




The Clinical and Biological Manifestations in Women with Iron Deficiency Without Anemia Compared to Iron Deficiency Anemia in a General Internal Medicine Setting: A Retrospective Cohort Study

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Purpose: The clinical presentation of iron deficiency is not well understood. We aimed to identify the clinical manifestations of iron deficiency without anemia in women.

Patients and Methods: We conducted a retrospective cohort study of women who visited the general internal medicine outpatient department of a university hospital in Japan between 2016 and 2022. Women who were prescribed iron supplements were included in the study. Anemia was defined as hemoglobin levels below 12 g/dl. Iron deficiency was defined as serum ferritin levels < 30.0 µg/l. The primary outcome was the difference in symptoms between patients with iron deficiency with and without anemia. The secondary outcome was the ratio of symptom, hemoglobin, and serum ferritin improvement (levels > 30.0 µg/l after treatment), comparing the measurements at the beginning and after supplementation.

Results: A total of 147 women were included in the final analysis. There were no significant differences in the initial symptoms and the ratio of symptom improvement between the groups. Compared to patients with iron deficiency anemia, patients with iron deficiency without anemia had high initial serum ferritin levels (14.8 vs 7.1 µg/l, $p < 0.001$), and hemoglobin (13.2 vs 9.9 g/dl, $p < 0.001$). Iron supplements significantly improved the serum ferritin level in two groups and the hemoglobin in iron deficiency anemia. After treatment, iron deficiency without anemia still had high serum ferritin levels (37.7 vs 28.2 µg/l, $p = 0.017$) and hemoglobin (13.3 vs 12.3 g/dl, $p < 0.001$).

Conclusion: There were no differences in any of the investigated symptoms and the ratio of the symptom improvement depending on the anemic state in iron deficiency. After iron supplementation, the serum ferritin levels in the iron deficiency without anemia group improved. Hemoglobin and serum ferritin in iron deficiency without anemia were still highly comparable to that of iron deficiency anemia.

Keywords: women, hemoglobin, iron deficiency without anemia, serum ferritin

Introduction

Iron deficiency is a common form of nutritional deficiency worldwide.^{1,2} The overall mean prevalence of iron deficiency is > 20%.³ Although more common in developing countries, the estimated prevalence of iron deficiency was 9–16% in young females in the United States in 1999–2000.⁴ Classification of iron deficiency without anemia or iron deficiency with anemia is based on hemoglobin levels. Hemoglobin levels below 12 g/dl in women is conventionally defined as anemia by the World Health Organization.⁵ Approximately half of all anemia cases are caused by iron deficiency.⁵ Iron deficiency anemia is a late manifestation of iron deficiency, with a clear predominance in adolescents and menstruating females.⁶

Iron deficiency is a multisystem condition with a wide range of clinical manifestations, including reduced cognitive function,^{7–9} poor physical performance,¹⁰ pica, restless legs syndrome, and impaired immunological function.¹¹ Anemia

is an extreme manifestation of iron deficiency. Even without anemia, fatigue can be observed in people with iron deficiency.¹² Iron deficiency is defined when an abnormal value is detected in at least two of the following three indicators: serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin.⁴ Serum ferritin concentration is the most sensitive and specific test used for iron deficiency.¹³ The utility of the red cell distribution width, and mean corpuscular volume in diagnosing iron deficiency has also been reported.¹⁴ These characteristics, observed in complete blood counts, could be markers of iron deficiency and would help the study of iron kinetics to be considered in general clinical practice. Iron deficiency without anemia may be challenging to diagnose because of its nonspecific symptoms and the lack of awareness of the existence of such a variety in healthcare providers.

In our general internal medicine department, some of the women presenting with a variety of symptoms, including fatigue, who were undiagnosed after the usual clinic-based investigation were eventually diagnosed with iron deficiency without anemia. Iron supplementation occasionally improves the symptoms, especially fatigue.^{15,16} Since iron deficiency anemia is an extreme form of iron deficiency, diagnosing iron deficiency without anemia before it progresses to iron deficiency anemia will have a positive effect on the subsequent clinical consequences. Clinicians could detect iron deficiency early on by focusing on the manifestations caused by iron deficiency without anemia. However, these clinical and biological manifestations are not known well. Therefore, we investigated the differences in clinical and biological symptoms depending on the anemic state of iron deficiency. We also attempted to evaluate whether the effect of iron supplementation intervention on iron deficiency without anemia would be different from the effect of iron supplementation intervention on iron deficiency anemia.

