

Soluble Transferrin Receptor (sTfR) and sTfR/log Ferritin Index for the Diagnosis of Iron-Deficiency Anemia

A Meta-Analysis

Ilenia Infusino,^{1,2} Federica Braga,^{1,2} Alberto Dolci, MD,² and Mauro Panteghini, MD,^{1,2}

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Upon completion of this activity you will be able to:

- apply the gold standard for iron deficiency diagnosis.
- describe the main characteristics of the soluble transferrin receptor (sTfR).
- apply the clinical evidence derived from the meta-analysis.
- describe the most relevant problem related to sTfR commercial assays.

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Abstract

Determination of serum soluble transferrin receptor (sTfR) is proposed to distinguish between iron-deficiency anemia and anemia of chronic disease. Here we conducted a meta-analysis of the literature to evaluate the diagnostic efficacy of sTfR and sTfR/log ferritin index. The meta-analysis included 18 sTfR and 10 sTfR index studies. Three sTfR index studies were, however, eliminated as outliers. The odds ratio was significant for both sTfR (22.9, 95% confidence interval [CI], 9.6-55.0) and sTfR index (9.5, 95% CI, 5.0-18.1) in a heterogeneous set of studies. Meta-analysis for sensitivity, specificity, and likelihood ratios (LRs) was performed only in a subset of 10 sTfR studies. The overall sensitivity, specificity, and positive and negative LRs were 86%, 75%, 3.85, and 0.19, respectively, with an area under summary receiver operating characteristic curve of 0.912 (standard error, 0.039). Additional studies are needed to define the overall diagnostic accuracy of sTfR.

Iron deficiency is a common condition that is usually diagnosed using conventional laboratory tests of iron status, such as serum ferritin and transferrin saturation.¹⁻³ However, both ferritin and transferrin proteins are markedly influenced by inflammation, behaving as acute-phase reactants and making it difficult to differentiate between iron-deficiency anemia (IDA), which occurs when iron deficiency is severe enough to reduce erythropoiesis, and anemia of chronic disease (ACD) occurring with infection or malignancy.² Differentiating between IDA and ACD and identifying coexistence of ACD and IDA (mixed IDA+ACD) is a frequent diagnostic problem, which is clinically relevant because inadequate treatment including iron supplementation could have a detrimental effect on patients with ACD.⁴ Bone marrow examination (BME) establishing the absence of stainable iron remains the gold standard for a diagnosis of iron deficiency. BME is, however, invasive, expensive, and requires technical expertise, so that it cannot be performed routinely in clinical practice.⁵ Technical limitations have also been reported.⁶

Soluble transferrin receptor (sTfR) protein is a single polypeptide chain of 85 kDa that can be measured in human serum, derived from transferrin receptor, a transmembrane cellular protein of 190 kDa, primarily expressed in cells that require iron. Transferrin receptor is composed of 2 disulfide-linked monomers of 95 kDa, each containing 760 amino acids, and organized into 3 major portions: a large C-terminal extracellular domain of 671 amino acids, a transmembrane domain of 28 amino acids, and an N-terminal cytoplasmic domain of 61 amino acids. A proteolytic cleavage by a matrix metalloproteinase between arginine-100 and leucine-101 of the extracellular domain forms the sTfR.⁷

Plasma sTfR concentration reflects the receptor density on cells and the number of cells expressing receptors; therefore, it is closely related to cellular iron demands and to erythroid proliferation rate.^{7,8}

In contrast to serum ferritin and transferrin concentrations, sTfR has been shown to be unaffected by concomitant chronic disease and inflammation. Therefore, it may be useful in distinguishing between ACD and IDA, and extremely valuable in identifying mixed IDA+ACD, because serum sTfR concentrations are expected to rise in IDA, but not in ACD.⁹ In addition, it has been proposed that the use of sTfR/log ferritin ratio (ie, the sTfR index), taking advantage of the reciprocal relationship between the 2 variables influenced by iron deficiency (increase of sTfR and decrease of ferritin concentrations), could increase the diagnostic efficacy of sTfR alone in differentiating IDA from ACD, as well as mixed IDA+ACD from ACD alone.^{8,9}

To date, only 1 systematic review has been published examining the clinical value of sTfR in detecting iron deficiency.¹⁰ Nine prospective studies were included, and we concluded that sTfR was useful in the diagnosis of IDA, especially in the presence of coexisting chronic inflammatory or neoplastic disease.¹⁰ However, to our knowledge, a meta-analysis of available data was not done. Therefore, we conducted, for the first time, a meta-analysis of available data, and evaluated the efficacy of sTfR and sTfR index in the differential diagnosis of IDA and ACD and in the identification of mixed IDA+ACD.

