

## Description of the Etiologies in Patients with Hyper ferritinemia in the biochemistry laboratory- Avicenna Military hospital-Marrakesh

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### Abstract

**Objectives of the study:** The aim of this study was to identify the underlying causes of hyperferritinemia in patients and to analyze their clinical and epidemiological characteristics. Data were collected from 188 patients at the Avicenne Military Hospital in Marrakech between January 2019 and December 2022.

**Patients and methods:** Patients aged over 18 with plasma ferritin levels > 600 µg/L were included. They were stratified into three categories: moderate elevation (600-1000 µg/L), significant elevation (1000-1500 µg/L) and extreme elevation (> 1500 µg/L). Demographic data, clinical parameters and laboratory results were collected and analyzed using descriptive statistics. Plasma ferritin levels were determined by electrochemiluminescence and CRP levels were assessed by immunoturbidimetry.

**Résultats:** Of the 188 patients, 109 were male and 79 female, with a mean age of 51 years. Infections were identified as the most common cause of hyperferritinemia (34.5%), followed by nephropathies (28.9%), systemic diseases (12.4%), malignancies (9.3%) and hepatopathies (4.3%). Less frequent etiologies included metabolic syndrome, hemochromatosis, diabetes and repeated transfusions. Bacterial infections accounted for the majority of infectious cases (80%).

**Conclusion:** Hyperferritinemia is a frequent biochemical abnormality with multifactorial etiologies, infections being the most frequent cause. Rapid identification of the underlying etiology is essential for effective management. A collaborative approach involving clinical and laboratory expertise is essential to optimize results and reduce associated morbidity and mortality.

**Keywords:** Hyperferritinemia; Infections; Ferritin Levels; Etiologies; Systemic Inflammation

### 1. Introduction

Ferritin is a crucial protein for iron storage in the body and helps regulate its absorption in the intestines. Normal ferritin levels range from 30 to 300 µg/L in men and 20 to 200 µg/L in women. Low ferritin levels usually signal an iron deficiency, while high levels do not necessarily indicate an excess of iron. Elevated ferritin levels are common and often discovered incidentally; identifying their cause is generally straightforward with the tests available. [1].

The dynamic regulation of ferritin during normal iron metabolism is an essential host regulatory mechanism.

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Further research into primary inflammatory disorders suggests that, in addition to this rolehomeostatic role, ferritin may be a key marker and pathogenic player in inflammatory pathology. through its signaling as part of the innate immune response and modulation of lymphocyte function [2].

The diagnostic process aims to identify the cause of elevated ferritin levels and assess for possible liver iron overload. A systematic approach generally facilitates an accurate diagnosis and effective treatment in most cases.

The aim of our study is to investigate the causes of hyperferritinemia diagnosed in 188 patients at the Military Hospital Avicenna in Marrakesh between January 2019 and December 2022. Additionally, we aim to analyze the epidemiological and clinical characteristics of these patients and to establish the range of underlying causes for these elevated ferritin levels and compare them with data from the literature.

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## 2. Materials and methods

This retrospective study, conducted from January 2019 to December 2022 at the Military Hospital Avicenna in Marrakesh, involved collecting all plasma ferritin test requests from various departments.

We have included in this study patients of both sexes, age > 18 years old, with ferritin levels above 600 µg/L. For patients with multiple ferritin values exceeding 600 µg/L, we selected the highest value.

The pediatric population and patients with ferritin < 600 µg/l were excluded.

The study used a pre-established data collection form to review patient medical records, gathering information on demographics (age, sex), requesting departments, ferritin levels, and the causes of hyperferritinemia. Patients were systematically examined for known conditions that cause high ferritin levels. Based on their ferritin levels, patients were categorized into three groups:

- Group 1 (moderate elevation: 600–1000 µg/L)
- Group 2 (significant elevation: 1000–1500 µg/L)
- Group 3 (extreme elevation: >1500 µg/L).

The study then analyzed the distribution of different causes within these groups.

Blood samples were collected after fasting in heparinized tubes and analyzed quickly after centrifugation. Plasma ferritin was measured using electro-chemiluminescence (ECLIA) with a Cobas® 6000 system, with normal values ranging from 30 to 300 µg/L for men and 20 to 200 µg/L for women. Plasma CRP levels were measured using an immunoturbidimetric method on the same system, with normal values below 5 mg/L. Lipemia and hemolysis can affect CRP results, but slight lipemia can be managed by dilution.