Materials and Methods

This retrospective, single-center cohort study included all women who were prescribed iron supplementation in the general internal medicine outpatient department (Department of Diagnostic and Generalist of Medicine) of Dokkyo Medical University Hospital, Mibu, Tochigi, Japan, from April 1, 2016 to March 31, 2022. The institution is a tertiary teaching hospital. This study was conducted in accordance with the current version of the Declaration of Helsinki. The protocol was approved by the Ethics Committee of Dokkyo Medical University (No. R-56-13J). As this was a retrospective cohort study, and the study data were anonymous, the requirement for informed consent was waived by the ethics committee.

Patient Population

Of 187 women aged > 15 years who were prescribed iron supplementation in the general internal medicine department during the study period, 16 were excluded because of iron supplement use within two weeks prior to the index visit. A further 11 women were excluded because their serum ferritin levels were > 30 µg/l (2 for viral infection, 2 collagen disease, 1 menopause, 1 ulcer colitis, 1 post bleeding, 1 anxiety disorder, 3 unknown). Eight women were excluded because of blood transfusion therapy within two weeks prior to the index visit. Five other women were excluded because of the lack of data. In total, 147 women were enrolled in this study. A flow diagram of the patient selection is shown in Figure 1. All iron supplements were prescribed at the discretion of the treating doctor.

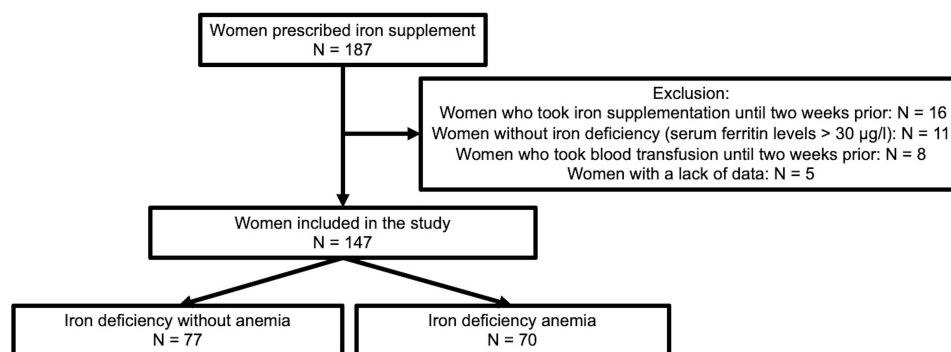


Figure 1 Flowchart of patient inclusion and exclusion in the study.

Definition and Outcome

Anemia was assessed using hemoglobin, hematocrit, and complete blood count. In this study, we defined hemoglobin levels below 12 g/dl for women, according to the World Health Organization.⁵

Iron deficiency was defined as an abnormal value for at least two of the following three indicators: serum ferritin, transferrin saturation, and free erythrocyte protoporphyrin.⁴ Serum ferritin concentration is the most sensitive and specific test used for iron deficiency (without inflammation), with levels less than 30 µg/l being generally indicative of low body iron stores.¹³ Therefore, we defined iron deficiency as a serum ferritin level < 30 µg/l in this study. Iron supplementation included ferrous fumarate, sodium ferrous citrate, dried ferrous sulfate, and ferric pyrophosphate.

The primary study outcome was the difference in the symptoms between the iron deficiency without anemia and iron deficiency anemia groups. The secondary outcome was the ratio of symptom, hemoglobin, and serum ferritin improvement, comparing the measurements at the beginning and after supplementation. We defined symptom improvement as any symptom improving within 12 weeks of treatment with iron supplementation. We collected the latest laboratory data following iron supplementation as post-treatment data. Improvement in serum ferritin was defined as serum ferritin levels above 30 µg/l within 12 weeks of treatment with iron supplementation.

