Research Article

Differential Effects of BMI Adjustment on Ferritin Levels in Anemic Patients

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Article Info

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Keywords

Ferritin, BMI, Obesity, regression, inflammation, Iron deficiency, anemia

Abstract

Background: The prevalence of obesity and anaemia is consistently increasing in India. Obesity is a chronic inflammatory state and is associated with dysregulation of iron homeostasis. Ferritin, a marker for cellular iron stores, is also an acute phase reactant that remains elevated during inflammation. Previous studies have used inflammation-adjusted serum ferritin to address this. This current study aims to calculate body mass index (BMI)-adjusted ferritin using a regression correction and evaluate its effects across gender and BMI category in anemic patients.

Methods: De-identified data were retrieved from hospital records and laboratory information systems. BMI-adjusted ferritin was estimated using a regression correction formula: ln(adjusted ferritin) = ln(unadjusted ferritin) − β(BMI − median BMI).

Results: A total of 458 subjects were included, of whom 62% were female and 95% were anemic. Adjusted ferritin levels were slightly lower than unadjusted levels in the normal BMI group (59.8 vs 60) and in males (102.3 vs 113.75). In contrast, adjusted ferritin levels were marginally higher in the overweight/obese group (29.9 vs 28.9) and in females (22.7 vs 22.1). The percentage change in ferritin following adjustment ranged from −0.33 to 10.07

Conclusion: BMI-based regression correction had differential effects across BMI categories and gender. The adjustment substantially attenuated higher ferritin levels in normal BMI and males. In contrast, a minimal increase was observed in overweight/obese individuals and in females with lower baseline ferritin levels. Notably, the magnitude of these percentage change in ferritin is small relative to the reported within-person biological variation (BV) of ferritin, suggesting limited clinical impact.

Highlights

- Obesity, a chronic low-grade inflammatory state, influences iron homeostasis.
- BMI-adjusted ferritin can be estimated using a regression correction approach.
- BMI-adjustment shows differential effects on serum ferritin levels in anemic individuals
- The adjustment effects varied based on gender and BMI categories
- These percentage change in ferritin observed after adjustment less likely to have a clinical impact.

Introduction

Iron is an essential trace mineral required for various biological functions such as oxygen transport and storage, electron transport chain, DNA synthesis, DNA repair, detoxification, and cofactors for certain enzymes. Levels of iron are tightly controlled and is essential for maintaining systemic and cellular iron homeostasis. Hepcidin is master regulator of systemic iron homeostasis. It binds to ferroportin and triggers its internalisation and ubiquitin mediated degradation, thereby controlling the intestinal iron absorption and release of recycled iron from macrophages that phagocytose senescent red blood cells [1].

Deficiency of iron leads to iron deficiency anemia (IDA) which is the major public health problem in India [2]. The laboratory work up of anemia includes an iron profile study which comprises of serum iron, ferritin, total iron binding capacity (TIBC), percentage transferrin saturation and complete blood count [3]. Reduced levels of serum ferritin, serum iron and percentage transferrin saturation are indicative of iron deficiency. Iron is stored as ferritin in the liver cells, and structurally a single molecule of ferritin can accommodate ~4500 iron atoms [4]. Hence, serum ferritin is considered as the maker of total body iron stores and its levels are crucial in diagnosing and monitoring iron deficiency. Iron is transported in blood by transferrin, a transporter protein produced by liver. Free iron is detrimental as it has increased propensity to form reactive oxygen species (ROS), which leads to cellular damage [5].

Ferritin is also an acute phase reactant and it is non-specifically elevated in inflammatory conditions like chronic kidney diseases, infections, autoimmune disorders, and malignancy[6]. This inflammation induced elevation of ferritin can obscure the true iron deficiency in an individual. Obesity, a growing global health concern is characterised by a state of chronic low-grade systemic inflammation. In obese adipose tissue, there is evident infiltration of macrophages leading to the production of pro-inflammatory cytokines such as interleukin-1,6 (IL-1, IL-6) and tumor necrosis factor – alpha (TNF-α) [7]. IL-6, is a potent pro-inflammatory cytokine and is known to increase the expression of ferritin and hepcidin. There are studies that has reported the influence of obesity on serum ferritin.