Materials and Methods

Meta-analyses were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹¹

Search Strategy

We searched the published peer-reviewed literature from 1986 to 2011 in the Medline and Embase databases, using the terms “receptors” and “transferrin” and setting limits as “humans,” “English language,” and “abstract availability.” The reference lists of retrieved articles for meta-analyses and of a previous systematic review¹⁰ were screened to identify further studies for possible inclusion.

Study Selection

Two reviewers (F.B. and I.I.) evaluated title and abstract of the records identified in the initial search to determine whether the study was relevant to the aim of the meta-analysis. Observational studies, case reports, narrative reviews, letters to the editor, and other similar contributions were excluded. Only investigations involving adult anemic population with

diagnoses of ACD, IDA and/or IDA+ACD, and with quantitative data of sTfR and/or of sTfR index available were included in the meta-analyses. A specific reason for exclusion (not relevant, no patients with ACD, and/or no quantitative data) was assigned to excluded articles.

Data Abstraction

The following information was abstracted from each study included in the meta-analysis: authors; year of publication; number of anemic subjects; diagnosis group (IDA and/or IDA+ACD) and its prevalence; sTfR analytic method and cutoff; use of BME as diagnostic reference standard; and quantitative data of sTfR and sTfR index, ie, sensitivity, specificity, correlation (*P* value), mean, and SD.

Statistical Analysis

All quantitative data of selected studies were evaluated as odds ratio (OR) or effect size (ES), with corresponding 95% confidence intervals (CI), using the Comprehensive Meta-Analysis (CMA) software, version 2.2 (Biostat, Englewood, NJ). Using CMA, a test for outliers was performed and studies with residual *P* value less than .05 were eliminated. *Q* and *I*² statistics were used to test the homogeneity among ES results. To calculate overall combined ES, CMA provides different meta-analytic models: the random effect model is used if the assumption of heterogeneity is identified; otherwise, the fixed-model is adopted. Resulting ORs were presented as forest plots with the corresponding CI. The *Q* statistic was also used to test the significance of moderators. Egger linear regression method (available in CMA) was used to estimate potential publication bias. *P* values less than .05 were considered statistically significant.

For studies with binary data available, we also considered sensitivity and specificity as ES using Meta-Analysis of Diagnostic and Screening Test (Meta-DiSc) program, version 1.4 (freeware).¹² Data were presented as forest plots with the corresponding CI. True (sensitivity) and false (1 – specificity) positive values were summarized in the receiver operator characteristic (ROC) curve (SROC), where the area under the curve (AUC) and *Q** values were calculated. The *Q** value corresponds to the intersection of SROC with the diagonal line where sensitivity equals specificity. Positive and negative likelihood ratios (LR), corresponding to sensitivity/(1 – specificity) and (1 – sensitivity)/specificity, were also estimated and included in the meta-analysis.

Results

The search strategy retrieved a total of 1,458 potential studies; 3 duplicate records were excluded and 1,455 titles and abstracts were screened. After examination of titles and

abstracts, 1,433 studies were excluded because they were not relevant to the aim of the study, and 22 articles were selected for full-text examination.^{9,13-33} Of 22 articles retrieved for further examination, 18 and 10 definitively met criteria to be included in sTfR and sTfR index meta-analysis, respectively (Figure 1). The reasons for excluding articles after full-text examination were the following: not relevant to the aim of the study,⁹ no data on patients with ACD,^{15,31} and no quantitative

data about sTfR²¹ or about sTfR index.^{18,20,22,24,26,28-30,33} Main characteristics of selected studies are summarized in Table 1.

