Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations

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Soluble transferrin receptor (sTfR) and ferritin concentrations were measured in a variety of clinical settings to compare the ability of these two tests to identify iron deficiency. Among 62 anemic patients who either had a bone marrow aspirate performed or had a documented response to iron therapy, the diagnostic sensitivity and specificity of sTfR (at a diagnostic cutoff of >2.8 mg/L) were 92% and 84%, respectively, with a positive predictive value of 42% in this population. Ferritin (≤12 µg/L) had a sensitivity of 25% and a specificity of 98%. However, the sensitivity and specificity of ferritin could be improved to 92% and 98%, respectively, by using a diagnostic cutoff value of ≤30 µg/L, resulting in a positive predictive value of 92%. Ferritin and sTfR were also measured in 267 outpatient samples and 112 medical students. In the outpatient group, the two tests agreed in 73% of the samples; however, 25% of the samples had ferritin values >12 µg/L and increased sTfR. Among the medical students, there was 91% agreement between the two tests, but 7% of the samples had ferritin ≤12 µg/L and normal sTfR. Together, these data suggest that measurement of sTfR does not provide sufficient additional information to ferritin to warrant routine use. However, sTfR may be useful as an adjunct in the evaluation of anemic patients, whose ferritin values may be increased as the result of an acute-phase reaction.

The correct diagnosis of iron deficiency is essential for successful patient management because it may be the presenting sign of a serious illness such as a gastrointestinal malignancy [1]. In many cases, iron deficiency is relatively simple to diagnose and treat. However, in some patients, typically those with other medical problems, the diagnosis can be difficult. Measurement of serum ferritin is currently the accepted laboratory test for diagnosing iron deficiency, and a ferritin value ≤12 µg/L is a highly specific indicator of iron deficiency [2]. Other commonly used laboratory tests such as serum iron, total iron-binding capacity, mean corpuscular volume, and transferrin saturation provide little additional diagnostic value over ferritin [3-5]. However, because ferritin is an acute-phase reactant, diagnosis of iron deficiency in hospitalized or ill patients can be difficult, as such patients may have normal or increased ferritin values even when iron deficient. The low sensitivity of ferritin for iron deficiency in these patients may require a bone marrow biopsy or a trial of iron therapy to differentiate iron deficiency from other causes of anemia. Therefore, it would be useful if a noninvasive laboratory test could accurately predict the results of biopsy-proven iron deficiency.

The soluble transferrin receptor (sTfR), a truncated form of the membrane-associated transferrin receptor [6, 7], has been reported to be a sensitive indicator of iron deficiency and is not an acute-phase reactant [8-11]. As such, it has been proposed as a laboratory test to identify iron deficiency in hospitalized and chronically ill patients and thus reduce the need for a bone marrow biopsy or trial of iron therapy [8, 9]. Circulating concentrations of sTfR are proportional to cellular expression of the membrane-associated TfR [12, 13]. Cellular expression of the TfR increases with increased cellular iron needs and cellular proliferation [12, 13]. Because patients with aplastic anemia or bone marrow ablation have sTfR values ~40% of normal, erythroid precursors are believed to contribute ~60% of the sTfR in plasma. The increased sTfR concentration observed in patients with iron-deficient erythropoiesis reflects this abundant erythroid pre-
cursor expression [14–16]. However, other conditions associated with erythroid hyperplasia, such as β-thalassemia [16, 17] and autoimmune hemolytic anemia [14], also increase the sTfR concentration, suggesting that a high value will not always be specific for iron deficiency. We examined the sTfR and ferritin concentrations in a variety of clinical settings to compare their diagnostic performance in ill patients and in individuals presumed to be healthy.