A study done in adolescents has shown that BMI explained the variation in serum ferritin levels to an extent that it did not reflect the true iron deficiency in those with obesity and overweight [8]. A significant linear positive association exist between serum ferritin and BMI [9] and it varies based on gender in adults [10]. Individuals with high BMI and high CRP had increased levels of serum ferritin despite low levels of iron [11]. These observations suggest serum ferritin levels tend to be higher in those with inflammation and could obscure the true iron deficiency. To address this, a study proposed calculation of inflammation adjusted serum ferritin by employing a regression-based approach to calculate CRP-adjusted ferritin. It was found a substantial variation was observed in classification of iron deficiency compared to unadjusted ferritin [12]. Studies that explored the effect of BMI-adjusted ferritin are limited.

This study employed a regression-based approach to calculate BMI-adjusted ferritin levels and to determine its effects across BMI category, gender and on classification on iron deficiency status.

Materials and Methods

Subjects

This study was done using de-identified patient data retrieved from laboratory information system (LIS) and medical records of a tertiary care hospital in South India. The data was retrieved for the period of 11 months from July 2024 to June 2025 (n=599). The data was screened and these who had complete data of serum ferritin age, gender, body weight and height were included (n=458). Individuals with missing values for any of these parameters were excluded from the analysis (n=141). The data of serum iron, total iron binding capacity and hemoglobin were retrieved. Hematological parameters were estimated on a Beckman DXH-800 analsyer. Serum iron and total iron-binding capacity were estimated by the ferrozine colorimetric method on Toshia 120 FR. Serum ferritin was estimated by electro chemiluminescence immunoassay (Roche Cobas e411).

Calculation of BMI-adjusted serum ferritin

A regression correction (RC) approach was employed to calculate BMI-adjusted serum ferritin levels [12] for the patients included in the study. A step-by-step procedure to calculate BMI-adjusted ferritin using internal regression correction is detailed in Table 1.

Table 1: Calculation of BMI-adjusted serum ferritin.

Step 1:

A: Natural log-transform (ln) the outcome variable

- ln(Ferritin_unadjusted)

(Note: BMI need not be log transformed as linear relationship exists between BMI and Ferritin)

B: Construct linear regression model (lm) to identify the beta coefficient (beta)

- lnFerritin_unadjusted = α + β × BMI
- lm (lnFerritin_unadjusted ~ BMI)

(Note: where α represents the intercept , β the regression coefficient and lm represents linear regression model)

Step 2:

A: Determine the median BMI value of the study group

The median BMI of the study population (or subgroup) was determined and used as the reference BMI (BMI_ref)

B: Calculate BMI Adjusted Ferritin using the regression correction equation

Input data from Step 1B and Step 2A.

lnFerritin_adjusted = lnFerritin_unadjusted – (β * (BMI – BMI_ref))

(Note: The adjustment was restricted to individuals whose BMI exceeded the subgroup-specific median BMI)

C: Back transform the adjusted ferritin

Adjusted Ferritin = Exp^(lnFerritin_adjusted)

The median BMI was observed to be 22.92 (males), 23.01 (females), 22.65 (normal BMI) and 27.49 (overweight/obesity). The beta coefficient for normal BMI group is 0.023511, overweight-obese group is −0.00426, males is 0.03896, females is −0.02312. The alpha-intercept for normal BMI group is 3.51348, overweight-obese group is 3.7796, males is 3.5403, females is 4.1185. These values were used to calculate BMI-based adjustments of ferritin in the respective groups . The subgroup specific equations for BMI-based adjustment of ferritin (Table 2).

Table 2: Subgroup-Specific Equations for BMI-Based Adjustment of Ferritin.