None of the sTfR studies were identified as outliers, but 3 sTfR index studies^{25,27,32} displayed a residual *P* value less than .05 and were eliminated. Figure 2 displays random overall combined ES shown as a forest plot of the ORs and corresponding CI. ES was significant for both sTfR (22.9; CI, 9.6-55.0) and sTfR index (9.5; CI, 5.0-18.1) in a heterogeneous

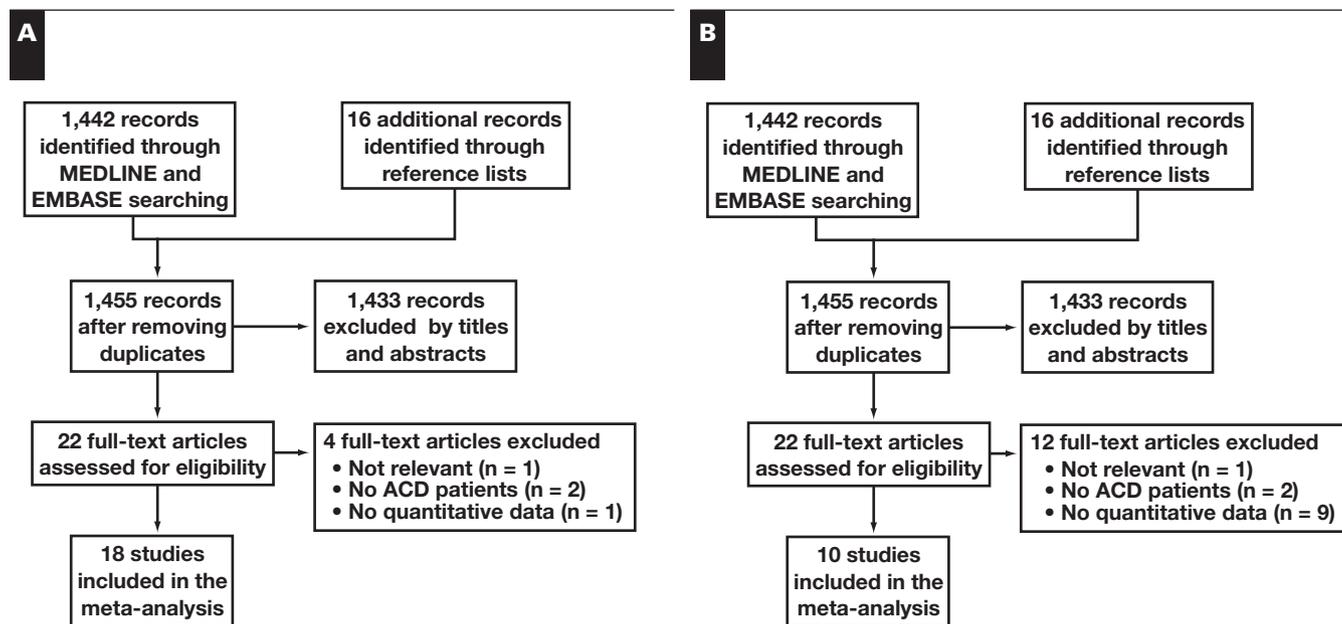


Figure 1 Flow charts of study selection for soluble transferrin receptor (sTfR) (A) and sTfR/log ferritin ratio (B) meta-analyses. ACD, anemia of chronic disease.

Table 1 Main Characteristics of Selected Studies for sTfR and/or sTfR Index Meta-Analyses

Study	No. of Anemic Subjects	Diagnosis Group	sTfR Analytic Method	BME as Diagnostic Reference Standard	Data Presentation
Skikne et al ¹³	145	IDA and IDA+ACD	ICMA	No	Binary data
Oustamanolakis et al ¹⁴	42	IDA and IDA+ACD	ELISA	No	Correlation
Markovic et al ¹⁶	118	IDA and IDA+ACD	IN	No	Binary data
Margetic et al ¹⁷	96	IDA	IT	No	Correlation
Hanif et al ¹⁸	176	IDA	IEMA	Yes	Means
Genc et al ¹⁹	29	IDA	IT	No	Correlation
Baillie et al ²⁰	20	IDA+ACD	IEMA	Yes	Binary data
Rimon et al ²¹	63	IDA	ELISA	Yes	Binary data
Joosten et al ²²	72	IDA	ELISA	Yes	Binary data
Matsuda et al ²³	72	IDA	ELISA	Yes	Means (sTfR); correlation (sTfR index)
Fitzsimons et al ²⁴	27	IDA+ACD	ELISA	Yes	Binary data
Lee et al ²⁵	120	IDA and IDA+ACD	IT	Yes	Binary data
Wigns et al ²⁶	72	IDA	ELISA	No	Binary data
Ho ²⁷	88	IDA	IEMA	Yes/No	Means
Means et al ²⁸	145	IDA	ELISA	Yes	Binary data
Chua et al ²⁹	40	IDA	ELISA	No	Means
Juncà et al ³⁰	27	IDA+ACD	IEMA	Yes	Binary data
Punnonen et al ³²	129	IDA and IDA+ACD	EIA	Yes	Binary data
Ferguson et al ³³	58	IDA	ELISA	Yes	Means

