Cent. Eur. J. Med. • 9(1) • 2014 • 115-120
DOI: 10.2478/s11536-013-0256-4

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Central European Journal of **Medicine**

Significance of Extremely Elevated Ferritin Level in Medical Inpatients

Research Article

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Received 16 August 2013; Accepted 15 November 2013

Abstract: The diagnostic and prognostic utility of extremely elevated ferritin values in hospitalized medical patients is lacking. We aimed to determine the clinical significance of ferritin levels ≥ 1000 ng/mL in adults hospitalized in the general medical service. We scanned the hospital laboratory database for ferritin values ≥ 1000 ng/mL, and evaluated the medical history, diagnoses, and survival of patients hospitalized in the general medical service. We compared the characteristics and outcomes of patients with values up-to versus above 2,999 ng/mL. Ferritin samples ranging from 1,003 to 12,170 ng/mL from 422 patients in the lower and 94 in the higher ferritin groups were included. Malignancy, repeat blood transfusions and recent chemotherapy were more prevalent in the higher ferritin group ($p=0.003$, $p=0.002$, and $p<0.001$, respectively). Infection (58.7%), chronic kidney disease (22.0%), and solid or hematological malignancies (21.6% and 17.1%, respectively) were the leading conditions associated with elevated ferritin. One-year survival was low, and significantly lower in patients in the higher ferritin group (10.8% vs. 16.9%, $p=0.004$). In conclusion, extremely elevated ferritin values in patients admitted to the general medical service are associated with multiplicity of clinical conditions and poor outcome.

Keywords: *Internal Medicine • Ferritin • Differential Diagnosis • Prognosis*

1. Introduction

Ferritin is the iron storage molecule of the body [1,2]. Its concentrations may be elevated due to increased iron load, and an increased transferrin saturation is warranted to differentiate between high and low iron load states [3,4]. In certain clinical settings ferritin levels can rise out of proportion to iron stores, reflecting its acute-phase reactant properties, resulting from increased apoferritin (or L ferritin) synthesis and secretion, and increased ferritin release from injured cells [5]. In acute hospital settings increased ferritin levels have been associated in the past with liver disease, renal disease, human immunodeficiency virus (HIV) infection, systemic infections or inflammation, malignancies, chronic red-cell transfusion, and sickle cell syndrome [6]. However, characterization of the clinical presentation and outcomes of extremely elevated ferritin levels in patients admitted to the general medical service is lacking. The objective of this study is to describe the clinical significance of ferritin levels greater than 1,000 ng/mL in patients hospitalized in the general medical service, and to compare the clinical characteristics and outcomes between two patient groups: one with ferritin levels between 1,000 and 2,999 ng/mL, and the other with ferritin levels equal to or higher than 3,000 ng/mL.

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2. Methods

2.1. Patients

The study was conducted in a 450-bed community-based university affiliated hospital in Haifa, Israel. The hospital laboratory electronic database was queried for serum ferritin assays performed between May 1st, 2006 and December 31st, 2010, in which levels of ferritin were equal to or higher than 1,000ng/mL. The analysis was limited to patients over 18 years of age who were admitted to the 110-bed division of Internal Medicine (IM).

2.2. Data collection

We retrospectively collected patients' demographics, medical history, concomitant medications, laboratory data, final diagnoses, and survival through at least one year of follow-up. The in-hospital data were retrieved from the hospital electronic medical records. The highest ferritin level during hospitalization was used as the index measurement. Diagnoses were deemed relevant to increased serum ferritin levels according to clinical judgment. Long term follow-up was available through an innovative system of hospital-community on-line medical records sharing (OFEK), in which diagnoses, medications, laboratory data, imaging results, outpatient visits, repeat hospitalization records and mortality are continuously captured [7].

2.3. Statistical methods

Descriptive statistics are shown for baseline data. Continuous variables are presented as mean ± SD and discrete variables as percent, and compared with a t-test and a chi-square test, respectively. Survival rates through 1 year are reported as Kaplan-Meier estimates and compared using log-rank statistic. Any significant differences in baseline characteristics, co-medication or ancillary laboratory values between the groups were included as covariates using Cox proportional hazards regression to assess the effect of ferritin level on death rates. All analyses were performed on IBM SPSS Statistics version 20.

The study was approved by the Institutional Review Board.