Data Collection

Data collected was for the purpose of conducting this study. The patients' medical records were reviewed by the primary researcher (TH). Another researcher (AH) independently double-checked the symptom classification¹⁷ and clinical course. In cases of disagreement, both researchers discussed together to decide the final judgment. All data were collected by the treating doctors in the context of clinical management. The baseline characteristics included age. We collected data on the presence of the following symptoms: fatigue, muscle pain/joint pain, dizziness/vertigo, menorrhagia, headache, anorexia, body weight loss, fever, palpitations, dyspnea, insomnia, edema, anxiety/depressive mood, hair loss, heartburn, pica, genital bleeding, melena, and memory loss. For symptoms and hemoglobin levels, the data up to 12 weeks prior to the index visit were included in the analysis. Laboratory findings for iron deficiency assessment included hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, transferrin saturation, iron, unsaturated iron-binding capacity, total iron-binding capacity, white blood cells, platelets, C-reactive protein, erythrocyte sedimentation rate, serum folate, serum vitamin B12, and thyroid-stimulating hormone. All laboratory data were analyzed using automated methods.

Analysis

First, we compared the baseline characteristics between iron deficiency without anemia and iron deficiency with anemia. Then, we analyzed the change after treatment for symptoms and laboratory data of both groups.

Continuous variables are presented as medians and standard deviation (SD) or interquartile ranges (IQR) and were compared using the Mann–Whitney *U*-test. Categorical or binary variables are presented as numbers and were compared using the chi-squared test. A statistical power analysis was performed using the program G*power version 3.1.9.6 (Department of Psychology of Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Statistical significance was set at *P*-value < 0.05. All statistical tests were performed using R 3.6.0 for MacOS X (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics and symptoms were not different between patients with ferritin > 30 µg/l (N=11) and patients with ferritin < 30 µg/l (N=147), except for edema (5/11 [45.6%] vs 15/147 [10.2%], *p*<0.001) and menorrhagia (0/11 [0%] vs 44/147 [29.9%], *p*=0.034).

In total, 147 women were enrolled in the final analysis. Of these, the mean age of all patients was 41.5 ± 15.6 (SD) years. Fifty-five patients (55/147, 37.4%) complained of fatigue. The mean hemoglobin level was 11.6 ± 1.9 g/dl, while the mean serum ferritin level was 11.1 ± 9.1 µg/l. Ferrous fumarate was the most frequently prescribed iron supplement (68/147, 46.3%), followed by sodium ferrous citrate (46/147, 31.3%), dried ferrous sulfate (24/147, 16.3%), and ferric pyrophosphate (9/147, 6.1%). The median duration of iron supplementation was 106 (IQR 32–150) days.

Anemia was not observed in 77 patients (77/147, 52.3%) during the study period. The baseline characteristics and symptoms of the patients with iron deficiency without anemia and iron deficiency anemia are shown in Table 1. There were no significant differences between the groups in age (mean age 38.6 vs 44.7, $p=0.46$), the prevalence of fatigue (31/77 [40.3%] vs 24/70 [34.2%], $p=0.46$), muscle pain or joint pain (25/77 [32.5%] vs 21/70 [30.0%], $p=0.75$), dizziness or vertigo (26/77 [33.8%] vs 19/70 [27.1%], $p=0.39$), menorrhagia (21/77 [27.3%] vs 23/70 [32.9%], $p=0.46$), headache (22/77 [28.6%] vs 19/70 [27.1%], $p=0.85$), anorexia (16/77 [20.8%] vs 15/70 [21.4%], $p=0.93$), body weight loss (16/77 [20.8%] vs 12/70 [17.1%], $p=0.58$), and fever (12/77 [15.6%] vs 16/70 [22.9%], $p=0.26$).

The details of the complete blood counts are shown in Table 2. Compared to patients with iron deficiency anemia, the hemoglobin (mean 13.2 vs 9.9, $p<0.001$), hematocrit (40.2 vs 32.7, $p<0.001$), the red blood cells (4.57 vs 4.23, $p<0.001$), mean corpuscular volume (88.2 vs 78.0, $p<0.001$), mean corpuscular hemoglobin (28.9 vs 23.7, $p<0.001$), and mean corpuscular hemoglobin concentration (32.7 vs 30.3, $p<0.001$) of the iron deficiency without anemia group were high. Meanwhile, the red cell distribution width (13.5 vs 16.4, $p<0.001$) and platelet count (290 vs 338, $p=0.0045$) in the iron deficiency without anemia group were low.

