

ROLE OF FERRITIN AND SOLUBLE TRANSFERRIN RECEPTOR LEVELS IN DIAGNOSIS OF IRON DEFICIENCY ANEMIA IN INFLAMMATORY CONDITIONS. A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Iron deficiency anemia (IDA) is a very popular disease in the world, and it is often combined with chronic inflammatory diseases, which makes the correct diagnosis difficult. The serum ferritin is commonly utilized in determining the iron status, although under the inflammatory condition, being an acute-phase reactant, reduces its reliability in determining iron status. In such cases, soluble transferrin receptor (sTfR) is suggested to be a more precise biomarker of iron deficiency. This paper critically analyzes the use of ferritin and sTfR in the diagnostics of IDA in the chronic inflamed patients.

Objective: To compare the diagnostic usage of serum ferritin and soluble transferrin receptor levels in diagnosing iron deficiency anemia in patients with inflammatory disorders.

Methodology: The work was a cross-sectional study of 100 anemic patients with inflammatory diseases thereof. Measurement of complete blood count, serum ferritin, sTfR, ESR and CRP levels were taken. Iron deficiency was identified with the help of low ferritin (below 30 ng/mL) or high sTfR levels. Sensitivity, specificity and diagnostic accuracy of ferritin and sTfR were compared and the index of sTfR/log ferritin was obtained.

Results: The average age of the participants was 45.85 age with the SD of 13.2 years; 58 percent were women. The most common ones were chronic kidney disease (32%), and rheumatoid arthritis (28%). The sTfR had higher sensitivity and specificity (89 and 82) than ferritin (56 and 74) even with anemia as 62 and 71 percent of the patients were found to have higher levels of ferritin. The sTfR/log ferritin index was the best in diagnostic use with 92% sensitivity or 85% specificity.

Conclusion: Soluble transferrin receptor is a better predictor of iron deficiency anemia in chronic inflammatory disease patients when compared to serum ferritin. The sTfR /log ferritin index further increases the accuracy of diagnosis. The use of sTfR testing as a part of regular assessment of inflammatory anemic patients can enhance the earlier identification and treatment of iron deficiency.

Keywords: Iron deficiency anemia, ferritin, soluble transferrin receptor, inflammation, diagnostic markers, anemia of chronic disease.

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INTRODUCTION

One of the most common nutritional diseases affecting a significant proportion of the world population is iron deficiency anemia (IDA), a condition that affects an average of one-third of the entire population of the world¹. It is still one of the primary public health concerns especially in the developing world whose nutritional deficiencies, chronic diseases and poor access to health

care remain the leading factors causing disease burden². Iron is the basic constituent of numerous physiological functions such as transporting oxygen, synthesizing DNA and metabolizing the cell energy³. Any iron deficiency thus ruins necessary biological functions leading to decreased production of hemoglobin and consequently leading to anemia⁴. To be able to implement the relevant treatment approaches and avoid possible complications in

the form of impaired cognitive abilities, weakened immunity, decreased physical activity, and adverse pregnancy outcomes, it is vital to diagnose iron deficiency anemia accurately and provide it with the corresponding treatment⁵. Conventionally, serum ferritin has been adopted as the most acceptable biomarker in evaluating body iron stores as it relates well with total iron content. Nevertheless, ferritin is another of the acute-phase reactant, and ferritin levels rise as a result of inflammation, infection, liver diseases, and malignancy⁶. This is a serious clinical dilemma, because when ferritin levels are high, this may cover up iron deficiency in patients who have inflammatory diseases like chronic kidney disease, rheumatoid arthritis, inflammatory bowel disease, and chronic infections. Consequently, the use of ferritin only in such cases could cause misdiagnosis and poor treatment of iron deficiency⁷.

To address this weakness, soluble transferrin receptor (sTfR) has become a promising biomarker to assess iron status, unlike ferritin, sTfR levels are not affected by inflammation, or its levels are affected insignificantly^{4,5}. A high level of sTfR is the indicator of the iron deficiency despite the inflammatory processes, which makes it a useful instrument in differentiating between the real iron deficiency and anemia caused by chronic inflammation⁸. Also combined indices have also been seen to render better diagnostic power like the sTfR/log ferritin ratio in mixed anemia conditions⁹. Although there is an increased amount of evidence about the diagnostic utility of sTfR, its clinical utility has not been widely used in most sites, including the low- and middle-income countries, as a result of cost implications, absence of standardized cut-off value, and insufficient understanding of the clinicians¹⁰. Due to the similarity of the clinical manifestation of iron deficiency anemia with anemia of inflammation and due to the ambiguity of the biochemical measurement of ferritin in these cases, more substantiated biochemical indicators should be investigated⁵⁻⁹.