All our data was collected and processed in strict compliance with medical confidentiality.

The statistical study was carried out using Microsoft Excel program. The variables quantitative values were expressed as mean ± SD, qualitative variables were expressed as a percentage.

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## 3. Results

- 188 patients were studied with an average age of 51 years (SD of 13.12 years), ranging from 18 to 92 years.
- The number of women was 79 (42%) and men was 109 (58%) with a sex ratio of 1.4.
- The average plasma ferritin level was 922 µg/l (± 240 µg/l), with an average of 947 µg/l for women and 824 µg/l for men.

Distribution by requesting service: Outpatient: 52.3%, Internal medicine: 22.2%, Hematology: 15.3%, endocrinology: 4%, gastroenterology, and nephrology: 3.1% each

- Infections are the leading cause of hyperferritinemia, accounting for 34.5% of cases, nephropathies associated with hyperferritinemia are the second most common cause, representing 28.9%, Systemic diseases represent 12.4% of the causes, malignant diseases account for 9.3%, hepatopathies represent 4.3%, metabolic syndrome and

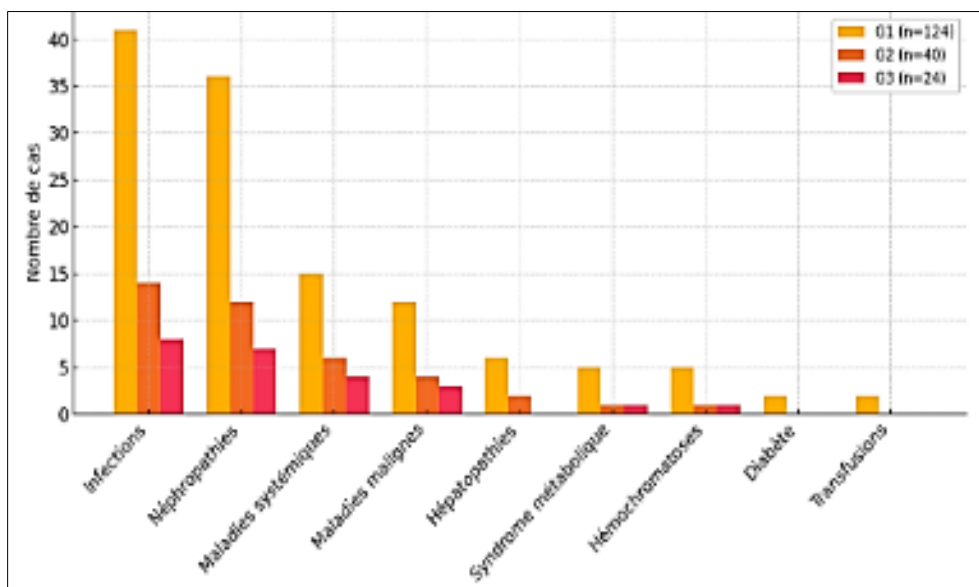
hemochromatoses each account for 4.2%, diabetes and repeated transfusions are the least common causes, each representing 1.1%.

Hyperferritinemic patients were classified into three groups based on ferritin levels: (Fig 1)

- Group 1: Moderately elevated ferritin (600–1000 µg/l) with 124 patients (66%).
- Group 2: Significantly elevated ferritin (1000–1500 µg/l) with 40 patients (21%).
- Group 3: Severely elevated ferritin (>1500 µg/l) with 24 patients (13%).

Distribution by sex:

- Group 1 (600-1000 µg/l): 56% male (70 patients) and 57% female (71 patients), with a male/female ratio of 1.
- Group 2 (1000-1500 µg/l): 39% male (16 patients) and 61% female (24 patients), with a male/female ratio of 0,7.
- Group 3 (>1500 µg/l): 61.5% male (14 patients) and 38.5% female (10), with a male/female ratio of 1.4.



**Figure 1** Case Distribution by Categories and Group (G1, G2, G3)

Infections are the most common cause of hyperferritinemia in the study, accounting for 34.5% of cases (63 patients), their distribution by origin is as below:

- Bacterial: 80% of cases.
- Parasitic: 3% of cases.
- Febrile syndromes of undocumented infectious origin: 17%.
- No viral infections found.
- Most frequent infections :
- Bronchopulmonary infections: (n= 37).
- Intra-abdominal infections :(n=14)
- Urinary tract infections : (n=5)
- Septicemias: (n=3)
- Malaria : (n=2)

Ferritin is mobilized as an iron chelator to fight against microbial invasion. Additionally, severe infections often lead to systemic inflammation, thereby increasing ferritin levels, since the latter is a positive inflammation protein.

