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Comparison of Diagnostic Performance of Soluble Transferrin Receptor and Soluble Transferrin Receptor-Ferritin Index Tests in the Diagnosis of Iron Deficiency Anemia

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***Abstract*—**In this research article, a comprehensive analysis is performed to compare the diagnostic performance of soluble transferrin receptor (sTfR) and sTfR/log ferritin index tests in the differential diagnosis of iron deficiency anemia (IDA) and anemia of chronic disease (ACD). The analysis is performed for both sTfR and sTfR/log ferritin index using a set of 11 studies. The overall odds ratios for sTfR and sTfR/log ferritin index were 36.79 and 119.32 respectively, using 95% confidence interval. The relative sensitivity, specificity. positive likelihood ratio (LR) and negative LR values for sTfR in relation to sTfR/log ferritin index were 81% vs 85%, 84% vs 93%, 6.31 vs 13.95 and 0.18 vs 0.14 respectively. The summary receiver operating characteristic (SROC) curves are also plotted for both sTfR and sTfR/log ferritin index. The area under SROC curves for sTfR and sTfR/log ferritin index was found to be 0.9296 and 0.9825 respectively. Although both tests are useful, the sTfR/log ferritin index seems to be more effective when compared with sTfR.

***Keywords*—**Anemia, sTfR, iron deficiency, ferritin, odds ratio, sensitivity.

I. Introduction

IDA and ACD are the predominant forms of anemia [1], [2]. Iron deficiency can be diagnosed using conventional tests such as serum ferritin, total iron binding capacity (TIBC) and transferrin saturation [3]-[8]. However, these conventional laboratory tests are directly influenced by chronic disease, thereby reducing the clinical interpretation of results when differentiating between IDA and ACD [9], [10]. Reduced ferritin levels in IDA became higher because of the acute phase reactants associated with the chronic disease. Similarly, the coexistence of IDA and ACD altered the concentration of transferrin saturation, TIBC and serum iron. These changes could have a negative effect on patients having inflammatory disease, thereby making the interpretation difficult [11]. Bone marrow examination (BME) is most suitable in the diagnosis of iron deficiency. However, it cannot be performed regularly, because it is expensive and demands some technical expertise [12], [13].

sTfR are the proteins in blood that help in the diagnosis of IDA [14], [15]. In contrast to serum ferritin, the sTfR has been found to be unaffected by the inflammation and chronic disease [16]-[20]. As a result, sTfR is not only used for differentiating IDA and ACD, it is also very effective in the diagnosis of mixed IDA+ACD. The sTfR levels are the indicator of the degree of availability of iron and its concentration is higher in IDA than in ACD [21]-[25].

The sTfR/log ferritin index (sTfR index) calculated from ferritin and sTfR levels offer an approximation of body iron [26]. The reciprocal relationship between sTfR concentration and ferritin value with iron deficiency increases the utility of sTfR index. It has been reported in many studies that the sTfR index increases the clinical utility in differentiating IDA and IDA+ACD from ACD [10], [25], [27]-[29].

In this study, a comprehensive analysis is performed to evaluate and compare the diagnostic performance of sTfR and sTfR index tests in the differential diagnosis of IDA or IDA+ACD and ACD using a set of 11 studies. The diagnostic tests, methods and the data used for meta-analysis have been discussed in Section II. Section III presents the results of the analysis with the diagnostic efficiency and comparison of sTfR and sTfR index tests.

II. Materials and Methods

The diagnostic performance of sTfR and sTfR index is evaluated and compared using a set of 11 studies. The quantitative data including sensitivity, specificity, mean, standard deviation, P-value and the cutoff value for both sTfR and sTfR index were analyzed from each selected study. The main characteristics of selected studies are listed in Table I.

The Comprehensive Meta-Analysis (CMA) software and MetaAnalysis of Diagnostic and Screening Test (Meta-DiSc) program [30] were used to evaluate the data of selected studies. Using 95% confidence intervals (CI), the data of selected studies are evaluated as odds ratio (OR) and the Q and I^2 statistics are used to test the homogeneity.