Subgroup	Equation to calculate "ln(Adjusted Ferritin)"	Condition for applying adjustment
Normal BMI	ln(Ferritin unadjusted) − 0.023511 × (BMI − 22.7)	BMI > 22.7
Overweight/Obese	ln(Ferritin unadjusted) − (−0.00426) × (BMI − 27.5)	BMI > 27.5
Males	ln(Ferritin unadjusted) − 0.03896 × (BMI − 22.9)	BMI > 22.9
Females	ln(Ferritin unadjusted) − (−0.02312) × (BMI − 23.01)	BMI > 23.01

Statistical Analysis

All statistical analysis was done using R programming language V.4.4.1. The data were checked for distribution using Shapiro Wilk Test and appropriate statistical tests were done. Chi Square test was used to compare the categorical data, and continuous data were compared using Mann-Whitney U or independent t test. Paired Wilcoxon signed rank test was done to compare the ferritin values before and after adjustment. A p-value of less than 0.05 will be considered as statistically significant.

Results

A total of 458 subjects were included in the study, comprising of 172 males (38%) and 286 females (62%). There was no difference in age and gender distribution between normal BMI group and overweight-obese group. Majority of the subjects were found to be anemic (95 % overall, 96% in normal BMI group and 95% in overweight-obese group) (Table 3). Hemoglobin, serum iron and TIBC levels were similar between the two groups. Levels of unadjusted serum ferritin were significantly lower in obese-overweight group. Levels of CRP were higher in obese-overweight group, but not statistically significant (Table 3).

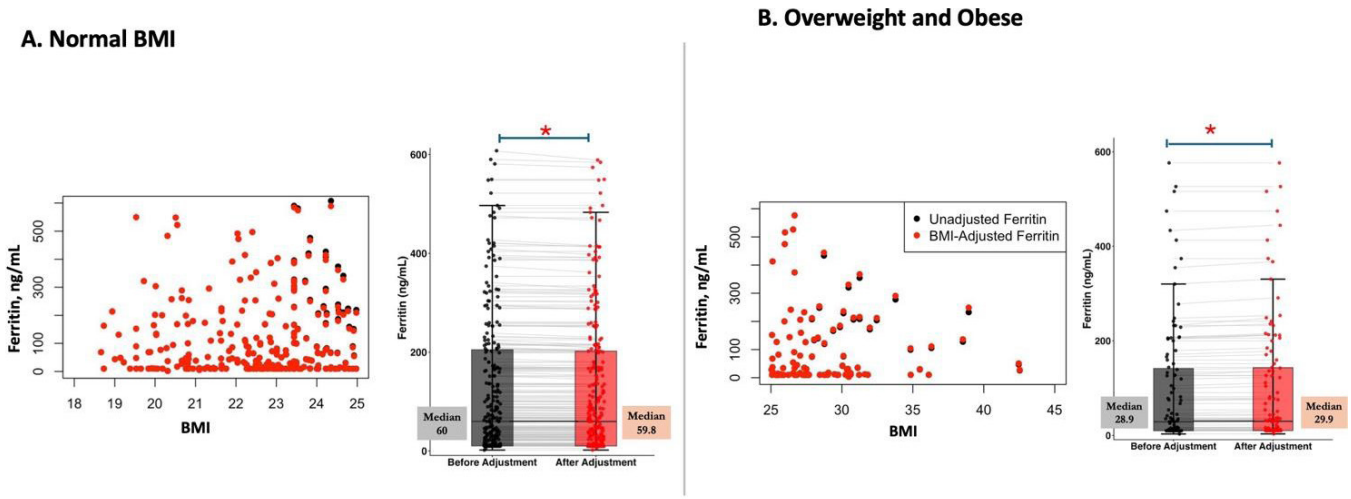
Table 3: Comparison of baseline characteristics and biochemical parameters based on BMI.