The details of the laboratory tests are shown in Table 3. Compared with patients with iron deficiency anemia, the initial serum ferritin (mean 14.8 vs 7.1, $p<0.001$), serum iron (80.1 vs 26.8, $p<0.001$), and serum transferrin saturation (22.3 vs 5.9, $p<0.001$) of the iron deficiency without anemia group were high. The total iron-binding capacity (mean 388 vs 414, $p=0.0049$), the unsaturated iron-binding capacity (311 vs 390, $p<0.001$) and erythrocyte sedimentation rate (13.4 vs 24.0, $p=0.003$) of the patients with iron deficiency without anemia were low.

The change in symptoms and laboratory data before and after treatment are shown in Table 4. The change in hemoglobin and serum ferritin before and after treatment for the iron deficiency without anemia group and the iron deficiency with anemia group are shown in Figures 2 and 3, respectively. Iron supplementation improved hemoglobin in iron deficiency anemia (mean 9.9 to 12.3, $p<0.001$) and mean corpuscular volume (78.0 to 84.9, $p<0.001$). It also improved serum ferritin in iron deficiency without anemia (14.8 to 37.7, $p<0.001$) and iron deficiency anemia (7.1 to 28.2, $p<0.001$). After treatment, hemoglobin (mean 13.3 vs 12.3, $p<0.001$), mean corpuscular volume (89.4 vs 84.9,

Table 1 Baseline and Symptoms of the Iron Deficiency Without Anemia Group Compared to the Iron Deficiency with Anemia Group

Variable	Iron Deficiency Without Anemia (n = 77)	Iron Deficiency Anemia (n = 70)	P value*
Age, y (SD)	38.6 (16.7)	44.7 (13.7)	0.46
Fatigue, n (%)	31 (40.3)	24 (34.2)	0.46
Muscle pain/Joint pain, n (%)	25 (32.5)	21 (30.0)	0.75
Dizziness/Vertigo, n (%)	26 (33.8)	19 (27.1)	0.39
Menorrhagia, n (%)	21 (27.3)	23 (32.9)	0.46
Headache, n (%)	22 (28.6)	19 (27.1)	0.85
Anorexia, n (%)	16 (20.8)	15 (21.4)	0.93
Body weight loss, n (%)	16 (20.8)	12 (17.1)	0.58
Fever, n (%)	12 (15.6)	16 (22.9)	0.26
Palpitation, n (%)	13 (18.2)	12 (17.1)	0.97
Dyspnea, n (%)	14 (18.2)	8 (11.4)	0.25
Insomnia, n (%)	10 (13.0)	9 (12.9)	0.98
Edema, n (%)	8 (10.4)	7 (10.0)	0.94
Anxiety/depressive mood, n (%)	7 (9.1)	4 (5.7)	0.44
Hair loss, n (%)	2 (2.6)	4 (5.7)	0.34
Heartburn, n (%)	3 (3.9)	3 (4.3)	0.91
Pica, n (%)	1 (1.3)	2 (2.9)	0.51
Genital bleeding, n (%)	0 (0.0)	2 (2.9)	0.14
Melena, n (%)	0 (0.0)	1 (1.4)	0.30
Memory loss, n (%)	1 (1.3)	0 (0.0)	0.35

Notes: *P values by chi-squared or Mann-Whitney U-test.

Table 2 Complete Blood Count Comparison Between Those with Iron Deficiency with and without Anemia

Variable	Iron Deficiency Without Anemia (n = 77)	Iron Deficiency Anemia (n = 70)	P value*
Hemoglobin, g/dl (SD)	13.2 (0.7)	9.9 (1.3)	< 0.001
Hematocrit, % (SD)	40.2 (2.0)	32.7 (3.4)	< 0.001
Red blood cells, $\times 10^{12}/L$ (SD)	4.57 (0.39)	4.23 (0.51)	< 0.001
Mean corpuscular volume, fl (SD)	88.2 (5.2)	78.0 (8.8)	< 0.001
Mean corpuscular hemoglobin, pg (SD)	28.9 (2.0)	23.7 (3.9)	< 0.001
Mean corpuscular hemoglobin concentration, g/dl (SD)	32.7 (1.0)	30.3 (1.9)	< 0.001
Red cell distribution width, % (SD)	13.5 (1.6)	16.4 (2.4)	< 0.001
White blood cell, $\times 10^9/l$ (SD)	6.23 (1.83)	6.33 (1.90)	0.71
Platelet, $\times 10^9/l$ (SD)	290 (64)	338 (101)	0.0045

Note: *P values by Mann–Whitney U-test.