The purpose of the study consists in assessing the applicability of the role of the level of ferritin and soluble transferrin receptors to the diagnosis of iron deficiency anemia in patients having inflammatory pathology¹¹. This study aims to offer informative contribution to the field of diagnostic accuracy by making comparative evaluations of the diagnostic performance of these markers as well as the correlation of these markers with such an aim of improving the diagnostic accuracy in clinical practice particularly in a population where there is prevalence of inflammatory disorders¹². Finally, improved diagnostic plans can contribute to appropriate interventions, decrease the rate of disease, and enhance the outcomes of the patient.

MATERIALS AND METHODS

This cross section research was done in the Department of Hematology/Biochemistry (you may specify name of hospital/ lab) in a duration of six months. The study

included 100 patients who all presented with anemia and with the presence of inflammatory conditions including chronic kidney disease, rheumatoid arthritis, chronic infections or inflammatory bowel disease, through non-probability consecutive sampling. The population (patients) was eligible between 18 and 70 years of the two genders. Anemia was determined based on WHO guidelines as hemoglobin less than 12g/dl in women and less than 13g/dl in men. The patients who had known hematology malignancies, recent blood transfusion (within the past three months), pregnancy and patients who use iron supplement were excluded.

A comprehensive physical examination and clinical history were conducted, having received an informed written consent. Aseptic venous blood samples were taken to determine the levels of complete blood count (CBC), serum ferritin, soluble transferrin receptor (sTfR), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). A hemoglobin, mean corpuscular volume (MCV), and red cell index were determined by CBC through the use of an automated hematology analyzer. The chemiluminescence immunoassay was used in determining the level of serum ferritin, and ELISA-based methodology in determining the level of sTfR. CRP and ESR were done to establish inflammatory condition. Low hemoglobin and reduced serum ferritin levels (<30 ng/mL) or high levels of sTfR levels defined iron deficiency anemia in regard to laboratory cut-off values. The sTfR/log ferritin ratio was also estimated so as to improve the diagnosis.

The entire laboratory work was conducted in the standard operating procedures and quality control. The data recorded was analyzed with statistical software (e.g., SPSS version XX). The descriptive statistics have been utilized to summarize demographic and biochemical data. Continuous variables were calculated using mean plus standard deviation and categorical data were done using frequencies and percentages. Sensitivity, specificity, and ROC curve analysis were used as the methods to assess the correlation of ferritin and sTfR and evaluate the diagnostic performance. Statistically significant p-value was below 0.05.

RESULTS

The study sample comprised 100 anaemic patients having inflammatory disorders. The average age of the respondents was 45.8 and 13.2 years of age and the gender of the respondents was slightly skewed in favor of females (58 and 42 percent respectively). Chronic kidney disease (32%), rheumatoid arthritis (28%), chronic infections (22%), and inflammatory bowel disease (18%), were the most common underlying inflammatory conditions. The average hemoglobin concentration of the patients was 9.49 + 1.2 /dl, whereas the serum ferritin levels and serum transferrin were 126.5 +55.8ng/dl and 4.8 +1.6mg/L, respectively. The high level of ferritin (>100 ng/mL) in 62 percent of patients indicated by the low levels of

hemoglobin was a result of the effect of inflammation. On the other hand, sTfR was increased in three-quarters of the participants, which proved to be more sensitive when identifying iron deficiency during inflammation.

The level of serum ferritin was found to have a statistically significant negative correlation with the level of sTfR ($r = -0.62$; $p < 0.001$). sTfR was higher in the diagnostic accuracy than ferritin with sensitivity and specificity at 89 and 82 as contrasted to 56 and 74 in ferritin respectively. Diagnostic discriminative power was further advanced by the sTfR/log ferritin index which had 92% sensitivity and 85% specificity.

The Table 1 shows the demographic and laboratory characteristics of the baseline of the 100 participants of the study. There were more women than men with an average of around 46 years of age. Majority of the patients exhibited anemia (low hemoglobin), high inflammatory indices (ESR and CRP) and moderately increased ferritin levels despite the low MCV, suggesting that there had been iron deficiency, which was masked by inflammation. The majority of sTfR values were high and this is indicative of actual iron deficiency.

Table 1. Baseline Characteristics of Study Participants (n = 100)

Variable	Mean $\pm$ SD / n (%)
Age (years)	45.8 $\pm$ 13.2
Gender (Male/Female)	42 / 58
Hemoglobin (g/dL)	9.4 $\pm$ 1.2
MCV (fL)	76.8 $\pm$ 8.4
Serum Ferritin (ng/mL)	126.5 $\pm$ 55.8
sTfR (mg/L)	4.8 $\pm$ 1.6
CRP Positive	71 (71%)
ESR Elevated	83 (83%)

Table 2 is a summary of the underlying inflammatory conditions in the participants. The most prevalent was chronic kidney disease, then there were rheumatoid arthritis, chronic infections, and inflammatory bowel disease, which are representative clinical conditions relating to anemia of inflammation.