Random effect model is used in the calculation of the overall OR, positive LR and negative LR. The relations for the positive LR (ρ^+), negative LR (ρ^-) and the diagnostic odds ratio (DOR) are respectively given as (1)-(3).

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TABLE I
MAIN CHARACTERISTICS OF SELECTED STUDIES FOR ANALYSIS OF STFR AND STFR INDEX

Reference	Total Anemic	Patients	Diagnosis	BME as Diagnostic	Data
Skikne et al. [1]	145	M: 48; F: 97; AG: 24-98	IDA and IDA+ACD	No	Binary
Markovic et al. [32]	118	M: 70; F: 46; Adults	IDA and IDA+ACD	No	Binary
Sema et al. [33]	44	M: 21; F: 23; AG: 63-94	IDA	No	Correlation
Lee et al. [34]	120	M: 58; F: 62; AG: 21-85	IDA and IDA+ACD	Yes	Binary
Sandra et al. [27]	96	M: 30; F: 66; AG: 20-69	IDA	No	Correlation
Punnonen et al. [10]	129	Adults	IDA and IDA+ACD	Yes	Binary
Pantelis et al. [35]	42		IDA and IDA+ACD	No	Correlation
Vazquez et al. [36]	251	Children; AG: 1-10	IDA	No	Correlation
Geon Park et al. [37]	177	AG: 18-81	IDA and IDA+ACD	Yes	Binary
Majkic S et al. [38]	118		IDA and IDA+ACD	No	Means
Leers et al. [39]	337	M: 210; F: 127	IDA	Yes	Means

M: Male; F: Female; AG: Age Group.

$$\rho^{+} = \frac{Sensitivity}{1-Specificity} \quad (1)$$

$$\rho^{-} = \frac{1-Sensitivity}{Specificity} \quad (2)$$

$$DOR = \frac{\rho^{+}}{\rho^{-}} \quad (3)$$

The data for sensitivity, specificity, positive LR and negative LR are also presented as forest plots using corresponding CI. The SROC curves are plotted using summarized true positive rate (sensitivity) and false positive rate (1−specificity) values and the area under the curve (AUC) is calculated.

The diagnostic parameters used to evaluate the performance of sTfR and sTfR index are listed in Table II for selected studies. Youden's index of both sTfR and sTfR index is calculated for each study and is listed in the last column of Table II. Youden's Index γ is given as [31]

$$\gamma = True\ Positive\ Rate - False\ Positive\ Rate \quad (4)$$

$$\gamma = Sensitivity - (1 - Specificity) \quad (5)$$

For sTfR, the diagnostic test for the prediction of IDA in the presence or absence of chronic disease is given as

$$x - \alpha \underset{H}{\overset{D}{\gtrless}} 0 \quad (6)$$

where x is the sTfR concentration and α is the resulting cutoff value for sTfR test given in Table II against each study. Similarly, for sTfR index, the diagnostic test for the differential diagnosis of IDA or IDA+ACD and ACD is given as

$$y - \beta \underset{H}{\overset{D}{\gtrless}} 0 \quad (7)$$

where y is the sTfR index value and β is the resulting cutoff value for sTfR index test given in Table II for each selected study.

III. RESULTS AND DISCUSSION

In this section, results are shown and discussed for both sTfR and sTfR index after performing an analysis using a same set of 11 studies for both tests. The forest plots of the DOR for both sTfR and sTfR index are shown in Fig. 1. The overall combined OR for sTfR and sTfR index is 36.79 and 119.32 respectively (for sTfR: Q = 92.28, $p < 0.0001$, I^2 = 89.2%; for sTfR index: Q = 100.95, $p < 0.0001$, I^2 = 90.1%). The overall ORs imply that both sTfR and sTfR index are useful tests in the differential diagnosis of IDA, but sTfR index appears to be more efficient than sTfR.