Abbreviations: IQR, interquartile range; SD, standard deviation.

Table 3 Laboratory Findings of Those with Iron Deficiency with and without Anemia

Variable	Iron Deficiency Without Anemia (n = 77)	Iron Deficiency Anemia (n = 70)	P value*
Serum ferritin, $\mu g/l$ (SD)	14.8 (8.1)	7.1 (8.5)	< 0.001
Serum iron, $\mu g/dl$ (SD)	80.1 (50.0)	26.8 (25.7)	< 0.001
Total iron-binding capacity, $\mu g/dl$ (SD)	388 (49)	414 (58)	0.0049
Unsaturated iron-binding capacity, $\mu g/dl$ (SD)	311 (72)	390 (60)	< 0.001
Serum transferrin saturation, % (SD)	22.3 (13.5)	5.9 (4.4)	< 0.001
C-reactive protein, mg/dl (SD)	0.14 (0.41)	0.39 (1.43)	0.57
Erythrocyte sedimentation rate, mm/hour (SD)	13.4 (9.4)	24.0 (17.8)	0.001
Serum folate, $\mu g/l$ (SD)	11.8 (10.4)	10.2 (9.6)	0.46
Serum vitamin B12, ng/l (SD)	439 (565)	336 (165)	0.57
Thyroid-stimulating hormone, mIU/l (SD)	1.35 (0.77)	4.6 (16.6)	0.82

Note: *P values by Mann–Whitney U-test.

Abbreviations: IQR, interquartile range; SD, standard deviation.

$p=0.024$), and serum ferritin (37.7 vs 28.2, $p=0.017$) with iron deficiency without anemia were still highly comparable to patients with iron deficiency anemia. Red cell distribution width (13.4 vs 17.7, $p<0.001$) with iron deficiency without anemia was still low compared to iron deficiency anemia. There were no significant differences between the groups in terms of symptom improvement (46/77 [59.7%] vs 43/70 [61.4%], $p=0.75$) and the ratio of serum ferritin improvement (33/53 [62.3%] vs 20/53 [37.7%], $p=0.07$).

There were no significant differences in terms of the type of iron supplementation or duration of prescription between the groups. The details of the treatments are shown in [Supplementary Table 1](#).

Power analysis revealed that the statistical power for comparing symptom improvement between both groups was 0.06. However, corresponding values in hemoglobin, serum ferritin, and serum ferritin improvement exceeded 0.99.

Discussion

This study has several main findings. First, there were no differences in any of the investigated symptoms and the ratio of symptom improvement depending on the anemic state. This suggests that the symptoms studied are not related to the

Table 4 Changes After Treatment for Symptoms and Laboratory Data of Those with Iron Deficiency with and without Anemia

Variable	Iron Deficiency Without Anemia (n = 77)	Iron Deficiency Anemia (n = 70)	P value*
Symptom improvement, n (%)	46 (59.7)	43 (61.4)	0.75
Hemoglobin, g/dl (SD)			
Before-treatment	13.2 (0.7)	9.9 (1.3)	< 0.001
After-treatment	13.3 (0.9)**	12.3 (1.8)***	< 0.001
Mean corpuscular volume, fl (SD)			
Before-treatment	88.2 (5.2)	78.0 (8.8)	< 0.001
After-treatment	89.4 (4.7)**	84.9 (12.2)***	0.024
Red cell distribution width, % (SD)			
Before-treatment	13.5 (1.6)	16.4 (2.4)	< 0.001
After-treatment	13.4 (1.3)**	17.7 (10.1)****	< 0.001
Serum ferritin, µg/l (SD)			
Before-treatment	14.8 (8.1)	7.1 (8.5)	< 0.001
After-treatment	37.7 (22.8)*****	28.2 (17.7)*****	0.02
Serum ferritin improvement, n (%)	33 (62.3)*****	20 (37.7)*****	0.07

