

Integrating Iron Overload Diagnosis with Electrocardiographic Abnormalities: Bridging Laboratory Findings to Primary Care Practice

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Abstract: *Objective:* To investigate the diagnostic status and electrocardiographic correlates in patients with biochemical evidence of iron overload. *Methods:* We conducted a retrospective cohort study of patients in our hospital with ferritin levels exceeding 500 ng/mL between January 1, 2011, and October 24, 2022 (corresponding to the pre-COVID-19 pandemic period in Beijing). Using ICD-10-CM coded medical records, we assessed the following: definitive diagnostic characterization (genetic or acquired), electrocardiographic (ECG) completion rates, and the prevalence of ECG abnormalities. Statistical analyses, encompassing chi-square tests and correlation studies, were performed using SPSS Statistics software (version 27.0). *Results:* Except for cases of malignancy, infectious diseases, hematological diseases, chronic diseases, for the unexplained diagnosis group found elevated ferritin during annual health checkup, there were 17 cases in the group with ferritin above 1,000 ng/ml and 36 cases in the group with ferritin ranging from 500 to 1,000 ng/ml, accounting for 23.2% and 25.8% of the entire ferritin analysis respectively, and the total proportion in the entire analysis was 24.0%. Among the cases indicating ferritin higher than 500ng/ml, 24.0% of the cases were of unknown diagnosis. ECG acquisition rate for was 55.7%, with 24% demonstrating abnormalities, including atrial fibrillation, sinus tachycardia arrhythmia, atrioventricular block, prolonged QT interval, T-wave inversion, and ST-segment depression. *Conclusion:* The study revealed that the proportion of unexplained diagnoses of ferritin overload remains relatively high, and the analysis of the ECG is also insufficient. There is a need to enhance clinicians' awareness and attention to iron overload in both diagnosis and ECG analysis.

Keywords: Ferritin; Electrocardiogram; ECG

Online publication: October 15, 2025

1. Introduction

Iron is an essential micronutrient for oxygen binding and transport in red blood cells, but it is also a stress-

responsive programmed cell death-inducing second messenger ^[1]. In the blood, iron mostly exists in the form of ferritin.

Iron overload, as elevated ferritin levels, is a condition involving excessive iron deposition in various organs such as the liver, heart, pancreas, joints, skin and reproductive system ^[2], causing liver damage ^[3], arrhythmia, abnormal blood sugar level, joint pain, skin pigmentation, and hypolibido. Studies have shown that excessive intracellular iron can interfere with the electrical function of the heart by generating a large number of free radicals or causing selective dysfunction of Na⁺ channels. Abnormal function of Na⁺ and K⁺ channels is associated with the etiology of prolonged QT syndrome, ventricular tachycardia, and atrial fibrillation ^[4].

Iron overload can be categorized into primary and secondary causes. Primary iron overload, so-called hereditary hemochromatosis, is due to genetic defects, like HFE mutations. It is a common disease in Caucasians but uncommon in Chinese. The genetic analysis of Chinese revealed the gene mutations in Chinese were different from Caucasians ^[5,6]. Secondary iron overload is a more diverse disease with many unclear areas to be explored. Secondary iron overload is more prevalent than primary iron overload and occurs as a consequence of various causes that differ significantly across geographic regions. The main causes of secondary iron overload are iron-loading anemia and chronic liver disease ^[7]. If iron overload has been excluded, evaluation for causes of hyperferritinemia should be pursued. Causes of hyperferritinemia include chronic liver disease, excessive infusion of red blood cells for treatment, ineffective hematopoiesis, malignancy, infections, kidney failure, and rheumatic conditions, such as adult-onset Still's disease or hemophagocytic lymphohistiocytosis ^[8,9].

As general practitioners, we encounter a wide range of diseases, including infections, tumors, chronic conditions, and health check-ups. Cases of unexplained elevated ferritin are frequently encountered. This study analyzed the diagnostic status and ECG findings in cases of elevated ferritin levels to raise awareness among clinicians.

2. Experimental design summary

Here, the study conducted an analysis on the diagnoses and ECG findings in outpatients and inpatients with elevated ferritin levels at our hospital over the past decade, from 2011 to 2022.

A ferritin level greater than 500 ng/mL is considered elevated ^[2]. We divided the cases into two groups for diagnostic analysis: the ferritin 500–1000 ng/mL group and the ferritin greater than 1000 ng/mL group.