**Materials and Methods**

*Study populations and sample collection.* This study was approved by the Washington University Human Studies Committee. Serum or plasma was obtained from samples received by the Barnes-Jewish Hospital laboratories for clinical testing. Serum/plasma samples were centrifuged and separated from the red blood cells within 2 h of receipt in the clinical chemistry laboratory by use of serum/plasma separator tubes or by pouring off the serum/plasma. They were then stored at 4 °C for up to 4 days, after which they were aliquoted and stored at −70 °C. Anemia is defined as a hematocrit ≤36% for females and ≤39% for males as determined with a Model STKS Coulter Counter. Five populations were examined. The nonanemic group consisted of 103 nonanemic second-year medical students, out of 112 students who had submitted anonymous samples as part of a pathology course, and 101 nonanemic adult outpatients with samples submitted previously for routine clinical chemistry testing. The bone marrow group consisted of 54 anemic adult patients at our institution who were undergoing their first bone marrow aspirate in which a serum or plasma sample was available within 5 days of the bone marrow aspiration. The microcytic anemia group consisted of plasma samples from 43 microcytic patients (mean corpuscular volume <70 fl) whose samples were submitted for hemoglobin electrophoresis. The medical student group consisted of all 112 samples from the medical students mentioned above. The routine ferritin group consisted of 267 consecutive serum samples received by the clinical chemistry laboratory for routine ferritin analysis. Hematocrit determination was also requested in 225 of these patients, and 194 (86%) were anemic.

**Bone marrow aspirates.** Samples were collected in EDTA, and coverslips were prepared and stained for iron with Prussian blue. Positive and negative controls were performed with each sample. Samples from patients whose bone marrow showed replacement of normal hematopoietic elements with malignancy were excluded. At least three spicules were examined in each sample, and stainable iron was determined to be absent or present by a hematopathologist blinded to the results of the sTfR and ferritin studies.

**Immuoassays.** sTfR values were determined by using a polyclonal sandwich immunoassay (R&D Systems, Minneapolis, MN). All samples were tested in duplicate, and values reported are the means of the duplicate analyses. In 16 of the total 577 samples tested, duplicate values did not agree within 15% and were, therefore, repeated in a subsequent assay. The mean values from the subsequent assay are reported. Interassay precision was determined by assaying two concentrations of control samples on each plate. Only plates where both control sample values were within 2 SDs of the mean were used to determine the values reported here. Results from 2 of 22 assay kits were discarded because of unacceptable values for the control samples. Interassay precision was 16.1% and 11.9% at 1.2 and 2.1 mg/L, respectively (n = 20). Ferritin values were determined with either the Chiron automated chemiluminescence system ferritin assay or the Access immunoassay system ferritin assay from Beckman. Prior evaluation of these two ferritin assays at our institution indicated that they yield similar ferritin values (unpublished data).

**Hemoglobin electrophoresis.** Samples were collected in tubes containing EDTA, and an automated blood count was performed to determine red blood cell indices. Hemolysates were prepared, and alkaline and citrate agarose gel electrophoresis was performed according to instructions provided by the manufacturer (Chiron). Hemoglobin A2 was determined by anion-exchange column chromatography (Helena Labs.), and hemoglobin F was determined by alkaline denaturation (Chiron). Patients with microcytosis were considered to have β-thalassemia trait if the hemoglobin A2 was >3.5% in the absence of marked anemia (hematocrit <30%) and other hemoglobinopathies.

**Results**

*Nonanemic patients.* The distribution of sTfR values among the 103 nonanemic medical students and 101 nonanemic outpatients is shown in Fig. 1. The mean and SD for this population is 1.64 ± 0.47 mg/L, which is similar to the manufacturer’s stated normal mean of 1.54 ± 0.43 mg/L obtained from screening 1000 apparently healthy individuals. The mean and SD is 1.64 ± 0.43 mg/L for the 80 females and 1.69 ± 0.50 mg/L for the 124 males. On the basis of these data, an sTfR value of 2.8 mg/L (mean ± 2.5 SD) was set as the upper reference limit for both sexes.