#### 4. Discussion

Many pathologies can lead to elevated ferritin levels. Although hyperferritinemia is generally considered pathological in the literature, an increase in ferritin levels does not necessarily indicate an iron overload.

In the literature, several studies have been conducted on hyperferritinemia in different hospital departments.

The average ferritin level in our series was 922 µg/l ( $\pm$  240 µg/l) pour une valeur seuil de 600 ug/l. This represents a relatively moderate increase in blood ferritin levels among patients of both sexes, with 824 µg/l in men and 947 µg/l in women. In our study

An average age of 51 years (SD of 13.12 years), ranging from 18 to 92 years.

The number of women was 79 (42%) and men was 109 (58%) with a sex ratio of 1.4.

These initial results concur with those cited by Senjo et al [3], who recorded 1,394 patients with hyperferritinemia on at least one of their hospital-based analyses. The mean age in their series was 66 years, with a male predominance, 63% of men versus 37% of women. The mean ferritin value was 1024 ug/L for a hyperferritinemia cut off level defined at 1000 ug/L.

They are partly consistent with the results of Moore et al [4] with a total of 627 adult patients and an overall male preponderance (57.3%). Patient ages ranged from 18 to 91 years, with a main age of 55%, however the mean ferritin value was 2647 Ug/L, which could be explained by the selection of a cut off level of 1000ug/L adopted by the authors compared to ours, which is much lower.

Infections constituting the most common cause of hyperferritinemia in the population studied in our series, with a percentage of 34.5%, our results consistent with the results of the literature. Hyperferritinemia often accompanies infectious processes, particularly bacterial infections, as part of the acute phase response. Ferritin is an acute phase reactant that increases in response to inflammation, infection, or tissue damage.

Elouadghiri et al [5] also found in their series a predominance of the infectious cause with a rate of 24.50%, followed by immune system diseases 18%, the difference in rates can be explained by the number of cases identified given that this is a study that was limited to a single service.

Ruiz-Ordoñez I and a [6], also put the infections at the top of the list with a percentage of 56.57%, followed by hemopathy causes (29.71%).

However, in the study of Moore et al [4], the rate of infections (15.5%) ranks third among the causes of elevated ferritin, after malignant diseases (24%) and excess iron (22%), this difference of their results compared to the literature studies was explained by alternative diagnoses, such as malignancies or chronic inflammation syndromes that had these patients instead of infections. Additionally, the study population, drawn from a tertiary medical center, may not reflect the prevalence of infections present in other clinical settings. These hospitals often receive patients referred from primary or secondary level hospitals.

Cansu et al, [7] also ranked the infectious cause second after rheumatological diseases with a rate of 27.3% given that the objective of the study was to examine patients with elevated ferritin levels in the context of rheumatological diseases.

Ferritin acts as a defense mechanism during infection by sequestering iron, thereby limiting its availability to pathogens and protecting immune cell function. Elevated ferritin levels can also help reduce free radical production and mediate immunomodulation. Additionally, hyperferritinemia is associated with significant macrophage activation and can indicate high mortality risk in infected individuals [8]

The primary diagnosis associated with hyperferritinemia that displayed the widest range of ferritin values was hematologic malignancy, with a range from 10,036 ng/mL to 143,931 ng/mL, according to Sakket et al [9]

Ferritin levels are important in sepsis [10] as they serve as an acute-phase reagent, with elevated serum ferritin indicating inflammation and correlating with disease severity and mortality. Elevated ferritin levels can predict the need

for intensive care and poor outcomes, with specific cut-off values used for prognosis. In addition, ferritin helps deprive bacteria of free iron, thus contributing to infection control while amplifying the inflammatory response. In our study, we recorded few cases of sepsis, we were unable to establish a special link between the two.

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## 5. Conclusion

Within the limits of this study, we can conclude that hyperferritinemia is a frequent biological anomaly, which can affect both sexes, of any age, infectious causes are the most frequent etiologies hindering the prognosis, and it is associated with morbidity, significant mortality, and often prolonged hospitalization duration, hence the need for close clinical-biological collaboration in order to adopt appropriate and rapid treatment.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

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