	Overall (n=458)	Normal BMI (BMI 18.5-24.9) (n=286)	Overweight and Obese (BMI >25) (n=111)	p value
Gender, n (%) Male Female	 172 (38) 286 (62)	 109 (38) 177 (62)	 36 (32) 75 (68)	0.348
Age, in years	50 (36-64)	53.5 (39-65)	49 (40-61)	0.3771
BMI, in kg/m^2	23 (21-25)	22.7 (21.4-23.4)	27.5 (26.3-30.4)	<0.0001
BMI status, n (%) Underweight Normal Overweight Obesity	 61 (13) 286 (62) 78 (17) 33 (7)	--	--	--
Anemia based on Hb* , n (%) Present Absent	 386 (95) 20 (5)	 239 (96) 10 (4)	 94 (95) 5 (5)	0.8917
Hb, g/dL$	8.5 (7-9.7)	8.4 (7.1-9.5)	8.7 (7-9.8)	0.405
Serum ferritin, ng/mL (unadjusted)	41.75 (10-179.9)	60 (10.3-205)	29 (10-142)	0.019
Serum iron, µg/dL$	27.5 (14-64)	27.5 (15-62.5)	29 (14-68)	0.800
Serum TIBC, µg/dL$	306 (210-393)	285 (202-377)	298 (241-426)	0.396
Serum CRP, mg/L$	16.9 (4.8-17.3)	17.5 (4.97-52.97)	47.65 (4.95-191)	0.113

*Data is represented in median and interquartile range. The p value is computed by comparing the obese-overweight and normal weight participants. *Anemia is diagnosed if Hb < 12g/dL in women and <13 g/dL in men. $ indicates paucity or missing data; Hb, serum iron, CRP and TIBC are available only in subset of participants.*

Regression correction was applied to derive BMI-adjusted serum ferritin values. In individuals with normal BMI, adjustment resulted in a minimal reduction in median ferritin levels (60.0 to 59.8 ng/mL; $p < 0.0001$; Figure 1A). In contrast, among obese individuals, a slight increase in median ferritin levels was observed following adjustment (28.9 to 29.9 ng/mL; $p < 0.0001$; Figure 1B).

Figure 1: Comparison of adjusted ferritin based on BMI status.



*Scatter (left) and box-and-whisker (right) plots show unadjusted (black) and BMI-adjusted (red) ferritin concentrations in normal weight group (A) and overweight-obese group (B). The adjustment was restricted to individuals whose BMI exceeded the median value of their respective group. Boxes indicate median and interquartile range and whiskers represents the values within 1.5 times the interquartile range. Grey lines denote paired observations. Paired Wilcoxon signed rank test was done to compare the ferritin values before and after adjustment. * indicates p < 0.05.*

In gender wise comparison, the age was significantly lower in females compared to males. BMI was slightly higher in females, however there were no difference in proportion of obesity, overweight between the two groups. Proportion of anemia were similar (93 % vs 96%) between two groups (Table 4). Hemoglobin and serum iron levels were similar between the two groups. Levels of unadjusted serum ferritin were significantly lower and TIBC levels were higher in females. Levels of CRP were higher in females, but not statistically significant (Table 4).