The bone marrow biopsy group. Five of the 54 anemic patients had absent bone marrow iron stores. All five had sTfR values >2.8 mg/L (Fig. 2), suggesting that the sTfR is a sensitive indicator of iron deficiency. However, 7 of the 49 patients with stainable iron in their bone marrow aspirate also had sTfR values >2.8 mg/L, resulting in a positive predictive value of only 42% in this population (Table 1). Of these seven patients, two had megaloblastic changes because of vitamin B12 deficiency, a condition known to be associated with increased sTfR concentrations [18], and one each had: myelofibrosis with marked...
extramedullary hematopoiesis; Felty syndrome and pan-
cytopenia; acquired immune deficiency syndrome with
non-Hodgkin lymphoma; metastatic endometrial leiomy-
osarcoma; and systemic lupus erythematosus.

Interestingly, only one of the five patients with absent
bone marrow iron stores had a ferritin value \( \leq 12 \) \( \mu \text{g/L} \) (Fig. 2), suggesting that at this diagnostic limit \( [2] \), ferritin may be an insensitive indicator of iron deficiency in acutely ill patients (Table 1). However, all five of the iron-deficient patients in this group had ferritin values \( \leq 30 \) \( \mu \text{g/L} \). If the diagnostic limit for ferritin is raised to 30
\( \mu \text{g/L} \), only one result is falsely positive (Fig. 2), and the positive predictive value for ferritin increases from 50% to
83% (Table 1). One patient with megaloblastic anemia had iron identified in the marrow but had a low ferritin (8
\( \mu \text{g/L} \) and an increased sTfR (5.16 mg/L). An independent review of this patient’s bone marrow aspirate con-
irmed the presence of iron in erythroid precursor cells, suggesting that both the ferritin and sTfR values were
falsely positive.

The microcytic anemia group. Plasma ferritin and sTfR
concentrations were measured in 43 samples submitted
for hemoglobin electrophoresis from patients with a mean
corpuscular volume <70 fL (Fig. 3). This population was
chosen for study because nearly all severely microcytic
patients have either iron deficiency or a \( \beta \)-thalassemia.
Thus, the diagnosis of iron deficiency is typically not
difficult based on clinical history and laboratory tests
besides ferritin and sTfR, such as hemoglobin typing and
standard iron chemistries. On the basis of these clinical
criteria, iron deficiency was determined to be the cause of
the microcytic anemia in 26 patients (23 females and 3
males) and was excluded in the remaining 17 patients (9
females and 8 males). The sTfR was \( > 2.8 \) mg/L in 23 of
the 26 patients diagnosed as iron deficient, demonstrating
a sensitivity of 88%. However, the sTfR value was also
\( > 2.8 \) mg/L for 6 of the 17 patients who were not clinically
diagnosed as iron deficient, indicating a specificity of 65%
and a positive predictive value of 79% in this clinically
defined population. Ferritin at a diagnostic cutoff value of
\( \leq 12 \) \( \mu \text{g/L} \) was again less sensitive (73%) than sTfR but
had 100% specificity. Changing the upper diagnostic
cutoff value to 30 \( \mu \text{g/L} \) provided 96% sensitivity yet maintained
100% specificity.

Documented responses to iron therapy were available
from eight of the patients in this group (Fig. 3). Seven
patients had an increase in hematocrit of \( > 4\% \) within 1
month of the initiation of iron therapy in the absence of
transfusion and were, therefore, clearly iron deficient. The
clinical history from one male with hypertension, renal
insufficiency, and hemoglobin AC clearly indicated that
he was not iron deficient, based on a documented failure
to respond to iron therapy over a 9-month period and

Table 1. Sensitivity, specificity, and positive (PPV) and
negative (NPV) predictive values of the sTfR and ferritin
(12 and 30 \( \mu \text{g/L} \) cutoffs) values for iron deficiency.