The forest plots of the positive and negative LR are shown in Figs. 2 and 3 respectively for both sTfR and sTfR index. The overall calculated positive LR of sTfR and sTfR index are 6.31 and 13.95 respectively. On the other hand, the overall combined negative LR for sTfR and sTfR index is 0.18 and 0.14 respectively.

TABLE II
DIAGNOSTIC PERFORMANCE OF STFR AND STFR INDEX TESTS IN THE SELECTED STUDIES

Reference	Test	Cutoff value	Sensitivity	Specificity	Youden's Index
Skikne et al. [1]	sTfR	1.55 mg/L	0.86	0.49	0.35
	sTfR index	1.03	0.81	0.83	0.64
Markovic et al. [32]	sTfR	2.07 mg/L	0.7713	0.9242	0.6955
	sTfR index	1.3	0.661	0.9545	0.6155
Sema et al. [33]	sTfR	4.5 mg/L	0.77	0.67	0.44
	sTfR index		0.69	0.78	0.47
Lee et al. [34]	sTfR	1.8 mg/L	0.97	0.88	0.85
	sTfR index	1.36	1	0.98	0.98
Sandra et al. [27]	sTfR	1.5 mg/L	0.886	0.961	0.847
	sTfR index	1.35	0.863	0.961	0.824
Punnonen et al. [10]	sTfR	2.7 mg/L	0.94	0.94	0.88
	sTfR index	1.5	0.98	1	0.98
Pantelis et al. [35]	sTfR	1.8 mg/L	0.81	0.80	0.61
	sTfR index	1.4	0.91	0.92	0.83
Vazquez et al. [36]	sTfR	2.5 mg/L	0.38	0.92	0.924
	sTfR index	2	0.89	0.96	0.85
Geon Park et al. [37]	sTfR	1.89 mg/L	1	0.924	0.924
	sTfR index	1.62	1	1	1
Majkic S. et al. [38]	sTfR	1.95 mg/L	0.78	0.909	0.689
	sTfR index	1.23	0.703	0.834	0.537
Leers et al. [39]	sTfR	4.3 mg/L	0.79	0.82	0.61
	sTfR index	2.5	0.87	0.96	0.83

The calculated positive and negative LRs of [1], [10], [34]-

[37] and [39] show that the sTfR index is superior overall when compared with sTfR and the resulting positive and negative LRs of [32], [33] show that the sTfR index is superior overall for confirming the presence of disease when compared with sTfR. On the other hand, the calculated positive and negative LRs of [27] and [38] show that the sTfR is superior overall when compared with sTfR index. However, the calculated positive and negative LRs of sTfR and sTfR index show that both are effective tests, but sTfR index is superior overall when compared with sTfR. The LR graph is plotted using overall combined true positive rate (TPR) and false positive rate (FPR) of sTfR and sTfR index and is shown in Fig. 4, where the red point shows sTfR and the blue point shows sTfR index values. It can also be confirmed from LR graph that the sTfR index is superior overall when compared with sTfR.

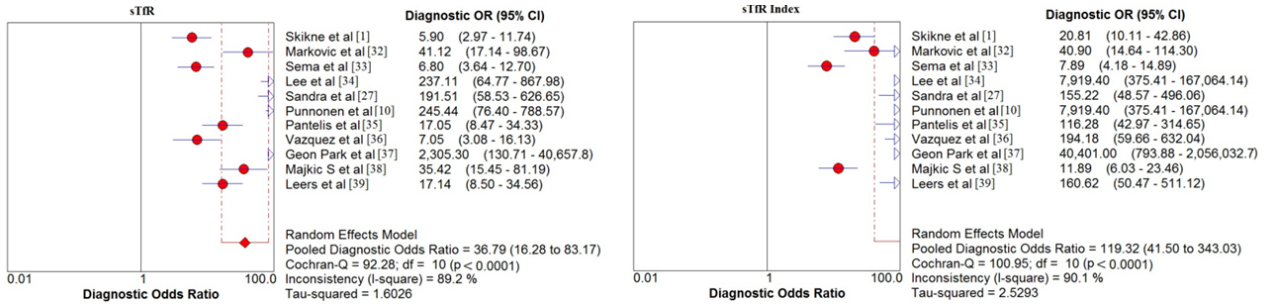

Fig. 1 The forest plots of the random overall DOR of sTfR and sTfR index showing that the pooled DOR is higher for sTfR index