3. Results

A total of 1,515 ferritin samples exceeding 1,000 ng/mL were detected. Of these, samples from 516 patients who were admitted to the IM division were included in our analysis. The mean (±SD) ferritin level was 2,225.9 (±1,754.9) ng/mL, ranging from 1,003 to 12,170 ng/mL. Of the patients included, 422 (81.8%) had a ferritin level between 1,000 and 2,999 ng/mL, and 94 (18.2%) had a ferritin level equal or greater than 3,000 ng/mL. In six patients ferritin levels exceeded 10,000 ng/mL.

Patients' demographics and medical history are summarized in Table 1. The mean (±SD) age was 71.4 (±15.3) years, and 57.9% (299/516) were males. Chronic kidney disease was present in 32.5% (166/510) of patients, of which 33.7% (56/166) were treated with dialysis. A diagnosis of malignancy was present in 30.4% (155/510) of the patients. Thirty one patients were repeatedly treated with blood transfusion (6.1%). Malignancy and repeat blood transfusion treatment were significantly more prevalent in the cohort with ferritin values greater than 3,000 ng/mL (43.5% vs. 27.4%, p=0.003, and 13.0% vs. 4.6%, p=0.002, respectively), as was chemotherapy treatment prior to admission (20.7% vs. 8.4%, p<0.001). Patients' baseline ancillary laboratory data are presented in Table 2. Mean serum iron level was significantly higher in cohort of patients with ferritin values greater than 3,000 ng/mL (100.2±68.2 vs. 73.8±62.1, p<0.001).

High ferritin values were associated with 8 major diagnostic groups. A total of 730 diagnoses were found to be potentially associated with elevated ferritin levels in 496 evaluable patients. The mean (±SD) number of potentially relevant diagnoses per patient was 1.41 (±0.62), and the number of patients with more than one potential diagnosis was 219 (42.5%). Infection was the most prevalent presumed cause for ferritin levels above 1,000ng/mL, followed by an associated chronic kidney disorder and malignancy (Figure 1). Of the infectious causes, pneumonia (35.7%), urinary tract infection (16.2%) and sepsis of unknown source (12.7%) were most prevalent. Solid malignancies included lung cancer (21.5%), breast cancer (13.1%) and prostate cancer (12.1%) and a variety of others, and the most prevalent hematological malignancy was lymphoma (37.6%), followed by myelodysplastic syndrome (31.0%). The rate of hematological malignancies was numerically higher in the group of patients with higher ferritin values. However, the overall distribution of diagnostic groups did not significantly differ between patients with lower or higher ferritin values (p=0.088).

The 30-day and 1-year survival rates were low, and were significantly lower in patients presenting with higher ferritin values (30-day: 40.0% vs. 57.2%, p=0.003; 1-year: 10.8% vs. 16.9%, p=0.004; Figure 1). After adjustment for significant covariates, the risk of 1-year death remained significantly lower in patients

Table 1. Patients Clinical Characteristics

Characteristic	Serum ferritin 1,000-2,999 ng/mL (n=422)	Serum ferritin ≥3,000 ng/mL (n=94)	All patients (n=516)	p-value
Age	71.9 (±15.1)	69.3 (±16.3)	71.4 (±15.3)	0.137
Male	58.3% (246/422)	56.4% (53/94)	57.9% (299/516)	0.613
Congestive heart failure	22.7% (95/418)	22.8% (21/92)	22.7% (116/510)	0.984
Ischemic heart disease	38.0% (159/418)	35.9% (33/92)	37.6% (192/510)	0.698
Hypertension	60.5% (253/418)	62.0% (57/92)	60.8% (309/509)	0.799
Diabetes mellitus	36.6% (153/418)	34.8% (32/92)	36.3% (185/510)	0.742
Chronic obstructive pulmonary disease	7.4% (31/417)	3.3% (3/92)	6.7% (34/509)	0.147
Asthma	4.1% (17/418)	4.3% (4/92)	4.1% (21/510)	0.902
Current smoker	9.8% (41/418)	10.9% (10/92)	10.0% (51/510)	0.759
Chronic kidney disease	33.3% (139/418)	29.3% (27/92)	32.5% (166/510)	0.469
Dialysis	11.7% (49/418)	7.6% (7/92)	11.0% (56/510)	0.253
Cirrhosis	0.7% (3/418)	0.0% (0/92)	0.6% (3/510)	0.415
Cancer	27.5% (115/418)	43.5% (40/92)	30.4% (155/510)	0.003
Organ transplantation	1.0% (4/418)	0.0% (0/91)	0.8% (4/509)	0.349
Bone marrow transplantation	0.2% (1/418)	2.2% (2/92)	0.6% (3/510)	0.028
Chronic blood transfusion treatment	4.6% (19/417)	13.0% (12/92)	6.1% (31/509)	0.002
Hemoglobinopathy	1.7% (7/418)	2.2% (2/92)	1.8% (9/510)	0.742