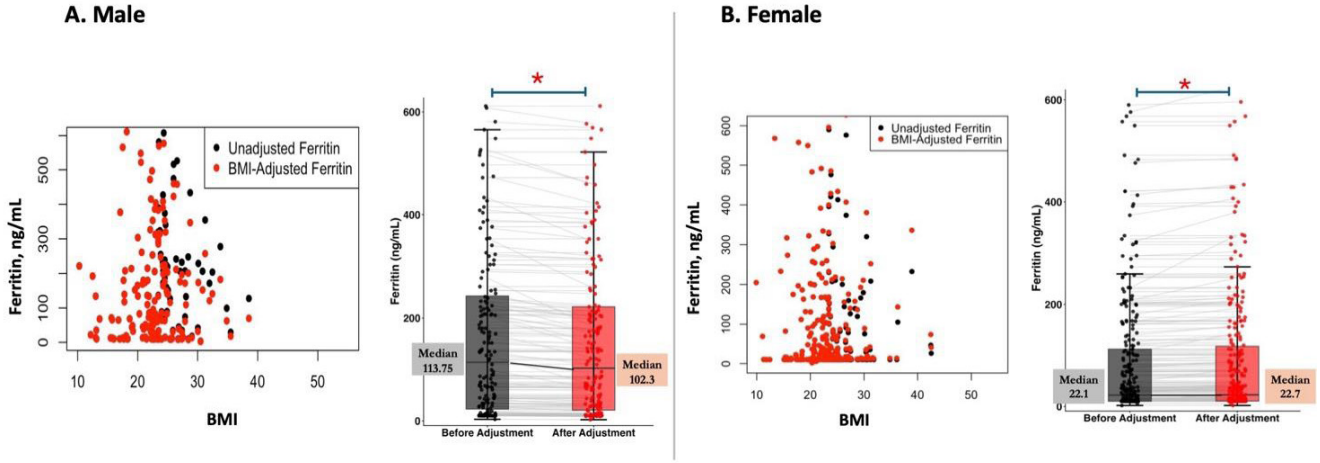
Table 4: Comparison of baseline characteristics and biochemical parameters based on gender.

	Overall (n=458)	Male (n=172)	Female (n=286)	p value
Age, in years	50 (36-64)	55 (41-68)	48 (35-60)	0.0024
BMI, in kg/m2	23 (21-25)	22.9 (20.9-24.5)	23.01 (20.8-25.1)	<0.0001
BMI status, n (%) Underweight Normal Overweight Obesity	 61 (13) 286 (62) 78 (17) 33 (7)	 27 (16) 109 (63) 25 (15) 11 (6)	 34 (12) 177 (62) 53 (19) 22 (8)	0.481
Anemia based on Hb * , n (%) Present Absent	 386 (95) 20 (5)	 140 (93) 10 (7)	 246 (96) 10 (4)	0.316
Hb, g/dL$	8.5 (7-9.7)	8.5 (7.4-9.9)	8.4 (6.8-9.5)	0.081
Serum ferritin, ng/mL (unadjusted)	41.75 (10-179.9)	113.75 (23-243)	22.1 (10-112)	<0.0001
Serum iron, µg/dL$	27.5 (14-64)	30.9 (17.8-54.5)	23 (13-70.2)	0.71
Serum TIBC, µg/dL$	306 (210-393)	237 (178-340)	343 (246-416)	0.002
Serum CRP, mg/L$	16.9 (4.8-17.3)	15.80 (4-72.8)	18.55 (5.45-97.25)	0.362

*Data is represented in median and interquartile range. The p value is computed by comparing the males and females. Anemia is diagnosed if Hb < 12g/dL in women and <13 g/dL in men. *Anemia is diagnosed if Hb < 12g/dL in women and <13 g/dL in men. $ indicates paucity or missing data; Hb, serum iron, CRP and TIBC are available only in subset of participants.*

In males, the adjustment attenuated higher ferritin values resulting in a reduction of the median ferritin level (113.75 ng/mL to 102.3 ng/mL, p < 0.0001) (Figure 2A). However, in females, the adjustment had resulted in a minimal increase in the median ferritin (22.1 ng/mL to 22.7 ng/mL, p <0.0001) (Figure 2B).

Figure 2: Gender-wise comparison of adjusted ferritin.



*Scatter (left) and box-and-whisker (right) plots show unadjusted (black) and BMI-adjusted (red) ferritin concentrations in males (A) and females (B). The adjustment was restricted to individuals whose BMI exceeded the median value of their respective group . Boxes indicate median and interquartile range and whiskers represents the values within 1.5 times the interquartile range. Grey lines denote paired observations. Paired Wilcoxon signed rank test was done to compare the ferritin values before and after adjustment. * indicates p < 0.05.*

The percentage change in ferritin before and after adjustment is shown in Table 5. It was -0.33 % in normal BMI and 3.46 % in overweight-obese group. It is -10.07 % in males and 2.71 % in females.