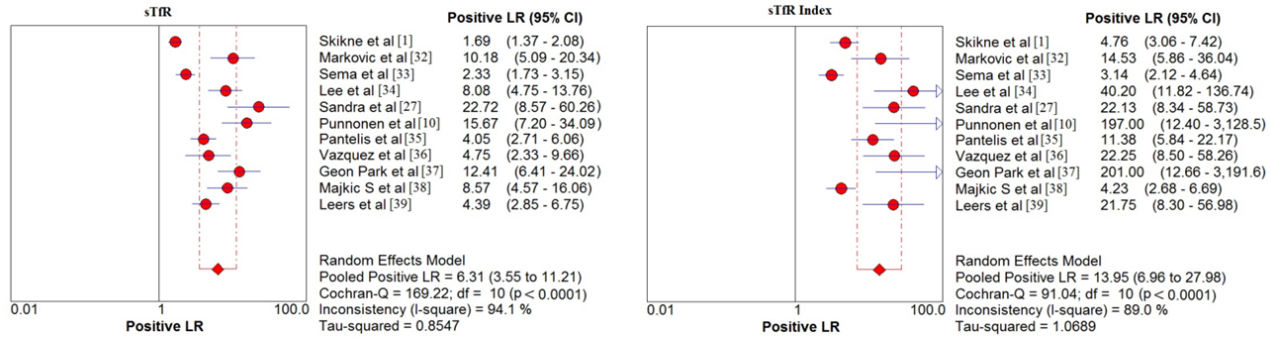

Fig. 2 The forest plots of the overall combined positive LR of sTfR and sTfR index indicating that the pooled positive LR of sTfR index is higher than sTfR

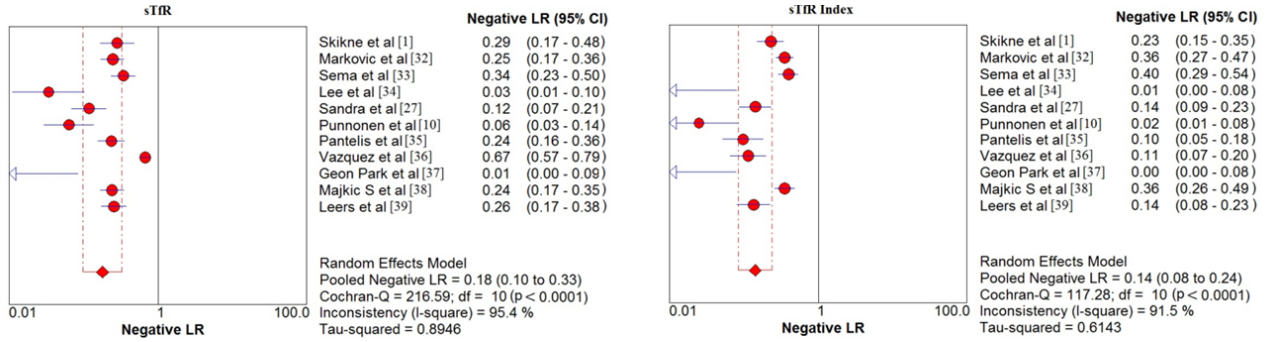

Fig. 3 The forest plots of the overall combined negative LR of sTfR and sTfR index indicating that the pooled negative LR of sTfR index is less than sTfR