Notes: *P values by chi-squared or Mann–Whitney U-test. **N = 57. ***N = 62. ****N = 56. *****N = 53.
Abbreviation: SD, standard deviation.

severity of iron deficiency. In future studies, iron deficiency and non-iron deficiency should be compared in a nonanemic population, especially for edema and menorrhagia. The relationship of each symptom with iron deficiency should be clarified. Second, biological data suggested that iron deficiency anemia is an extreme form of iron deficiency.^{6,13} Smaller red blood cell indices, higher red cell distribution, and higher platelet counts of iron deficiency anemia suggested a bone marrow response to anemia. Third, iron supplements improved serum ferritin levels in both groups and hemoglobin in iron deficiency anemia. However, hemoglobin, mean corpuscular volume and ferritin were still high (approximately 1.0 g/dl, 5 femtoliters, and 10 µg/l, respectively) and red cell distribution width was still low (approximately 5%) in iron

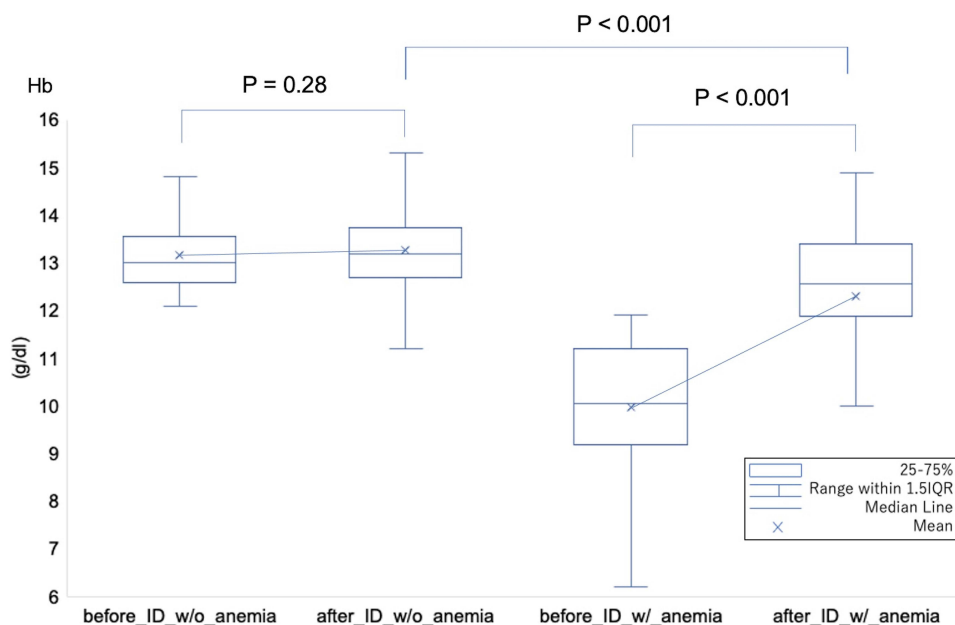


Figure 2 Change in hemoglobin by treatment of those with iron deficiency with and without anemia.
Abbreviations: ID, iron deficiency; w/o, without; w/, with; IQR, interquartile range.