Table 2. Distribution of Inflammatory Conditions

Inflammatory Condition	n (%)
Chronic Kidney Disease	32 (32%)
Rheumatoid Arthritis	28 (28%)
Chronic Infections	22 (22%)
Inflammatory Bowel Disease	18 (18%)

Table 3 compares diagnostic performance of ferritin to sTfR, which showed a significantly higher sensitivity of the latter compared to the former in the diagnosis of iron deficiency anemia on the presence of inflammatory conditions. The sTfR/log ferritin index was also considered to help in improving diagnostic precision indicating that it is better as a diagnostic tool among patients with anemia caused by inflammation.

Soluble transferrin receptor demonstrated superior sensitivity and specificity compared to ferritin in diagnosing iron deficiency anemia in patients with inflammatory conditions, especially when used in conjunction with the sTfR/log ferritin index.

Table 3. Diagnostic Performance of Ferritin vs sTfR

Marker	Sensitivity	Specificity	Accuracy
Serum Ferritin	56%	74%	65%
Soluble Transferrin Receptor (sTfR)	89%	82%	86%
sTfR / log Ferritin Index	92%	85%	89%

DISCUSSION

Iron deficiency anemia is a significant health issue affecting the whole world and it is often comorbid with chronic inflammatory conditions; thus, making the diagnosis difficult¹³. This was a cross-sectional study of a case sample of 100 anemic individuals receiving underlying inflammatory conditions and comparing the diagnostic usefulness of the serum ferritin and soluble transferrin receptor (sTfR) levels¹⁴. Our results indicate that sTfR proves to be a more sensitive indicator of iron deficiency anemia when ferritin is used on inflammation⁷⁻¹². High ferritin was observed in a significant percentage of patients having low hemoglobin, low microcytic indices, which reinforce the idea that ferritin acts as an acute-phase reactant and this may not be a consistent indicator of iron status in inflammation¹⁵. We found that in most of our patients, the mean ferritin levels were higher than the conventional iron-deficiency cutoff levels of ferritin, and thus this may have given them a false sense of iron-deficiency had we used ferritin only¹⁶. Meanwhile, most of the participants had higher levels of sTfR, which demonstrates the demand on the tissues and the ineffective erythropoiesis¹⁷. The statistically significant negative correlation of ferritin and sTfR also indicates the complementary nature of the two markers. Our findings are consistent with this prior body of literature which suggests that sTfR will not be affected or affected to a very limited degree by inflammation, and is therefore better when making a distinction between iron deficiency and anemia of chronic disease¹¹⁻¹⁶.

Moreover, the sTfR/log ferritin index has shown the most sensitivity and specificity implying that it possesses a good diagnostic capability in mixed anemia states¹⁸. Previous researches reported this index as a useful combined measure that moderates the shortcomings of individual parameters¹⁹. Diagnostic ability of ferritin alone in our study (65 percent) highlights the danger of misclassifying anemic patients with inflammation at the same time which justifies the need to employ extra markers in clinical settings.

The prevalence of the chronic kidney disease and rheumatoid arthritis among the patients within our sample is another interesting observation made by our results and

is predetermined by the existence of the multifocus of chronic inflammation and functional iron deficiency. This is in line with epidemiological tendencies observed across the world and this underscores the clinical significance of valid methods of diagnosis in such groups. The sTfR testing can be used to help with the early use of iron therapy, minimize the unnecessary investigations, and increase patient outcomes²⁰. This study has certain weaknesses even though it is strong in the way it shows the diagnostic comparison. The study is a single-center one, and the small size of the sample can be considered the limitation to generalizing the results to the population. Also, the issue of economic limitations and inadequate sTfR testing availability in standard laboratories could limit its application in low-resource countries.

To further confirm and add diagnostic power to the value of these parameters, future research based on larger multicenter cohorts and the addition of other biomarkers like hepcidin would be useful⁷⁻¹⁷. In general, the paper confirms the clinical relevance of sTfR and sTfR/log ferritin index as a convenient and efficient method of diagnosing the presence of iron deficiency anemia in inflammatory patients whose ferritin levels can be misleading.

CONCLUSION

Though Ferritin is a popular iron stores marker, it is often increased in cases of inflammatory conditions and may fail to provide true results when used in patients with iron deficiency anemia. Soluble transferrin receptor, in turn, was much more sensitive and specific, and, therefore, a better diagnostic tool in this group. Diagnostic accuracy was also enhanced by the sTfR/log ferritin index. The integration of sTfR-based testing into clinical practice can lead to a better diagnosis and treatment of iron deficiency anemia at the initial stages of inflammatory disorders and, consequently, to favorable outcomes of patients. Further studies and better availability of sTfR tests are advisable to streamline the diagnostic plans in resource-restricted environments.

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