ACD, anemia of chronic disease; BME, bone marrow examination; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ICMA, immunochemiluminescent assay; IDA, iron-deficiency anemia; IEMA, immunoenzymometric assay; IN, immunonephelometry; IT, immunoturbidimetry; sTfR, soluble transferrin receptor.

set of studies (for sTfR: $Q = 163.43, P < .0001, I^2 = 90\%$; for sTfR index: $Q = 13.51, P < .05, I^2 = 56\%$). Year of publication of the article, number of enrolled anemic subjects, sTfR analytic principle (ie, enzyme-linked immunosorbent assay [ELISA], immunoenzymometric assay, immunoturbidimetry, or immunonephelometry), diagnosis group, BME as a diagnostic standard, and type of data presentation were analyzed as moderators. For sTfR outcome, none of these parameters influenced total ES, whereas for sTfR index, the difference between studies presenting binary data ($n = 3$; overall OR = 17.9, CI = 6.8-47.1) and those giving correlation findings ($n = 4$; OR = 5.4, CI = 3.2-9.2) was significant ($Q = 4.55, P < .05$), making the way of data presentation a moderator for

sTfR index. In both cases, the ES was lower than the overall OR obtained for sTfR. No studies with means were available for sTfR index.

The difference among overall ORs obtained by grouping studies based on different analytic methods used for sTfR determination was statistically significant for both sTfR ($Q = 20.94, P = .001$) and sTfR index ($Q = 9.01, P = .03$). However, some groups included only 1 study, making the evaluation unreliable. Indeed, for either test, comparing only the 2 groups with the largest number of available studies, ie, ELISA (8 studies) and immunoenzymometric assay (4 studies) groups for sTfR and ELISA (3 studies) and turbidimetry (2 studies) for sTfR index, the analytic method did not perform