Medical history of included patients according to their ferritin level groups

Table 2. Baseline Laboratory Measurements

Laboratory measurement	Serum ferritin 1,000-2,999 ng/mL (n=422)	Serum ferritin ≥3,000 ng/mL (n=94)	All patients (n=516)	p-value
Ferritin [ng/mL]	1567.5 (±496.8)	5510.5 (±3448.4)	2285.8 (±2161.0)	N/A
C-reactive protein [mg/L]	147.3 (±97.5)	156.9 (±109.8)	149.0 (±99.7)	0.559
Platelets [K/μL]	374.0 (±184.2)	331.2 (±223.4)	366.4 (±192.2)	0.055
White blood cells [K/μL]	19.2 (±17.0)	17.0 (±12.2)	18.8 (±23.3)	0.407
Iron [μg/dl]	73.8 (±62.1)	100.2 (±68.2)	78.5 (±64.0)	<0.001
Transferrin [mg/dL]	144.8 (±55.2)	139.6 (±52.2)	143.8 (±54.6)	0.564

Ancillary laboratory data during the index hospitalization

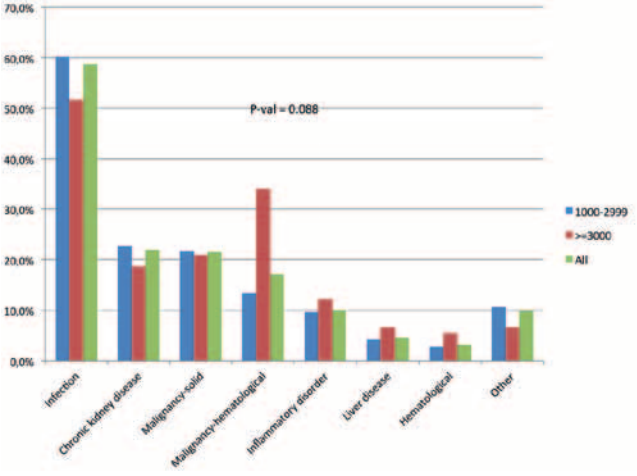
with ferritin level below 3,000 ng/mL (Hazard Ratio 0.54, 95% confidence interval 0.34 to 0.75, p<0.001).

4. Discussion

The clinical syndromes described in the current analysis as associated with ferritin elevation are well-known [8]. The present analysis sheds light on the diagnostic and prognostic utility of extremely elevated ferritin levels in hospitalized medical patients. The data presented depicts infection as the most common cause for extremely elevated ferritin levels in this setting, and highlights the additive effect of multiple contributing diagnoses on the rise of ferritin levels in this setting. Despite the lack of statistically significant differences between the clinical characteristics of the two ferritin groups, we have shown that patients in the higher ferritin cohort (≥3,000 ng/mL) are at increased risk for short and long term mortality, suggesting an extremely elevated ferritin value to be a surrogate marker of severe medical condition. This observation is further accentuated in light of the overall low survival rate in this highly selected population.

More modest elevations of ferritin levels of 300 ng/mL and above have been associated with increased mortality in the setting of multiple myeloma [9] and childhood neuroblastoma [10]. In lung cancer patients ferritin values above 300 ng/mL were significant predictors of survival even adjustment for covariates such as performance status, age, sex, TNM stage, and histological tumor type [11]. However, the medical literature is lacking descriptive reports on the clinical relevance of elevated ferritin outside the setting of distinct clinical scenarios. It is well recognized that very high serum ferritin is associated with iron overload states. Plasma ferritin has also been associated with various other