The analysis for overall sensitivity and specificity of sTfR and sTfR index is also performed. The forest plots of the sensitivity and specificity for both sTfR and sTfR index are shown in Figs. 5 and 6, respectively. The overall pooled sensitivity of sTfR and sTfR index is 81% (CI = 79%-84%) and 85% (CI = 83%-87%) respectively (for sTfR: Chi-square = 177.92, $p < 0.0001$, $I^2 = 94.4\%$; for sTfR index: Chi-square = 143.15, $p < 0.0001$, $I^2 = 93\%$). The overall pooled specificity of sTfR and sTfR index is 84% (CI = 82%-86%) and 93% (CI = 91%-94%) respectively (for sTfR: Chi-square = 132.16, $p < 0.0001$, $I^2 = 92.4\%$; for sTfR index: Chi-square = 84.83, $p < 0.0001$, $I^2 = 88.2\%$).

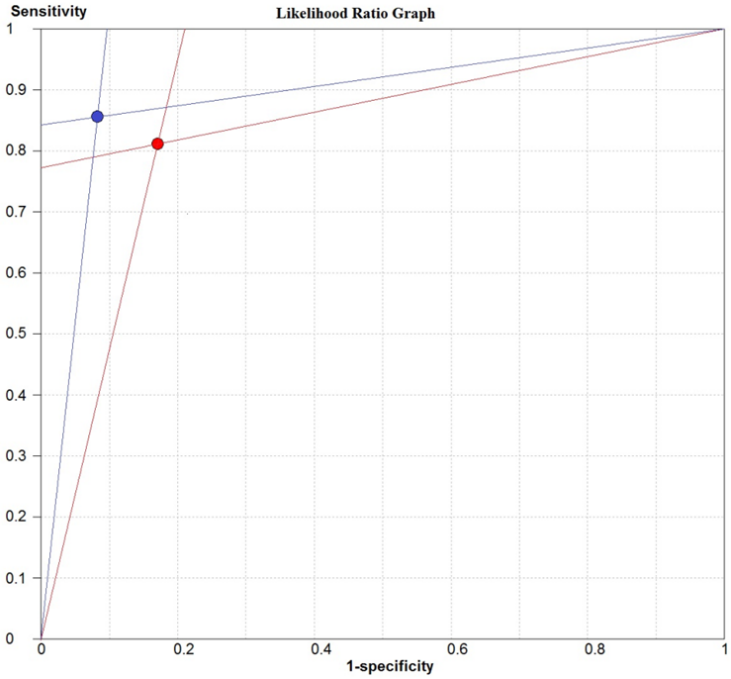

Fig. 4 The LR graph comparing sTfR and sTfR index using overall TPR and FPR (Red point: sTfR; Blue Point: sTfR index)

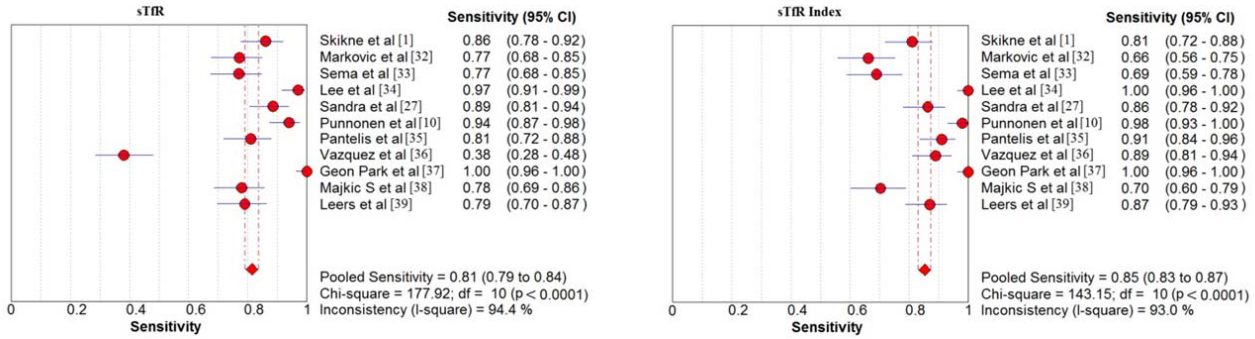

Fig. 5 The forest plots of the overall sensitivity of sTfR and sTfR index showing that the pooled sensitivity is higher for sTfR index