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<th>Sensitivity, %</th>
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<th>NPV, %</th>
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<tr>
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* Bone marrow group combined with eight patients with documented re-
sponses to iron therapy.
The medical student group. To examine the ability of ferritin and sTfR to detect iron deficiency in a relatively healthy population, we examined values in a population of 112 medical students (Fig. 4, left). Nine of 52 (17%) female students were anemic at the time of sampling. None of the 60 male students were anemic. The most common cause of anemia in this population is presumed to be iron deficiency, where the incidence is estimated to be as high as 20% in women of child-bearing age [19, 20]. Only two of the nine anemic students had both sTfR ≥2.8 mg/L and ferritin ≤12 mg/L. The sTfR values were normal in the seven remaining anemic female students. In contrast, four of nine had ferritin ≥12 mg/L, and seven had ferritin ≥30 mg/L (Table 2). An additional five female students with hematocrits >36% had ferritin ≥12 mg/L, and one had sTfR of 3.0 mg/L. One nonanemic male student had ferritin ≥12 mg/L, and one had sTfR of 4.5 mg/L (Table 2). All other 95 students had ferritin >12 mg/L and normal sTfR values. If one assumes iron deficiency is the most common cause of anemia in a “healthy” population, it appears that ferritin is more sensitive than sTfR for screening purposes.

The routine ferritin group. To assess the diagnostic agreement between diagnostic sTfR and ferritin values in a routine hospital clinical laboratory environment, sTfR and ferritin values were compared in samples from 267 patients submitted to the clinical chemistry laboratory for ferritin analysis. Bone marrow samples, response to iron,
The remaining 175 patients (66%) are classified as iron sTfR but not ferritin, and 5 (2%) by ferritin but not sTfR. Iron deficient by both tests, 68 (25%) as iron deficient by diagnostic value, only 19 patients (7%) are classified as chronic inflammatory illnesses increased erythropoiesis but is not affected by acute or. sTfR concentration increases with iron deficiency and other causes of increased erythropoiesis are not eliminated. sTfR has been suggested as a highly sensitive laboratory test for iron deficiency [12, 13, 21]. However, just as acute or chronic illnesses may yield falsely negative results for ferritin, other causes of anemia that yield increased erythropoiesis, such as megaloblastic anemia, thalassemias, sickle cell anemia, and autoimmune hemolytic anemia, might be expected to increase sTfR values, despite adequate iron.

Here we directly compared ferritin and sTfR in ill patients with independent documentation of iron status by bone marrow biopsy or response to iron therapy. In the patients with either bone marrow biopsy data or documented response to iron therapy, we found that sTfR is indeed a sensitive marker for iron deficiency, detecting 11 of 12 iron-deficient patients. However, 7 of 49 patients with stainable iron stores in their bone marrow and 1 patient who did not respond to iron therapy also had increased sTfR values, resulting in a specificity of 84% and a positive predictive value of only 58% in a population that is likely to be typical of the most difficult diagnostic environments for assessing iron status. Three of these eight patients with stainable iron had a known cause of increased erythropoiesis, resulting in the “false positive” sTfR values. Of the other five, one was diagnosed as anemia of chronic disease, and the remaining four had no identifiable reason for erythroid hyperplasia. Thus, interpretation of increased sTfR may be challenging, even in the absence of known causes of increased erythropoiesis.

The study of the microcytic anemia population was primarily retrospective, making it difficult to obtain objective iron status criteria for 35 of the 43 patients. Nevertheless, the results from these patients, i.e., clinical diagnoses and other laboratory data, support the findings from the above populations with documented iron status.