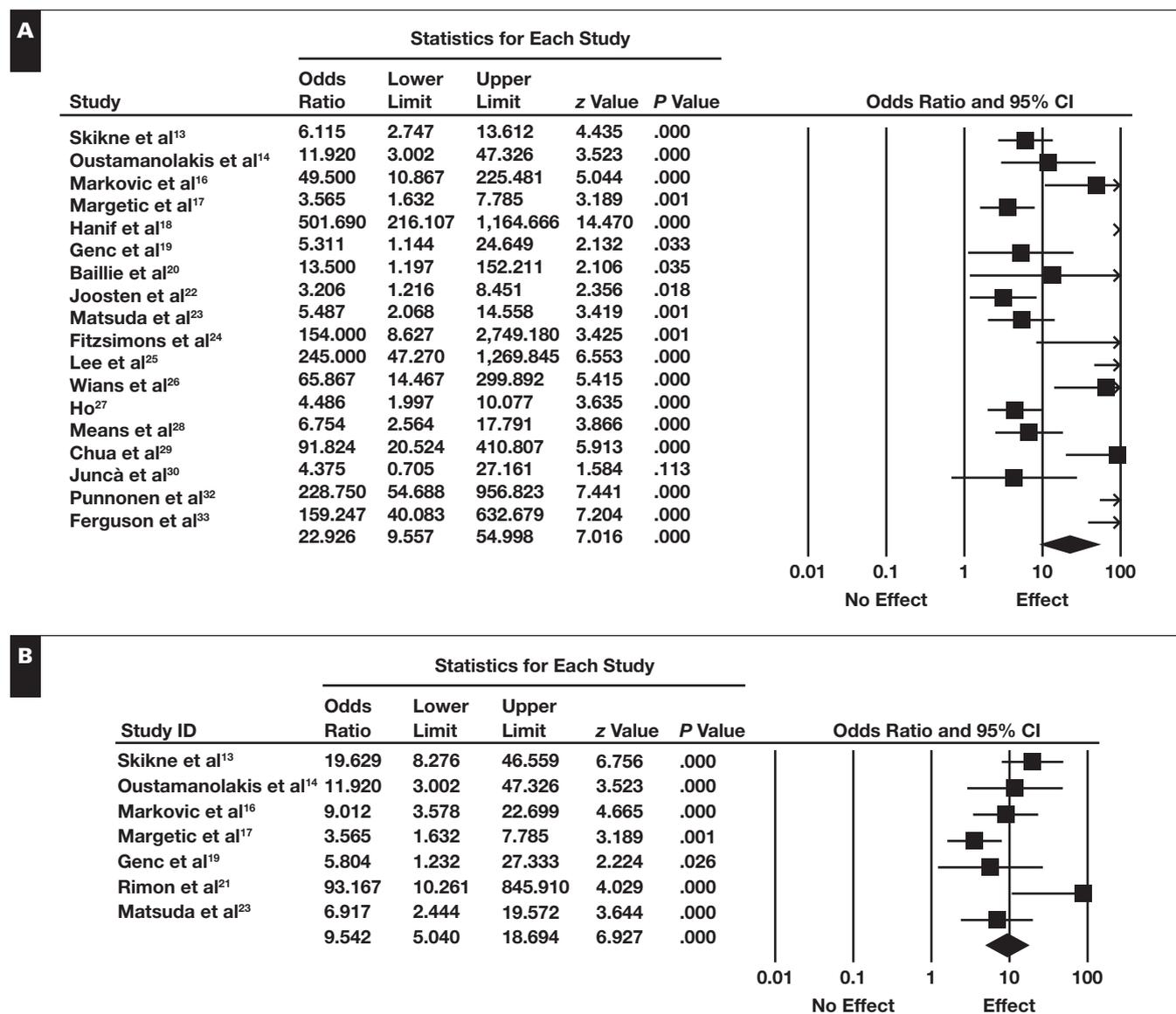


Figure 2 Random overall combined effect size of soluble transferrin receptor (sTfR) (A) and sTfR index (B) shown as forest plot of the odds ratio with 95% confidence intervals (CI).

as moderator (for sTfR: $Q = 0.003, P = .95$; for sTfR index: $Q = 3.21, P = .07$).

The Egger linear regression showed no publication bias for both outcomes: 2-tailed P values were .18 for sTfR and .26 for sTfR index, respectively.

Because of sample size, a meta-analysis with sensitivity, specificity, and LR as ES was performed only in a subset of 10 sTfR studies with available binary data.^{13,16,20,22,24-26,28,30,32}

Table 2 displays the commercial assay, the corresponding cutoff, and the diagnostic performance of sTfR in each of these studies, including the disease prevalence and estimated predictive values. Given the high heterogeneity of enrolled patient populations in different studies, a meta-analysis of predictive values was, however, not done. The meta-analysis revealed for sTfR an overall sensitivity of 86% (CI = 82%-89%) and a specificity of 75% (CI = 71%-79%) **Figure 3**. The SROC curve resulted in an AUC of 0.912 (SE = 0.039) and a Q^* value of 0.85 as the highest combined sensitivity and specificity value **Figure 4**. From these studies, the global OR was 24.3 (CI = 8.4-70.1) and positive and negative LR were 3.85 (CI = 2.23-6.63) and 0.19 (CI = 0.11-0.33), respectively.

Discussion

In this study we conducted for the first time a meta-analysis of available data to evaluate the efficacy of sTfR and sTfR index in the differential diagnosis of IDA and ACD and the

identification of mixed IDA+ACD. In general, the available studies were small with relatively few participants and their quality was often suboptimal. Particularly, a number of studies did not perform BME for classifying patients and applied other criteria and, in some cases, subjective clinical criteria to differentiate between IDA and ACD.^{16,17} Biochemical criteria based on conventional biomarkers of iron status, such as serum ferritin concentrations and transferrin saturation, were often adopted to make the diagnosis.^{14,19,26,29} Therefore, a patient misclassification could have been introduced because of the use of an inappropriate diagnostic reference standard. In our meta-analysis, the assumption of heterogeneity of studies was, however, identified using specific statistics and, when confirmed, the random effect model was used as the summary measurement.