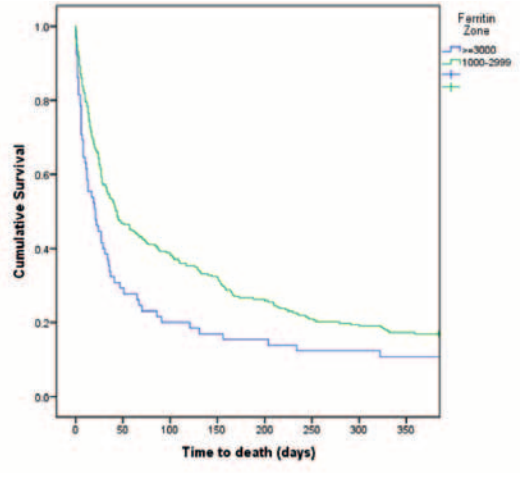
Figure 1. Final diagnostic groups



Diagnostic group	All patients (n=496)	Serum ferritin 1,000-2,999 ng/mL (n=405)	Serum ferritin ≥3,000 ng/mL (n=91)	P-value
Infection	58.7% (291)	60.2% (244)	51.6% (47)	0.132
Chronic kidney disease	22.0% (109)	22.7% (92)	18.7% (17)	0.401
Malignancy-solid	21.6% (107)	21.7% (88)	20.9% (19)	0.859
Malignancy-hematological	17.1% (85)	13.3% (54)	34.1% (31)	<0.001
Inflammatory disorder	10.1% (50)	9.6% (39)	12.1% (11)	0.482
Liver disease	4.6% (23)	4.2% (17)	6.6% (6)	0.326
Hematological	3.2% (16)	2.7% (11)	5.5% (5)	0.175
Other	9.9% (49)	10.6% (43)	6.6% (6)	0.245

Data is presented in %[n]

Figure 2. Freedom from death through 1 year



conditions such as in cases of anemia with inefficient erythropoiesis (beta-thalassemia, sickle-cell anemia, megaloblastic anemia, sideroblastic anemia) [12], as well as in states of increased metabolism, inflammation, tissue damage and neoplastic diseases [2]. Hereditary hypreferritinemia-cataract syndrome is a rare genetic syndrome associated with increased serum ferritin and no iron overload [12]. Extremely high serum ferritin exceeding 5,000 to 10,000ng/mL are traditionally associated with adult-onset Still's disease [13,14] and disseminated histoplasmosis and tuberculosis in HIV patients [15,16].

However, in the setting of hospitalized patients the diagnostic and prognostic utility of extremely elevated ferritin levels is less apparent. In a report published in 1995 by Lee et al., extremely elevated ferritin levels in 95 hospitalized patients was associated with liver disease (20.0%), renal disease (17.9%), malignant disease (17.9%), HIV infection (16.8%), non-HIV systemic infections (15.8%), chronic transfusions (10.5%) and sickle cell syndromes (10.5%) [6]. Another report by Ramirez et al. based on laboratory and clinical data from 135 patients found extremely serum ferritin levels higher than 2,000 ng/mL to be associated with hematological diseases (45.9%), liver diseases (23%), chronic renal failure (17.78%), neoplastic diseases (10.4%), systemic inflammatory diseases (7.4%), chronic transfusions (7.4%), and non-HIV systemic infections (5.9%). The

authors did not report whether their analysis included hospitalized patients [17]. Thus, to the best of our knowledge, this is the first report to describe the clinical significance of extremely elevated ferritin levels in acute hospitalization setting. As ferritin is used abundantly in the work-up of various medical conditions [2], it is valuable to describe its diagnostic and prognostic utility.

Our study has limitations. It is retrospective in design and based on assessment of past medical records. The medical conditions associated with increased ferritin levels are based on clinical reasoning, but the direct association with increased ferritin remains suggestive rather than confirmatory. We did not match our cohort to a cohort of patients hospitalized in IM departments with ferritin levels less than 1,000 ng/mL, and in that respect the analysis lacks control. This analysis is beyond the scope of the current report, as the aim of this study was to portrait a clinical finding that may be useful in a particular clinical and laboratory setup.

Our findings suggest that an extremely elevated ferritin level in patients hospitalized in the general medical service is associated with a variety and multiplicity of clinical conditions, and bares substantial prognostic value. Such findings, taken together with the presence or absence of other disease specific clinically relevant prognostic variables, should prompt hospitalists to unmask the underlying conditions and vigorously treat them. Future research is needed to determine whether or not repeat ferritin measurements could serve as a marker of disease progression or resolution.

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