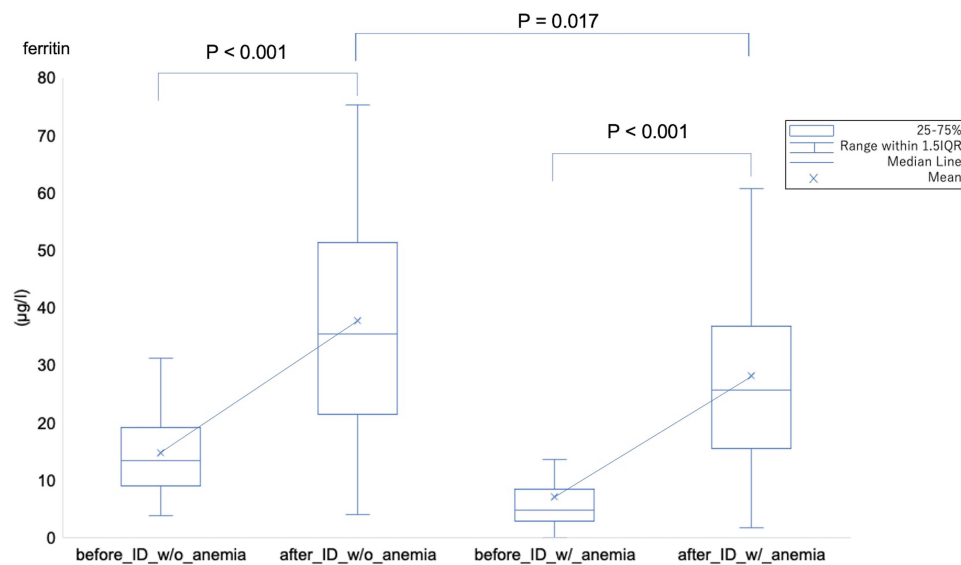


Figure 3 Serum ferritin change by treatment of those with iron deficiency with and without anemia. **Abbreviations:** ID, iron deficiency; w/o, without; w/, with; IQR, interquartile range.

deficiency without anemia compared to those of iron deficiency anemia. This could be because iron deficiency anemia is a severe manifestation of iron deficiency and may require a longer treatment period. These findings suggest that the early detection of iron deficiency would require a shorter duration of iron supplementation to normalize biological manifestations than iron deficiency anemia.

Red cell distribution width > 15% and mean corpuscular volume < 80 femtoliters are useful in diagnosing iron deficiency anemia in hospitalized patients.¹⁴ In this study, we also found similar results in the outpatient setting. Additionally, iron supplements reduced the mean corpuscular volume in iron deficiency anemia (approximately 7 femtoliters), but not the red cell distribution width. This suggested that the change in mean corpuscular volume could be used as an indicator to evaluate the efficacy of the ongoing treatment; these findings are similar to the results of the previous study.¹⁴

Iron supplementation reportedly decreases fatigue by 48% in non-anemic women with iron deficiency.¹⁶ Although a simple comparison is not accurate due to the differences in symptom evaluation and the lower serum ferritin cut-off levels (< 30 µg/l in ours vs < 50 µg/l in the previous study), the symptom improvement in our study (46% in iron deficiency without anemia) was similar to that of the previous study. This suggested that iron supplements could improve the investigated symptoms including fatigue.

This study had several limitations. First, as it was conducted in a single department at a single center, these results cannot be easily generalized to other settings. Fully powered research is required, especially for further investigating symptoms. Second, the treating doctors decided to investigate iron supplementation and other nutritional deficiencies and prescribed iron supplementation (including the interval) without clear criteria. Hence, 21.4% of iron supplementation cases were excluded. Therefore, there may have been selection bias when excluding cases of severe iron deficiency anemia with recent iron supplementation and blood transfusion. The bias may lead the difference of the investigated symptoms in both groups smaller. Third, we did not assess the change in symptoms in formatted questionnaires, such as the Likert scale, visual analog scale,¹⁴ or the multidimensional assessment of fatigue score.¹⁵ Fourth, we did not investigate the cost-effectiveness of the diagnosis and treatment of iron deficiency without anemia. In future studies, it would be necessary to investigate the cost-effectiveness of iron deficiency without anemia in the appropriate setting. Fifth, we did not compare iron deficiency and normal iron status. Therefore, we could not justify the link between iron deficiency and the investigated symptoms. The investigated symptoms could be the cause of either iron deficiency or anemia. For example, menorrhagia, bleeding, or fever would be the cause of anemia.¹ Therefore, in future studies the cause-effect association should be investigated.

Conclusion

There were no differences in any of the investigated symptoms or in the ratio of the symptom improvement depending on the anemic state of the patients with iron deficiency. After iron supplementation, the serum ferritin levels in the iron deficiency without anemia group improved. Hemoglobin and serum ferritin in iron deficiency without anemia were still high compared to that of iron deficiency anemia. Further studies that compare patients with iron deficiency and those with normal iron levels are required to validate the link between iron deficiency and the investigated symptoms.

Data Sharing Statement

The data used to support the findings of this study have not been made available for protection of privacy.

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Disclosure

The authors report no conflicts of interest in this work.

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