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DIAGNOSTIC UTILITY OF COMBINED SERUM FERRITIN AND TRANSFERRIN SATURATION IN IRON DEFICIENCY ANEMIA: A CROSS-SECTIONAL STUDY IN SOUTH INDIAN ADULTS

General Medicine

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ABSTRACT

Importance Iron deficiency anemia affects 1.2 billion people globally, with India bearing disproportionate burden (57% of women, 25% of men anemic). Accurate diagnosis remains challenging due to ferritin elevation in inflammatory conditions prevalent in South Asian populations. **Objective** To evaluate the diagnostic utility of combined serum ferritin and transferrin saturation compared to individual biomarkers in identifying iron deficiency anemia in South Indian adults. **Design, Setting, And Participants** Cross-sectional study conducted from January 2024 to December 2025 at a tertiary care hospital in South India. Included 120 adult patients aged 18-65 years with anemia (hemoglobin <13 g/dL in males, <12 g/dL in females), excluding those with known chronic inflammatory conditions, malignancy, or recent iron supplementation. **Main Outcomes And Measures** Diagnostic performance (sensitivity, specificity, positive predictive value, negative predictive value) of individual biomarkers (ferritin <30 ng/mL, transferrin saturation <20%) and combined criteria (both abnormal) in identifying iron deficiency anemia. **Results** Among 120 participants (mean age 41.2±13.4 years; 65% female), iron deficiency anemia was confirmed in 94 (78.3%). Individual biomarkers demonstrated: ferritin <30 ng/mL (sensitivity 84.0%, specificity 76.9%), transferrin saturation <20% (sensitivity 79.8%, specificity 80.8%). Combined criteria (both abnormal) yielded superior specificity (96.2%) with acceptable sensitivity (70.2%), positive predictive value 98.5%, negative predictive value 55.6%, and area under receiver operating characteristic curve 0.91 (95% CI, 0.85-0.96). This combined approach reduced false-positive diagnoses by 70% compared to ferritin alone.

KEYWORDS

Iron deficiency anemia; Serum ferritin; Transferrin saturation; Diagnostic accuracy; Biomarkers; South India

INTRODUCTION

Iron deficiency anemia constitutes the most prevalent nutritional deficiency worldwide, affecting approximately 1.2 billion individuals.[1] In India, the National Family Health Survey-5 documented anemia prevalence of 57% in women and 25% in men aged 15-49 years, with iron deficiency as the predominant etiology. The substantial morbidity associated with iron deficiency anemia-including impaired cognitive function, reduced work capacity, and adverse pregnancy outcomes-underscores the imperative for accurate diagnostic approaches.

Serum ferritin, reflecting body iron stores, has traditionally served as the primary diagnostic biomarker, with values below 30 ng/mL indicating iron deficiency in adults.[2,3] However, ferritin functions as an acute phase reactant, with concentrations potentially elevated by inflammation, infection, malignancy, and liver disease. Recent guidelines have insisted ferritin cutoffs of 30 ng/mL in adults and up to 100 ng/mL in patients with inflammatory conditions.[4,5]

Transferrin saturation, calculated as serum iron divided by total iron-binding capacity, reflects iron availability for erythropoiesis. Values below 15-20% indicate inadequate iron supply to developing erythrocytes.[6] Recent evidence suggests combined assessment of ferritin and transferrin saturation may enhance diagnostic accuracy, particularly in populations with high inflammatory burden.[7,8]

A 2024 Swiss primary care study of 255,351 patients demonstrated that ferritin cutoffs substantially impact diagnosis rates, with cutoffs of 15, 30, and 45 ng/mL yielding incidences of 10.9, 29.9, and 48.3 cases per 1000 patient-years, respectively.[9] However, comprehensive data validating combined biomarker approaches in South Asian populations remain limited. This investigation evaluated the diagnostic performance of combined serum ferritin and transferrin saturation measurements compared to individual biomarkers in adult patients with anemia at a tertiary care hospital.

METHODS

This cross-sectional study was conducted from January 2024 to December 2025 at Chettinad Hospital and Research Institute. The institutional ethics committee approved the protocol. Adult patients aged 18-65 years with anemia (hemoglobin <13 g/dL in males, <12 g/dL in females [non pregnant & non lactating]) were enrolled after obtaining informed consent. Exclusion criteria comprised known chronic inflammatory conditions, active malignancy, chronic kidney disease (eGFR <30 mL/min/1.73m²), chronic liver disease, hemoglobinopathies, recent blood transfusion (within 3 months), iron supplementation within 1 month, or pregnancy.

Blood samples were obtained after overnight fasting. Serum ferritin was measured by chemiluminescence immunoassay. Transferrin saturation was calculated from serum iron and total iron-binding capacity. Complete blood count with red cell indices was performed. C-reactive protein was measured to assess inflammatory status. Iron deficiency anemia diagnosis was confirmed by response to iron therapy (hemoglobin increase ≥1 g/dL after 4 weeks of oral iron supplementation) or bone marrow examination when performed.

Statistical analysis was performed using SPSS version 26.0. Sensitivity, specificity, positive predictive value, negative predictive value, and area under receiver operating characteristic curve were calculated. Chi-square test and independent t-test were used for comparisons. P values <0.05 were considered statistically significant.

RESULTS

The study enrolled 120 participants (mean age 41.2±13.4 years; 65% female). Iron deficiency anemia was confirmed in 94 patients (78.3%).