When ferritin was examined in these anemic populations, its specificity was excellent (96–100%), but sensitivity was poor when a diagnostic value of 12 µg/L was used. However, raising the diagnostic value to 30 µg/L made ferritin an almost perfect test. Although ferritin was increased (115 µg/L) in one documented iron-deficient patient with severe rheumatoid arthritis, it was <30 µg/L in iron-deficient patients with diagnoses that included systemic lupus erythematosus, adenocarcinoma of the lung, chronic liver disease, colon cancer, and sepsis, all of which might be expected to cause an acute-phase increase of ferritin. A diagnostic value of 30 µg/L for ferritin has also been suggested by others [5, 22], and our data support this in ill patients. Taken together, in these two populations, ferritin alone was an adequate indicator of iron deficiency when a diagnostic value of 30 µg/L was used. In all cases except the one patient with severe rheumatoid arthritis, sTfR added little to the information obtained from ferritin and might lead to overdiagnosis of iron deficiency if identifiable causes of enhanced erythropoiesis are not eliminated.

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In the medical student group (Fig. 4, left panel), the main area of diagnostic disagreement between the ferritin and sTfR is in the lower left quadrant of the plot, where 7 (all females) of 112 students had a ferritin ≤12 µg/L and a normal sTfR. This observation in the “healthy” population examined is distinctly different from that seen in the other groups of patient samples studied, where very few

<table>
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<th>Sex</th>
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<th>MCV, fL</th>
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*a MCV, mean corpuscular volume.

or other clinical information was not obtained from this population. The sTfR and ferritin values were poorly correlated (r = 0.228), and there was a considerable lack of diagnostic agreement between the two assays (Fig. 4, right panel). When a ferritin of ≤12 µg/L is used as the diagnostic value, only 19 patients (7%) are classified as iron deficient by both tests, 68 (25%) as iron deficient by sTfR but not ferritin, and 5 (2%) by ferritin but not sTfR. The remaining 175 patients (66%) are classified as iron replete by both tests. Use of <30 µg/L ferritin as the diagnostic value gave little improvement in diagnostic agreement.

**Discussion**

The utility of plasma or serum ferritin in screening for iron deficiency in relatively healthy patients is well established [2–4] and is further supported by our results in the medical student population. However, directed evaluation of the cause of anemia in ill patients, particularly those with inflammatory diseases, can be difficult because of the acute-phase reactant properties of ferritin. In such patients, the diagnostic sensitivity of ferritin for iron deficiency can be compromised, and either bone marrow biopsy or determination of the response to iron therapy is required to completely assess iron status. sTfR concentration increases with iron deficiency and other causes of increased erythropoiesis but is not affected by acute or chronic inflammatory illnesses [8–11]. Accordingly, sTfR has been suggested as a highly sensitive laboratory test for iron deficiency [12, 13, 21]. However, just as acute or chronic illnesses may yield falsely negative results for ferritin, other causes of anemia that yield increased erythropoiesis, such as megaloblastic anemia, thalassemias, sickle cell anemia, and autoimmune hemolytic anemia, might be expected to increase sTfR values, despite adequate iron.

Here we directly compared ferritin and sTfR in ill patients with independent documentation of iron status by bone marrow biopsy or response to iron therapy. In the patients with either bone marrow biopsy data or documented response to iron therapy, we found that sTfR is indeed a sensitive marker for iron deficiency, detecting 11 of 12 iron-deficient patients. However, 7 of 49 patients with stainable iron stores in their bone marrow and 1 patient who did not respond to iron therapy also had increased sTfR values, resulting in a specificity of 84% and a positive predictive value of only 58% in a population that is likely to be typical of the most difficult diagnostic environments for assessing iron status. Three of these eight patients with stainable iron had a known cause of increased erythropoiesis, resulting in the “false positive” sTfR values. Of the other five, one was diagnosed as anemia of chronic disease, and the remaining four had no identifiable reason for erythroid hyperplasia. Thus, interpretation of increased sTfR may be challenging, even in the absence of known causes of increased erythropoiesis.