Table 5: Percentage change in ferritin levels before and after adjustment.

Groups	Serum Ferritin (ng/mL)		Percent change, %
	Before adjustment	After adjustment	
Normal BMI	60 (10.3-205)	59.8 (10.21-202.15)	-0.33
Overweight and Obese	28.9 (10-142)	29.9 (10.2-143.3)	3.46
Males	113.75 (23-243)	102.3 (20.9-221.8)	-10.07
Females	22.1 (10-112)	22.7 (10.3-117.8)	2.71

*Serum ferritin levels were represented in medians (interquartile range). The percent change is calculated as (Adjusted Ferritin – Unadjusted Ferritin/ Unadjusted Ferritin)*100.*

Applying a standard cut-off of 30 ng/mL to classify iron deficiency were carried out using ferritin values before and after adjustment. The proportion of iron deficiency were similar before and after adjustment in gender-wise and BMI-based comparison (Table 6).

Table 6: Classification of iron deficiency status based on unadjusted and BMI-adjusted serum ferritin.

	Before adjustment ID / Non-ID, n (%)	After adjustment ID / Non-ID, n (%)	p value
Male (n=172)	123/49 (70/30)	122/50 (71/29)	1.00
Female (n=286)	155/131 (54/46)	153/133 (53/47)	0.933
Normal BMI (n=286)	114/172 (40/60)	115/171 (40/60)	1.00
Overweight Obese BMI (n=111)	57/54 (51/49)	56/55 (50/50)	1.00

Data is represented in numbers (percentages). Ferritin <30 ng/mL: iron deficiency (ID); ferritin ≥30 ng/mL: non-iron deficiency (Non-ID). Pearson Chi-Squared test was done to compare the proportion of iron deficiency before and after adjustment in each group.

Discussion

In this study, a regression correction was applied to derive BMI-adjusted serum ferritin values in the participants, the majority of whom were anaemic. The BMI-based adjustment resulted in a minimal reduction in ferritin levels in individuals with normal BMI. However, a slight increase was observed in those with overweight and obesity. The adjustment caused substantial attenuation of higher ferritin values in males, whereas in females, the adjustment resulted in a minimal increase. There were no difference in the classification of iron deficiency status between adjusted and unadjusted ferritin levels.

Adjusting for BMI produced a minimal decline in serum ferritin levels in those normal BMI (60 vs 59.8). The median CRP levels in these patients was 17.5 mg/L (>10, cut-off for inflammation) suggesting the presence of systemic inflammation. The adjustment led to a more pronounced reduction in individuals with higher ferritin levels, which may reflect correction for inflammation-driven elevations. However, the adjustment had a very minimal reduction in those who had already low ferritin levels. This may be because these individuals are likely to be iron deficient, where the effect of iron deficiency predominates over that of adiposity-induced inflammation. The adjustment produced an opposite effect on serum ferritin levels in those with overweight and obesity i.e. adjusted ferritin levels were higher compared to unadjusted ferritin levels (28.9 vs 29.9). The levels of ferritin increased post-adjustment. This contrasts with the expectation that adiposity has a positive influence, and that BMI-based adjustment is likely to cause a reduction in serum ferritin levels. These participants also had systemic inflammation as suggested by their CRP levels (median 67.5 mg/L) indicating a substantial inflammatory burden. This highlights the intricate relationship between adiposity-associated inflammation and its impact on iron homeostasis [13]. While adiposity association inflammation induces ferritin, as a positive acute-phase reactant, it is also associated with increased expression of hepcidin [13]. Hepcidin is the master regulator of systemic iron homeostasis. It binds to and causes the degradation of ferroportin, thereby reducing intestinal iron absorption and leading to hypoferremia and iron deficiency anemia [1]. In this study, the obese overweight participants had a lower baseline ferritin value (28.9 ng/mL), so BMI-