The random overall ORs suggest that both sTfR and sTfR index are useful in distinguishing between ACD and IDA, but sTfR (OR = 22.9) seems to be more efficient than sTfR index (OR = 9.5). This is a relevant conclusion, because previous studies claimed that sTfR index may improve diagnostic accuracy, providing higher sensitivity and specificity than sTfR determination alone.^{10,23,32,34}

The overall probability of a patient with IDA to have a positive sTfR test result is approximately 23-fold higher than for a patient with ACD. However, even though a relatively large OR was estimated, no definitive conclusion can be made about the diagnostic power of this marker. In general, relatively few studies with binary data are available to make

Table 2
Diagnostic Performance of Soluble Transferrin Receptors in the Subset of Studies Using Binary Data Presentation

Study	Company/Platform	Cutoff, mg/L	Diagnosis Group	Disease Prevalence, %	Patient Enrollment	Sensitivity	Specificity	PPV	NPV
Skikne et al ¹³	Beckman Coulter/Access	1.55	IDA and IDA+ACD	61	Consecutive	0.86	0.49	0.72	0.70
Markovic et al ¹⁶	Siemens/Nephelometer	2.07	IDA and IDA+ACD	73	Consecutive	0.77	0.94	0.97	0.60
Baillie et al ²⁰	Orion Diagnostica/IEMA IDeA	3.30	IDA+ACD	35	Consecutive	0.86	0.69	0.60	0.90
Joosten et al ²²	R&D Systems/ELISA	2.07*	IDA	47	NA	0.68	0.61	0.60	0.68
Fitzsimons et al ²⁴	R&D Systems/ELISA	2.07*	IDA+ACD	56	NA	0.93	0.92	0.93	0.92
Lee et al ²⁵	Roche Diagnostics/Hitachi 7600	1.80	IDA and IDA+ACD	60	NA	0.97	0.88	0.89	0.95
Wians et al ²⁶	R&D Systems/ELISA	2.18*	IDA	57	NA	0.93	0.84	0.88	0.90
Means et al ²⁸	R&D Systems/ELISA	2.07*	IDA	16	Consecutive	0.71	0.74	0.35	0.93
Juncà et al ³⁰	Orion Diagnostica/IEMA IDeA	2.80	IDA+ACD	44	NA	0.83	0.47	0.56	0.78
Punnonen et al ³²	R&D Systems/EIA Clinigen	2.70	IDA and IDA+ACD	50	Consecutive	0.94	0.94	0.94	0.94

ACD, anemia of chronic disease; EIA, enzyme immunoassay; IEMA, immunoenzymometric assay; IDA, iron-deficiency anemia; NA, not available; NPV, negative predictive value; PPV, positive predictive value.

* Original cutoff values in nmol/L converted to mg/L by using a multiplication factor of 0.0738.

a reliable estimate of sTfR diagnostic accuracy. The overall sensitivity of 86% associated with a specificity of 75% shows that the sTfR diagnostic performance is far from ideal, possibly making sTfR a fairly good test for IDA screening, but not for confirmatory purposes. LR values confirm this conclusion, showing a substantially small effect of sTfR on clinical decision making.³⁵ SROC curve plotted with sensitivity and specificity data reported in the selected sTfR studies gave an AUC of 0.912, indicating a relatively high accuracy of the test for diagnosing IDA.³⁶ However, the SROC curve displayed a large CI, because of the wide scatter of points representing

sensitivity and specificity of each study, confirming the need for more studies focusing on sTfR diagnostic accuracy.