A total of 12,238 ferritin tests were conducted in the laboratory. Among these, 11,920 tests (97.4%) showed ferritin levels below 500 ng/ml; 222 tests (1.81%) had ferritin levels between 500 and 1000 ng/mL, which corresponded to 155 patients (including repeated tests for the same individuals); and 96 tests (0.78%) had ferritin levels above 1000 ng/ml, corresponding to 66 patients.

The diagnostic categories were classified as follows: (1) Tumors; (2) Infections; (3) Hematologic diseases; (4) Other diseases, which include chronic conditions such as hyperlipidemia, diabetes mellitus, systemic lupus erythematosus, and other autoimmune diseases, cases not classified as tumors, infections, or hematologic diseases were grouped here; (5) Unknown causes, with many cases identified during health check-ups. Some cases underwent genetic testing for hemochromatosis (HH) and thalassemia, but no definitive diagnosis was ultimately confirmed.

ECG Categories: (1) Normal ECG, including sinus bradycardia; (2) Abnormal ECG, which includes atrial fibrillation, sinus tachycardia, arrhythmia, atrioventricular block, prolonged QT interval, T-wave inversion, ST-segment depression and other similar findings; (3) No ECG was done.

3. Statistical methods

The statistical software SPSS 27.0 was used for data processing. Measurement data were analyzed using Pearson's correlation and variance analysis.

4. Result

4.1. Age

There were a total of 221 cases, with an average age of approximately 50.79 years old and a standard deviation of 19.64 years old, which belonged to a non-normal distribution. Among them, the youngest age was 2 months old and the oldest age was 98 years old. Grouped by the degree of increase in ferritin, the average age of the ferritin 1000 ng/mL group (a total of 66 cases) was approximately 48.65 years old, and the average age of the ferritin 500–1000 ng/mL group (a total of 155 cases) was approximately 51.70 years old. The *P* value was 0.320, indicating that there was no significant statistical difference in the age data between the two groups of cases (**Figure 1, Table 1**).

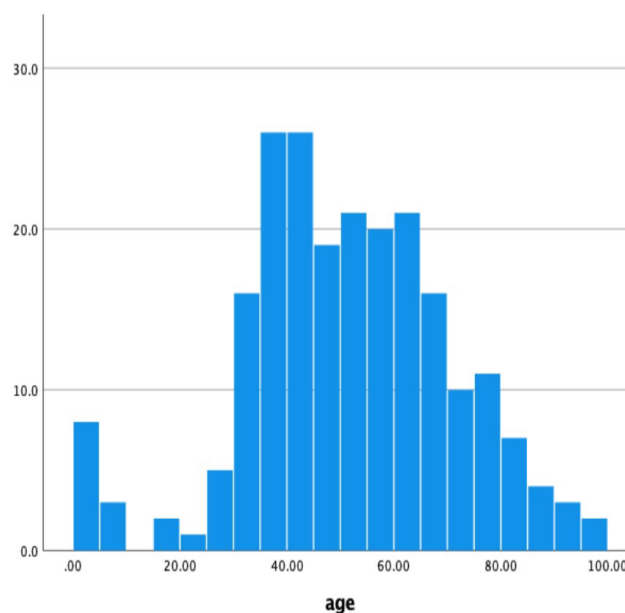


Figure 1. Variation of ferritin with age.

Table 1. Age distribution of patients by ferritin level group

Ferritin group	Count	Average value	Standard deviation	Standard error of the mean
> 1000 ng/mL	66	48.6553	21.56024	2.65388
500–1000 ng/mL	155	51.6984	18.76425	1.50718

4.2. Gender

Among them, there were 160 male cases and 61 female cases. Grouped by the degree of increase in ferritin, there were 51 males and 15 females in the ferritin > 1000 ng/mL group (a total of 66 cases), and 109 males and 46 females in the ferritin 500–1000 ng/mL group (a total of 155 cases). The *P* values were all < 0.001, showing significant statistical differences. Among the different degrees of elevated ferritin, the number of male cases was significantly higher than that of female cases (**Figure 2, Table 2**). The possible causes may be due to a female with

menses bleeding, which promotes iron metabolism and improves the condition of iron overload.