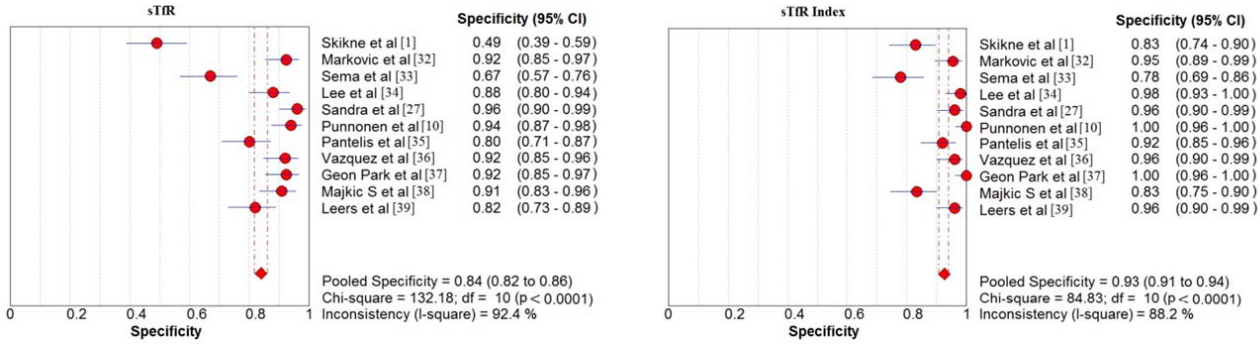

Fig. 6 The forest plots of the overall specificity of sTfR and sTfR index showing that the pooled specificity is higher for sTfR index

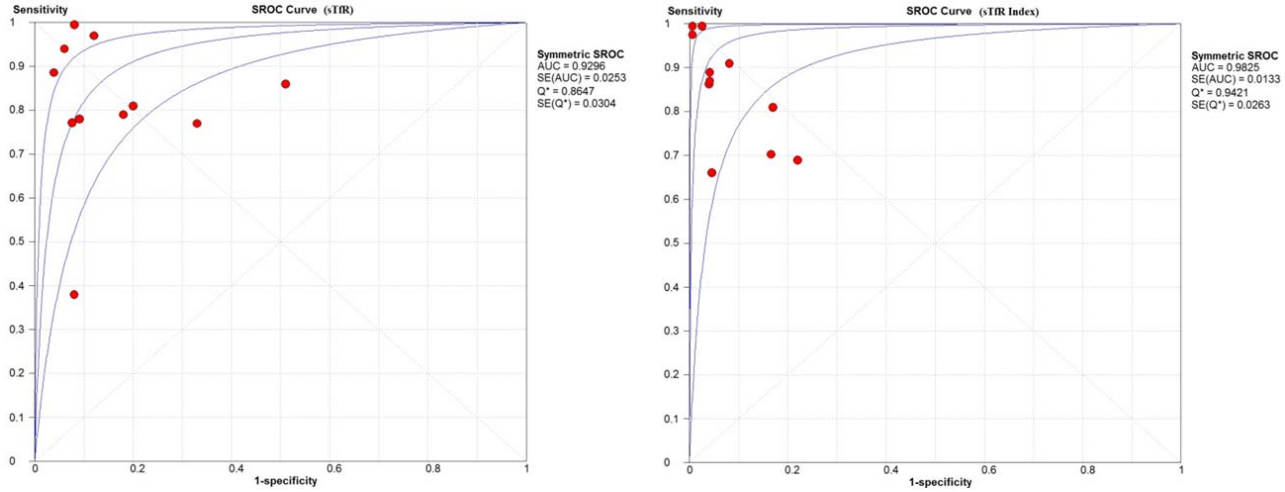

Fig. 7 The SROC curve analysis of sTfR and sTfR index showing diagnostic accuracy of both tests