The lack of standardization of sTfR measurement also limits the diagnostic power of the test because it makes it difficult to compare sTfR results among different studies. Some commercial assays measure sTfR using as calibration standard a material containing transferrin receptor isolated from human placenta.^{20,30} Other companies calibrate assays using sTfR purified from pools of human serum samples.^{16,25} It has been clearly shown that the use of placental transferrin receptor as calibration material in immunologic assays for

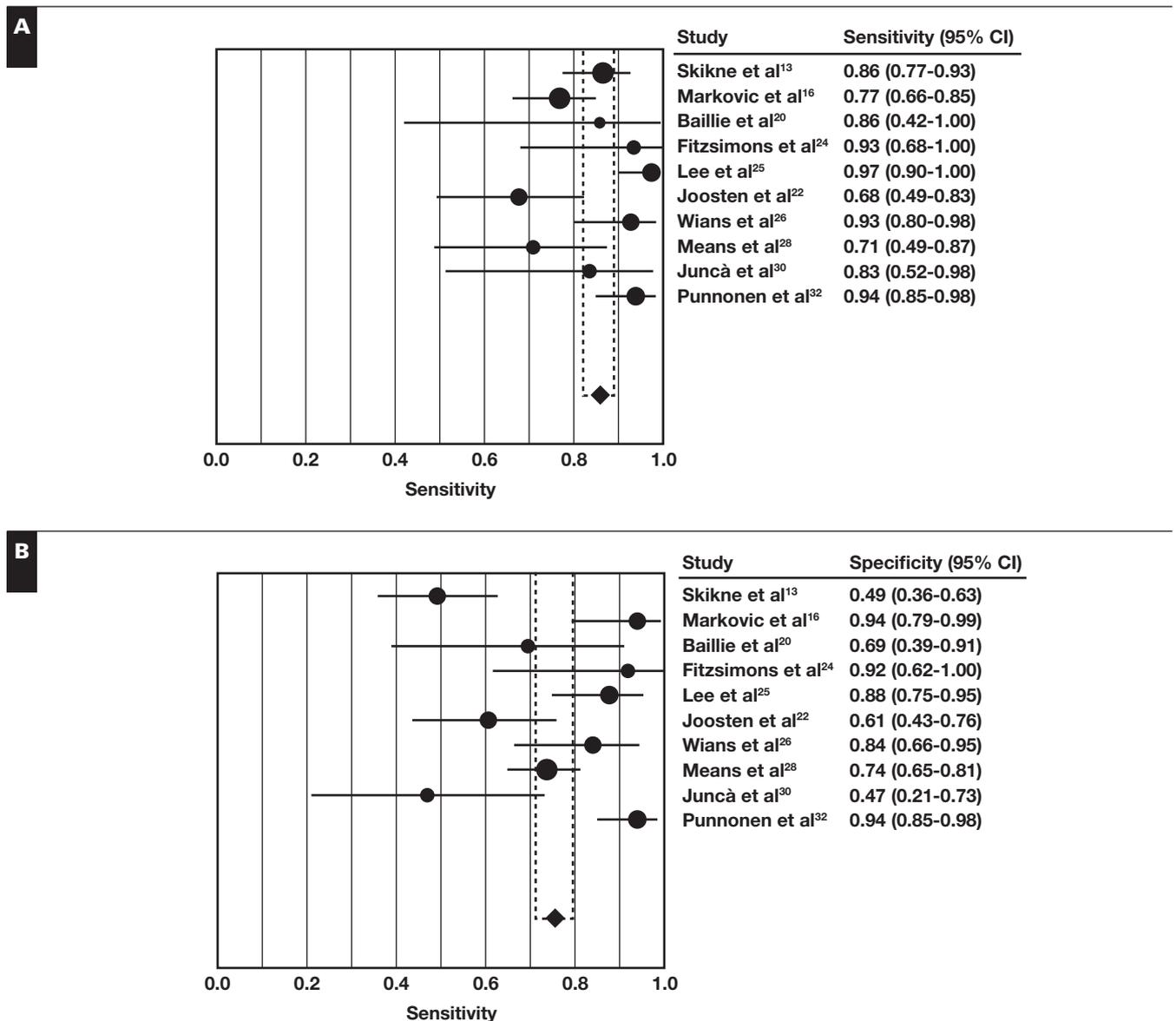


Figure 3 **A**, Sensitivity plot of soluble transferrin receptor determination in the diagnosis of iron deficiency anemia. Pooled sensitivity = 0.86 (0.82-0.89); $\chi^2 = 33.78$; degrees of freedom (df) = 9 ($P = .0001$); inconsistency (1-square) = 73.4%. **B**, Specificity plots. Pooled specificity = 0.75 (0.71-0.79); $\chi^2 = 58.96$; df = 9 ($P = .0000$); inconsistency (1-square) = 84.7%. CI, confidence interval.