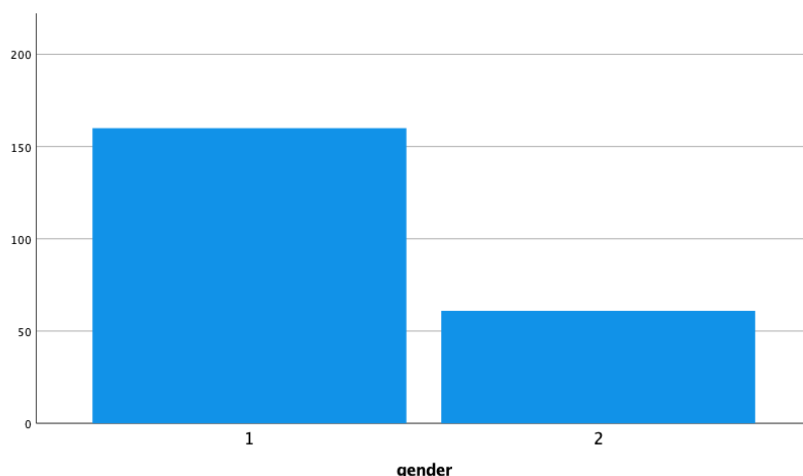


Figure 2. Variation of ferritin with gender.

Table 2. Distribution of gender by ferritin level group

Ferritin group		Gender		Total
		Male	Female	
> 1000 ng/mL	Count	51	15	66
	% within Group	77.3%	22.7%	100.0%
	% within Gender	31.9%	24.6%	29.9%
	% within Total	23.1%	6.8%	29.9%
500–1000 ng/mL	Count	109	46	155
	% within Group	70.3%	29.7%	100.0%
	% within Gender	68.1%	75.4%	70.1%
	% within Total	49.3%	20.8%	70.1%
Total	Count	160	61	221
	% within Group	72.4%	27.6%	100.0%
	% within Gender	100.0%	100.0%	100.0%
	% within Total	72.4%	27.6%	100.0%

4.3. Significant intergroup ferritin difference

The overall Pearson Chi-square value was 16.823, with a significance of 0.002, $P < 0.05$. There was a significant difference, indicating that there was a significant difference between groups. Among them, the Other diseases group (which includes chronic conditions such as hyperlipidemia, diabetes mellitus, systemic lupus erythematosus, and other autoimmune diseases, cases not classified as tumors, infections or hematologic diseases were grouped here), there was a significant statistical difference. In the Other diseases group, there were a total of 60 cases, only 6 cases (accounting for 10.0%) had a low proportion of ferritin greater than 1,000 ng/mL. The remaining 54 cases (accounting for 90.0%) had ferritin within the range of 500–1,000 ng/mL. It is indicated that the cases of ferritin

above 1,000 ng/mL in chronic diseases such as hyperlipidemia, diabetes, and systemic autoimmune diseases are significantly less than those in other diagnostic groups, such as tumors, infections, and the hematological diseases group. However, when comparing among the tumor group, the infection group, the blood group, and the healthy population group, there was no statistically significant difference (**Table 3**).

Table 3. Diagnosis & ferritin group

Diagnosis		Ferritin group		Total
		> 1000 ng/mL	500–1000 ng/mL	
Tumor group	Count	15 _a	24 _a	39
	Expected count	11.6	27.4	39.0
	% within Diagnosis Group	38.5%	61.5%	100.0%
	% within Ferritin Group	22.7%	15.5%	17.6%
Infectious diseases group	Count	22 _a	34 _a	56
	Expected count	16.7	39.3	56.0
	% within Diagnosis Group	39.3%	60.7%	100.0%
	% within Ferritin Group	33.3%	21.9%	25.3%
Hematological diseases group	Count	6 _a	7 _a	13
	Expected count	3.9	9.1	13.0
	% within Diagnosis Group	46.2%	53.8%	100.0%
	% within Ferritin Group	9.1%	4.5%	5.9%
Other diseases group	Count	6 _a	54 _b	60
	Expected count	17.9	42.1	60.0
	% within Diagnosis Group	10.0%	90.0%	100.0%
	% within Ferritin Group	9.1%	34.8%	27.1%
Unknown causes group	Count	17 _a	36 _a	53
	Expected count	15.8	37.2	53.0
	% within Diagnosis Group	32.1%	67.9%	100.0%
	% within Ferritin Group	25.8%	23.2%	24.0%
Total	Count	66	155	221
	Expected count	66.0	155.0	221.0
	% within Diagnosis Group	29.9%	70.1%	100.0%
	% within Ferritin Group	100.0%	100.0%	100.0%

Subscript letters denote homogeneous subsets of group categories where column proportions do not differ significantly at $\alpha = 0.05$ based on post-hoc pairwise comparisons.

