg/L in the malignancy group and 4799 μg/L in the inflammation group [9]. Both studies mentioned above reflect the overall hospital results. In the literature, only a small number of studies investigated the cause of hyperferritinemia in the setting of the rheumatology department. Orbach et al. investigated the frequency of hyperferritinemia by considering only primary rheumatic diseases. They detected hyperferritinemia in 23% of SLE patients, 15% of dermatomyositis patients, and 4% of RA patients [11]. They accepted hyperferritinemia as a ferritin level above the normal value. They would likely have ended up with lower rates if they had applied a similar cut-off

value as in other studies, instead of the upper limit of normal range.

According to a newly published review, the rate of rheumatologic/inflammatory diseases in patients with hyperferritinemia, which includes general hospital data, ranges from 1.8% to 32.6% [14]. Our results indicate that the most common causes of hyperferritinemia are rheumatologic diseases and infections, which were identified in 59.1 and 27.3%, respectively. While the mean ferritin level was 2820 ng/mL across the entire group, it was 3360 ng/mL in the rheumatologic diseases group and 1650 ng/mL in the infection group. AOSD, RA, vasculitis, and SLE were the first 4 most common rheumatologic diseases causing hyperferritinemia.

Most of the studies on hyperferritinemia have investigated the causes of extreme hyperferritinemia by accepting different ferritin cut-off values. In a study encompassing 83 adult patients for whom ferritin cut-off was taken as ≥ 3000 µg/L, transfusion and liver diseases have been identified as the most common reasons with respective ratios of 25 and 19% [7]. Only one AOSD case was detected in this study [7]. Senjo H et al. have identified the most frequent of extreme hyperferritinemia causes as non-HIV infections, unlike the other studies. In their study, rheumatologic/inflammatory diseases were identified as the cause of hyperferritinemia in 14.5% of the group [5]. In another study evaluating 113 patients by taking a higher ferritin cut-off value (ferritin ≥ 50,000 µg/L), the most common cause of hyperferritinemia was identified as renal failure and hepatocellular damage, which was followed by infections, hematologic malignancy, and rheumatologic diseases [10]. We have also handled extreme hyperferritinemia (ferritin ≥ 10,000 ng/mL) separately in our whole-study group. While there were solely one or two patients with AOSD to blame as the etiologic cause in the other extreme hyperferritinemia studies in the literature; there were 17 patients with extreme hyperferritinemia in our study and, unlike the literature, 15 of the cases (88.2%) were due to AOSD (mean ferritin of 19,183 ng/mL), one was due to HLH, and one was due to infection [7–9]. We believe that this difference has resulted from the fact that our study population was selected from the patients followed in rheumatology only.

It has been investigated in several studies that the cut-off value of hyperferritinemia may be diagnostic for some diseases. Although the sensitivity was low in one study, a ferritin level of ≥ 2500 µg/L was determined as the cut-off value for the diagnosis of AOSD [15]. In our study, according to the ROC analysis that we performed to distinguish adult AOSD disease from all the other reasons across the entire group, we detected that the serum ferritin level > 1757 ng/mL was sufficient to make the diagnosis of AOSD with 85.71% sensitivity and 81% specificity.

Hyperferritinemia is one of the key predictors of mortality in patients with clinical presentation of MAS [16]. Although mortality was not evaluated in most hyperferritinemia studies, Wormsbecker et al. have reported the mortality rate was 22%. Any predictive factors for mortality were not specified [7]. In a study evaluating patients with AOSD, no correlation was found between ferritin level and mortality, while CRP levels were found as a parameter predicting mortality [17]. In our study, 8.6% of the whole-study group died within 3 months. The CRP level was our only independent predictor to identify the 3 month mortality in the whole patient group.

One of the limitations of our study is its retrospective design. Another limitation is that our patient population is not representative of the general population, since it was sampled from a tertiary-care rheumatology unit. This might have led to a bias because rheumatologists may check ferritin levels in their patients more commonly than other specialists because they know the diagnostic role of ferritin in rheumatology practice. On the other hand, one of our study's strengths is that it elucidates in detail the causes of hyperferritinemia in rheumatologic diseases in terms of both laboratory parameters and demographics and thus offers an insight to rheumatologists in this respect.

In conclusion, the current study indicated that in rheumatology practice, the most common causes of hyperferritinemia are rheumatologic diseases (AOSD, RA, SLE, and vasculitis) and infections. CRP level behaved as a predictor for mortality in the patients with having hyperferritinemia. Rheumatologists should keep in mind other causes of hyperferritinemia other than rheumatologic diseases and should pay attention to CRP level in terms of prognosis.

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Declarations

Conflict of interest All the authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Approval with the decision no. 49 dated 14 July 2020 was obtained from Eskişehir Osmangazi University Ethics Committee.

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