sTfR leads to a marked overestimation of sTfR concentrations in serum samples.³⁷ Recent efforts have focused on characterizing recombinant sTfR as reference material for harmonizing results found with different immunoassay kits.³⁸ Preliminary collaborative studies demonstrated that the inter-assay agreement would be significantly improved with the use of this material as common calibrator.³⁸ The adoption of this preparation by manufacturers to standardize sTfR assays will possibly minimize their analytic influence on future clinical assessment of sTfR determination.

Our study had some limitations. It is widely recognized that meta-analyses of diagnostic test performance do not have the same strength as those analyzing drug effects in randomized controlled trials. One reason is the poorer quality and higher heterogeneity of studies on the diagnostic accuracy of biomarkers.³⁹ This heterogeneity can partially confound meaningful interpretation of the meta-analysis. Specific checklists, such as Quality Assessment of Diagnostic Accuracy Studies (QUADAS), have been proposed to highlight areas of bias in the primary studies included in a diagnostic meta-analysis. In our study, we first tested studies to exclude outliers and then performed specific statistics for evaluating homogeneity (or the lack of it) among ES results: because we studied a heterogeneous set of studies, we used the random effect model, which allowed inclusion of the studies in the meta-analysis, while acknowledging their flaws. Displayed forest plots also revealed information about heterogeneity.

A limitation of comparing the diagnostic accuracy of sTfR and sTfR index is that an SROC curve for sTfR index was not created, because only 3 studies evaluating the sTfR index reported binary data to calculate sensitivity and specificity values.^{13,16,21} Only random overall combined ORs for both markers were used to demonstrate the highest diagnostic accuracy of sTfR. Nevertheless, it should be noted that CIs of ORs for sTfR and sTfR index partially overlapped.

In conclusion, although ORs for detecting IDA were significant for both sTfR and sTfR index tests, sTfR may have a greater clinical value. More studies are, however, needed to define the overall diagnostic accuracy of this test and its possible position in the diagnostic flowchart of IDA. Particularly, its added value to serum ferritin determination in the detection of IDA in a population of anemic patients with and without inflammatory or neoplastic disease should be demonstrated.⁴⁰

From the ¹Centre for Metrological Traceability in Laboratory Medicine (CIRME), University of Milan, Milan, Italy, and ²Clinical Biochemistry Laboratory, 'Luigi Sacco' University Hospital, Milan.

Address reprint requests to Ms Infusino: Laboratorio Analisi, Ospedale Luigi Sacco, Via GB Grassi 74, 20157 Milano, Italy; infusino.ilenia@hsacco.it.

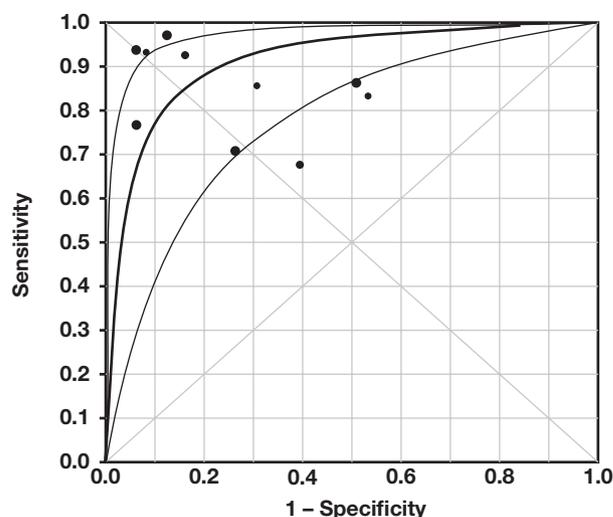


Figure 4 Summary receiver operating characteristic (SROC) curve analysis of diagnostic accuracy of soluble transferrin receptor determination in the diagnosis of iron deficiency anemia. Each point represents a study contributing to the SROC curve (thick line). Thin lines denote the 95% confidence interval of SROC.

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