Except for tumors, infectious diseases, hematological diseases, other diseases group, for the unknown causes group found during health checkup, there were 17 cases in the group with ferritin above 1,000 ng/mL and 36 cases in the group with ferritin ranging from 500 to 1,000 ng/mL, accounting for 23.2% and 25.8% of the entire ferritin analysis respectively, and the total proportion in the entire analysis was 24.0%. Among the cases indicating ferritin

higher than 500 ng/mL, 24.0% of the cases were of unknown diagnosis.

4.4. Electrocardiogram:

Among all the cases, 70 cases (31.7%) had normal electrocardiograms, 53 cases (24.0%) had abnormal electrocardiograms, and 98 cases (44.3%) had no electrocardiograms. In the group with ferritin above 1000, there were 17 cases (25.8%) with normal electrocardiograms, 16 cases (24.2%) with abnormal electrocardiograms, and 33 cases (50%) with no electrocardiograms. In the ferritin 500–1000 ng/mL group, 53 cases (34.2%) had normal electrocardiograms, 37 cases (23.9%) had abnormal electrocardiograms, and 65 cases (41.9%) had no electrocardiograms.

ECG acquisition rate was 55.7%, with 24% demonstrating abnormalities, including atrial fibrillation, sinus tachycardia, arrhythmia, atrioventricular block, prolonged QT interval, T-wave inversion, ST-segment depression and other similar findings. Current clinical practice demonstrates suboptimal recognition of cardiac sequelae in hyperferritinemia, with only half cases receiving electrocardiogram screening despite established associations with arrhythmogenic risks ^[10–15]. (Table 4 and Table 5)

Table 4. Electrocardiogram analysis of the ferritin group above 1000 ng/mL

Diagnosis		ECG			Total
		Normal ECG	Abnormal ECG	No ECG	
Tumor group	Count	3	7	5	15
	% within Diagnosis Group	20.0%	46.7%	33.3%	100.0%
	% within ECG Group	17.6%	43.8%	15.2%	22.7%
Infectious diseases group	Count	4	5	13	22
	% within Diagnosis Group	18.2%	22.7%	59.1%	100.0%
	% within ECG Group	23.5%	31.3%	39.4%	33.3%
Hematological diseases group	Count	1	0	5	6
	% within Diagnosis Group	16.7%	0.0%	83.3%	100.0%
	% within ECG Group	5.9%	0.0%	15.2%	9.1%
Other diseases group	Count	2	2	2	6
	% within Diagnosis Group	33.3%	33.3%	33.3%	100.0%
	% within ECG Group	11.8%	12.5%	6.1%	9.1%
Unknown causes group	Count	7	2	8	17
	% within Diagnosis Group	41.2%	11.8%	47.1%	100.0%
	% within ECG Group	41.2%	12.5%	24.2%	25.8%
Total	Count	17	16	33	66
	% within Diagnosis Group	25.8%	24.2%	50.0%	100.0%
	% within ECG Group	100.0%	100.0%	100.0%	100.0%

Table 5. Electrocardiogram analysis of the ferritin group 500–1000 ng/mL

Diagnosis		ECG			Total
		Normal ECG	Abnormal ECG	No ECG	
Tumor group	Count	5	7	12	24
	% within Diagnosis Group	20.8%	29.2%	50.0%	100.0%
	% within ECG Group	9.4%	18.9%	18.5%	15.5%
Infectious diseases group	Count	7	8	19	34
	% within Diagnosis Group	20.6%	23.5%	55.9%	100.0%
	% within ECG Group	13.2%	21.6%	29.2%	21.9%
Hematological diseases group	Count	2	3	2	7
	% within Diagnosis Group	28.6%	42.9%	28.6%	100.0%
	% within ECG Group	3.8%	8.1%	3.1%	4.5%
Other diseases group	Count	17	16	21	54
	% within Diagnosis Group	31.5%	29.6%	38.9%	100.0%
	% within ECG Group	32.1%	43.2%	32.3%	34.8%
Unknown causes group	Count	22	3	11	36
	% within Diagnosis Group	61.1%	8.3%	30.6%	100.0%
	% within ECG Group	41.5%	8.1%	16.9%	23.2%
Total	Count	53	37	65	155
	% within Diagnosis Group	34.2%	23.9%	41.9%	100.0%
	% within ECG Group	100.0%	100.0%	100.0%	100.0%