The SROC curves are plotted and shown in Fig. 7 for both sTfR and sTfR index, where each point represents a study contributing to SROC curve. In case of sTfR, the SROC curve shows a large CI compared to sTfR index. The AUC of sTfR and sTfR index resulting from the SROC curves is 0.9296 and 0.9825 respectively. The standard error (SE) of the AUC for sTfR and sTfR index is 0.0253 and 0.0133 respectively. The Q^* values resulting from the intersection of SROC curves with the diagonal line where sensitivity equals specificity are found to be 0.8647 and 0.9421 respectively for sTfR and sTfR index (for sTfR: SE = 0.0304; for sTfR index: SE = 0.0263). The AUC of sTfR and sTfR index shows that both are good tests in the differential diagnosis of IDA and ACD, but sTfR index is better when compared with sTfR.

IV. Conclusion

The purpose of this study is to evaluate and compare the diagnostic performance of sTfR and sTfR index tests in the differential diagnosis of IDA or IDA+ACD and ACD. The comparison between sTfR and sTfR index is performed using a subset of 11 studies. The overall DOR for sTfR and sTfR index are calculated and found to be 36.79 and 119.32 respectively. The overall sensitivity, specificity, positive LR and negative LR values are also calculated for both sTfR and sTfR index. The overall ORs and positive and negative LR values suggests that sTfR index is overall superior when compared with sTfR. The SROC analysis is also performed and the AUC was found to be 0.9296 and 0.9825 respectively for sTfR and sTfR index. The SROC analysis revealed that both tests are useful, but the sTfR index seems to be more effective than sTfR.

References

[1] S. S. Barry, P. Kari, and H. C. Paul et al., "Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the stfr/log ferritin index," *Am J Hematol*, vol. 86, pp. 923–927, 2011.

[2] W. Guenter, and T.G. Lawrence, "Anemia of chronic disease," *N Engl J Med*, vol. 352, pp. 1011–1023, 2005.

[3] I. Ilenia, B. Federica, and D. Alberto et al., "Soluble transferrin receptor (stfr) and stfr/log ferritin index for the diagnosis of iron-deficiency anemia a meta-analysis," *Am J Clin Pathol*, vol. 138, pp. 642–649, 2013.

[4] A. B. Carl, R. A. Edward, and E. B. David, "Tietz textbook of clinical chemistry and molecular diagnostics," Elsevier Health Sciences, 2012.

[5] F. G. Andrew, W. J. Martin, and S. M. Alistair et al., "Guidelines for the management of iron deficiency anaemia," Gut 2011; gut–2010.

[6] M. Manuel, A. G. Jose, and R. Francisco, "Disorders of iron metabolism. Part ii: iron deficiency and iron overload," *J. Clin. Pathol*, vol. 64, pp. 287–296, 2011.

[7] J. F. Beverly, S. Barry, and M. Karen et al., "Serum transferrin receptor distinguishes the anemia of chronic disease from iron deficiency anemia," *J Lab Clin Med*, vol. 119, pp. 385–390, 1992.

[8] J. E. ALLAN, "Anemia of chronic disease," fifth ed., McGraw-Hill, New York, 1995.

[9] N. N. Alan, N. D. Emmanuel, and B. K. Sanford, "The pathogenesis of anemia in rheumatoid arthritis: a clinical and laboratory analysis," *In Seminars in arthritis and rheumatism*, vol. 19, pp. 209–223, 1990.

[10] P. Kari, I. Kerttu, and R. Allan, "Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency," *Blood*, vol. 89, pp. 1052– 1057, 1997.

[11] B. Fernando, and G. Santiago et al., "A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases," *World J Gastroenterol*, vol. 15, pp. 4638–4643, 2009.