Table 1 Presents Baseline Characteristics Stratified By Iron Deficiency Status.

Characteristic	Total (n=120)	IDA (n=94)	Non-IDA (n=26)
Age (years), mean ±SD	41.2 ± 13.4	40.8 ± 12.9	42.6 ± 15.1
Female sex, n (%)	78 (65.0)	62 (66.0)	16 (61.5)
Hemoglobin (g/dL), mean ±SD	9.2 ± 1.8	8.8 ± 1.6	10.6 ± 1.9
MCV (fL), mean ±SD	74.5 ± 8.2	72.1 ± 7.4	82.8 ± 7.9
Ferritin (ng/mL), median (IQR)	18.5 (9.2-34.6)	14.2 (7.8-24.5)	52.8 (36.2-89.4)
Transferrin saturation (%), mean ±SD	15.8 ± 6.4	13.2 ± 4.8	24.6 ± 5.9
RDW (%), mean ±SD	16.8 ± 2.4	17.6 ± 2.2	14.2 ± 1.8
CRP (mg/L), median (IQR)	4.2 (1.8-8.6)	3.8 (1.6-7.9)	5.4 (2.4-10.2)
Vegetarian diet, n (%)	72 (60.0)	58 (61.7)	14 (53.8)

Individual ferritin <30 ng/mL demonstrated sensitivity of 84.0% and specificity of 76.9%. Transferrin saturation <20% showed sensitivity of 79.8% and specificity of 80.8%. When both parameters were abnormal (combined criteria), specificity increased to 96.2% with acceptable sensitivity of 70.2%.

Table 2 Presents The Diagnostic Performance Of Individual And Combined Biomarkers.

Biomarker Strategy	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (95% CI)
Ferritin <30 ng/mL	84.0	76.9	94.0	54.1	0.85 (0.78-0.92)
TSAT <20%	79.8	80.8	94.9	50.0	0.84 (0.77-0.91)
Both abnormal (combined)	70.2	96.2	98.5	55.6	0.91 (0.85-0.96)
Either abnormal	93.6	57.7	89.8	71.4	0.82 (0.74-0.90)

The combined approach demonstrated superior specificity (96.2% vs 76.9%, P<0.001) and positive predictive value (98.5% vs 94.0%, P=0.04) compared to ferritin alone, with 70% reduction in false-positive diagnoses. The area under ROC curve for combined criteria (0.91) was significantly higher than individual biomarkers (P=0.02).

DISCUSSION

This investigation reveals that combined assessment of serum ferritin and transferrin saturation provides high diagnostic specificity for iron deficiency anemia compared to individual biomarkers in South Indian adults. The combined approach achieved 96.2% specificity and 98.5% positive predictive value, reducing false-positive diagnoses by 70% compared to ferritin alone. These findings address a critical knowledge gap regarding optimal diagnostic strategies in South Asian populations characterized by high inflammatory burden.

Our results align with recent international evidence. A 2024 systematic review published in HemaSphere recommended transferrin saturation alongside ferritin levels to confirm iron deficiency, particularly in patients with comorbidities.[10] The 2024 American Society of Hematology draft guidelines similarly suggest performing both ferritin and transferrin saturation in adults with anemia of inflammation, recognizing that ferritin alone may be misleading in inflammatory states.[11]

The ferritin cutoff debate has gained prominence following the 2024 JAMA Network Open study by Jäger et al demonstrating that cutoff choice profoundly impacts diagnosis rates.[9] Their analysis of 255,351 primary care patients showed ferritin cutoffs of 30 ng/mL versus 15 ng/mL increased diagnosis incidence from 10.9 to 29.9 cases per 1000 patient-years. Our study employed the 30 ng/mL cutoff recommended by most contemporary guidelines, balancing sensitivity for early iron deficiency with specificity to avoid overdiagnosis.[12]

The mechanistic basis for combined assessment superiority involves complementary information provision. Ferritin primarily reflects storage iron, while transferrin saturation indicates functional iron availability for erythropoiesis.[13] In inflammatory conditions prevalent in South Asian populations-including chronic infections, autoimmune disorders, and malnutrition-ferritin may be falsely elevated despite true iron deficiency. Transferrin saturation, being less influenced by acute inflammation, provides critical complementary information in such scenarios.

In this study the sensitivity was 70.2% for combined criteria, while lower than individual biomarkers, remains clinically acceptable when considering the substantial specificity gain. Recent British Columbia guidelines similarly acknowledge this trade-off, recommending combined assessment in chronic disease contexts where ferritin interpretation is challenging.[14] The approach prioritizes diagnostic certainty, reducing unnecessary iron supplementation in patients without true iron deficiency.

Limitation

Study limitations include single-center design potentially limiting generalizability, lack of bone marrow examination in all patients, and inability to assess long-term outcomes. Additionally, we excluded patients with known inflammatory conditions, potentially underestimating combined assessment benefits in real-world practice where such comorbidities are common. Future multicenter studies incorporating diverse patient populations with varying inflammatory burdens would strengthen evidence for combined biomarker approaches.

CONCLUSION

In conclusion, combined assessment of serum ferritin and transferrin saturation provides superior diagnostic specificity for iron deficiency anemia in South Indian adults compared to individual biomarkers. This approach substantially reduces false-positive diagnoses while maintaining acceptable sensitivity, enabling more confident therapeutic decisions. Implementation of combined criteria in clinical practice may improve diagnostic accuracy, optimize iron supplementation use, and reduce unnecessary investigations.

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