4.5. Special cases

A 3-year-old girl with transfusion-dependent β -thalassemia major exhibited severe growth retardation (< 3rd percentile for height, weight 3%, WHO growth charts) and iron overload (ferritin 2615.2 ng/mL), no electrocardiogram was done. Genetic testing was completed for some cases diagnosed as hereditary hemochromatosis. The genetic testing of two European Americans diagnosed with hemochromatosis showed the classic HFE gene mutation. But in one case, a Chinese patient with ferritin exceeding 500 ng/mL developed atrial fibrillation and underwent ablation treatment. Nuclear magnetic resonance indicates mild iron deposition. Typical hemochromatosis HFH examination was conducted and the result was negative. However, after genetic testing related to hemochromatosis in China, the result was a heterozygous mutation in exon 5 of SUGP2, which is different from the typical HFE gene mutation of hemochromatosis and is a special gene mutation of hemochromatosis in China. In a retrospective study, a case was found where atrial fibrillation occurred when the ferritin level was above 1000 ng/mL. After bloodletting therapy, the electrocardiogram returned to normal when the ferritin level recovered to around 300 ng/mL.

The application of genetic testing and other technologies to confirm the presence or absence of iron-related gene mutations, especially in the field of heterozygote gene testing, requires more research. For instance, a young Chinese male with a history of hyperlipidemia and fatty liver. Health checkup revealed elevated ferritin levels, fluctuating between 588 and 766 ng/mL. Transferrin saturation was normal. Abdominal MRI indicated mild iron

deposition in the liver. No classic hemochromatogenic gene variations were detected in the submitted samples (HFE, HJV, HAMP, TFR2, SLC40A1, DENND3, SUGP2 gene mutation detection and next-generation sequencing). Further next-generation sequencing detected a heterozygous variation of c.2724 + 3A > G in the intron 6 region of the ZYFVE16 gene. Literature-based research indicates that the ZYFVE16 genetic variant modulates systemic iron homeostasis and potentially promotes iron deposition. Subsequent functional studies will be undertaken to delineate its precise role in iron metabolism.

5. Discussion

There are many cases of unknown causes, which require more attention from us clinicians. For example, technologies such as genetic testing should be applied to confirm whether there are iron-related gene mutations^[16,17]. Especially in the aspect of heterozygous gene examination and gene mutations of hemochromatosis and iron metabolism in the Chinese population, more research is needed^[2,5].

The correlation analysis between ferritin values and abnormal electrocardiograms indicated that there was no linear correlation between the two. Studies have shown that the myocardium is more sensitive to iron than other muscle cells. So some patients may experience abnormal electrocardiograms when the ferritin level does not exceed 1000 ng/mL. In other diagnostic groups (chronic diseases, autoimmune diseases, etc.), although the proportion of ferritin above 1,000 ng/mL was relatively low, the proportion of abnormal electrocardiogram was the same as that in other groups. This suggests that whether the ferritin value is significantly elevated or slightly elevated, we need to conduct an electrocardiogram assessment and follow-up monitoring as early as possible^[14].

This study indicates that the etiology and diagnostic nature of ferritin overload have not received extensive attention in clinical practice. The status of electrocardiogram acquisition rate and follow-up is also very low. If the diagnosis is clear and the treatment is timely, ferritin can be controlled as early as possible, which can mitigate pathological iron accumulation and prevent damage to the myocardium, liver, and other irreversible end-organ damage^[18].

6. Conclusion

In summary, this study highlights two significant clinical challenges: a substantial proportion of hyperferritinemia cases remain undiagnosed, and concomitant electrocardiographic (ECG) analyses are frequently overlooked. These findings underscore the imperative to enhance clinical vigilance and improve comprehensive assessment for iron overload, encompassing both etiological investigation and routine ECG evaluation, to facilitate earlier diagnosis and intervention.

Disclosure statement

The authors declare no conflict of interest.

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