based adjustment may produce a minimal increase in ferritin levels among individuals with low baseline ferritin, where the influence of iron deficiency outweighs that of adiposity-related inflammation. Hence, the net effect of adiposity on ferritin is not straightforward and may vary depending on baseline iron status and inflammatory state. Therefore, despite lower baseline ferritin levels in the overweight/obese group, the application of BMI-based regression correction remains physiologically justifiable, as it attempts to account for these underlying adiposity-related influences. Furthermore, the inverse relationship observed between BMI and ferritin in our dataset further supports the need to explore how such an adjustment behaves in iron-deficient populations. There is limited evidence evaluating BMI-based ferritin adjustment in populations with a high burden of anaemia.

In this study, BMI-based adjustment caused substantial attenuation of higher ferritin values in males (102.3 vs 113.75), whereas in females, the adjustment resulted in a minimal increase (22.7 vs 22.1). The unadjusted ferritin levels were higher in males despite majority of them being anemic suggesting the possible influence of inflammation rather than true iron status. This is supported by higher CRP levels in both males and females indicating an underlying inflammatory state. In contrast, lower baseline ferritin levels in females are more consistent with iron deficiency, potentially explaining the minimal increase after adjustment. This pattern is also observed in those with overweight and obesity, where the influence of iron deficiency may predominate alongside coexisting inflammation. Gender difference in the levels of ferritin are well known and may be attributed to varied reasons such as hormonal influences, dietary iron intake and menstrual blood loss [14,15].

BMI-based regression correction resulted in modest and variable changes in ferritin across subgroups, with a minimal reduction in individuals with normal BMI (−0.33%), slight increases in those with overweight/obesity (+3.10%) and females (+2.71%), and a more pronounced reduction in males (−10.07%). Importantly, the magnitude of these changes is small relative to the reported within-person biological variation (BV) of ferritin (5.37%–39.13%, mean 21.64%) [16] , suggesting that most differences are unlikely to be clinically meaningful.

Adjusted ferritin did not impact the classification of iron deficiency. This could be because most of the study participants were anemic (i.e. 95%) with median Hb of 8.5 g/dL. Additionally, the serum iron levels were low in the participants, indicating iron deficiency as the major possibility of anemia.

Limitations

It is a retrospective study and included data retrieved from medical records and LIS. This study design is not ideal to determine the causal effect of BMI on iron deficiency and serum ferritin. In this study, there is no data regarding the presence of other inflammatory conditions, dietary history and intake of iron supplements. The sample size is limited and there is paucity of data on iron related proteins and inflammatory marker. A larger sample size with equally distributed non-anemic participants would be needed to confirm these findings.

Conclusion

BMI-based regression correction had differential effects across BMI categories and gender. The adjustment substantially attenuated higher ferritin levels in normal BMI and males. In contrast, a very minimal increase was observed in overweight/obese individuals and in females with lower baseline ferritin levels. Notably, the magnitude of these percentage change in ferritin is small relative to the reported within-person biological variation (BV) of ferritin, suggesting limited clinical impact. These findings may be explained by the predominance of iron deficiency over adiposity-related inflammatory effects in individuals with lower baseline ferritin.

Implications

In the Indian context, where obesity and iron deficiency anemia are increasingly prevalent, BMI-adjusted ferritin may offer additional value in interpreting ferritin variability and in more accurately identifying true iron deficiency.

Author's Disclosures

Conflict of interests

The authors do not have any competing interests to declare in this study.

Ethics approval and consent to participate

This study is approved by Institutional Ethics Committee (VMCIEC/184/2025).

Authors contribution

JR: Study Design, Conceptualization, Writing – Original Draft, Reviewing And Editing, Data Visualization, Validation, Methodology, Formal Analysis And Supervision. DB – Formal analysis, Data curation, Writing – review and editing

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Availability of data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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