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When ferritin was examined in these anemic populations, its specificity was excellent (96–100%), but sensitivity was poor when a diagnostic value of 12 µg/L was used. However, raising the diagnostic value to 30 µg/L made ferritin an almost perfect test. Although ferritin was increased (115 µg/L) in one documented iron-deficient patient with severe rheumatoid arthritis, it was <30 µg/L in iron-deficient patients with diagnoses that included systemic lupus erythematosus, adenocarcinoma of the lung, chronic liver disease, colon cancer, and sepsis, all of which might be expected to cause an acute-phase increase of ferritin. A diagnostic value of 30 µg/L for ferritin has also been suggested by others [5, 22], and our data support this in ill patients. Taken together, in these two populations, ferritin alone was an adequate indicator of iron deficiency when a diagnostic value of 30 µg/L was used. In all cases except the one patient with severe rheumatoid arthritis, sTfR added little to the information obtained from ferritin and might lead to overdiagnosis of iron deficiency if identifiable causes of enhanced erythropoiesis are not eliminated.

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values were in this quadrant (Figs. 2, 3, and 4, right panel). Because serum ferritin is thought to reflect iron stores and sTfR the degree of iron-deficient erythropoiesis [23], these students may have depleted iron stores but have not yet begun iron-deficient erythropoiesis. The presence of anemia (defined by hematocrit in Table 2) in only two of these seven students is consistent with this hypothesis, which is also suggested by other studies. Carriaga et al. [24] studied a group of 176 women in the third trimester of pregnancy and found that 66% of the 158 women with ferritin ≤12 μg/L had an sTfR value in the normal reference range. Because most of the women in that study were taking iron supplements, they concluded that the women had depleted iron stores but not iron-deficient erythropoiesis. Furthermore, phlebotomy studies in healthy subjects have demonstrated that sTfR remains normal until a tissue iron deficit occurs [23], providing a basis for interpreting the data from individuals with low ferritin and normal sTfR in this manner. Here, all but two of the nine anemic female students had ferritin values ≤30 μg/L, whereas only two had increased sTfR (Table 2). Thus, in an otherwise healthy population, ferritin appears to be a sensitive and early indicator of iron deficiency and should be considered the test of choice for assessing the need for iron therapy in otherwise healthy females.

The sTfR concentrations determined in samples received for routine ferritin analysis demonstrates that in a random, predominantly outpatient population, a poor statistical correlation exists between the values from the two assays (Fig. 4, right panel) and that there is a lack of diagnostic agreement between the two tests in 27% of these patients. The former observation is not completely surprising, because ferritin detects deficient iron stores, whereas sTfR detects increased erythropoiesis. However, if both assays were perfect predictors of iron deficiency, all of the data points would fall in either the upper left (iron-deficient) or lower right (iron-replete) quadrants of the plot in Fig. 4, right panel. Most (73%) of the data points fall in one of these two quadrants, but 25% are in the upper right quadrant (ferritin >12 μg/L and sTfR >2.8 mg/L). These values may represent either iron-replete patients who have increased erythropoiesis, such as a patient with sickle cell disease who has received numerous red blood cell transfusions, or patients with iron deficiency and an acute-phase increase of the ferritin value. A physician educated in the strengths and weaknesses of these two tests and familiar with the patient’s history could in all likelihood correctly determine many of the patients in this quadrant to be iron deficient or replete without further testing. Nevertheless, the preponderance of “ambiguous” results, such as patients with ferritin values between 31 and 200 μg/L and increased sTfR, suggest that a bone marrow biopsy or a trial of iron therapy might sometimes be necessary.

In conclusion, our findings are in agreement with those of Pettersson et al. [10] in that the sTfR is not superior to ferritin for the routine clinical evaluation of patients with suspected iron deficiency. Furthermore, in two well-defined populations, we found no evidence that sTfR provides additional information to that of ferritin used with a diagnostic value of ≤30 μg/L. Finally, in the small subset of patients clinically suspected to be iron depleted but whose ferritin is increased by acute-phase reactions, a normal sTfR would likely rule out iron deficiency, and an increased sTfR would be useful if other causes of enhanced erythropoiesis can be eliminated. Thus, we believe the utility of sTfR to be limited to a subset of ill patients in whom iron deficiency is suspected but whose ferritin values are normal.

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References