[12] B. Z. Michael, "Methods to assess iron and iodine status," *Br. J. Nutr*, vol. 99, pp. S2–S9, 2008.

[13] A. B. Beth, D. H. James, and T. Ayalew, "A bone marrow report of absent stainable iron is not diagnostic of iron deficiency," *Ann Hematol*, vol. 80, pp. 166–169, 2001.

[14] M. S. Marijn, S. Reinhart, and R. D. Joris, "Biological and clinical aspects of soluble transferrin receptor," *Crit. Rev. Clin. Lab. Sci*, vol. 47, pp. 213–228, 2010.

[15] S. Barry, "Serum transferrin receptor," *Am J Hematol*, vol. 83, pp. 872–875, 2008.

[16] T. Ketil, and R. Inge, "The transferrin receptor: its diagnostic value and its potential as therapeutic target," *Scand J Clin Lab Invest*, vol. 53, pp. 113–120, 1993.

[17] K. Yutaka, N. Yoshiro, and K. Hitoshi et al., "Serum transferrin receptor as a new index of erythropoiesis," *Blood*, vol. 70, pp. 1955–1958, 1987.

[18] A. Namanjeet, J. L. Carol, and B. Robert et al., "Iron deficiency and anemia of chronic disease in elderly women: a discriminant analysis approach for differentiation," *Am J Clin Nutr*, vol. 61, pp. 590–596, 1995.

[19] C. H. Flowers, B. S. Skikne, and A. M. Covell et al., "The clinical measurement of serum transferrin receptor," *J Lab Clin Med*, vol. 114, pp. 368–377, 1989.

[20] M. Basora, R. Deulofeu, and F. Salazar et al., "Improved preoperative iron status assessment by soluble transferrin receptor in

elderly patients undergoing knee and hip replacement," *Clinical & Laboratory Haematology*, vol. 28, pp. 370–375, 2006.
[21] J. D. Cook, B. S. Skikne, and R. D. Baynes, "Serum transferrin receptor," *Annu Rev Med*, vol. 44, pp. 63–74, 1993.
[22] K. Punnonen, K. Irjala, and A. Rajamäki, "Iron-deficiency anemia is associated with high concentrations of transferrin receptor in serum," *Clin. Chem*. vol. 40, pp. 774–776, 1994.
[23] B. S. Skikne, C. H. Flowers, and J. D. Cook, "Serum transferrin receptor: a quantitative measure of tissue iron deficiency," *Blood*, vol. 75, pp. 1870–1876, 1990.
[24] F. J. Baillie, A.E. Morrison, and I. Fergus, "Soluble transferrin receptor: a discriminating assay for iron deficiency," *Clinical & Laboratory Haematology*, vol. 25, pp. 353–357, 2003.
[25] T. Berlin, A. Meyer, and P. Rotman et al., "Soluble transferrin receptor as a diagnostic laboratory test for detection of iron deficiency anaemia in hospitalized patients with acute illness," *Isr Med Assoc J*, vol. 13, pp. 96–108, 2011.
[26] B. Yves, "Soluble transferrin receptor for the evaluation of erythropoiesis and iron status," *Clinica Chimica Acta*, vol. 329, pp. 9–22, 2003.
[27] M. Sandra, F. Dragica, and K. Marina et al., "Soluble transferrin receptor and transferrin receptor-ferritin index in iron deficiency anemia and anemia in rheumatoid arthritis," *Clin. Chem. Lab. Med*, vol. 43, pp. 326–331, 2005.
[28] S. Pauli, M. Timo, and R. ALLAN et al., "Single values of serum transferrin receptor and transferrin receptor ferritin index can be used to detect true and functional iron deficiency in rheumatoid arthritis patients with anemia," *Arthritis & Rheumatism*, vol. 43, pp. 1016, 2000.
[29] M. Akira, B. Masami, and M. Shigehisa et al., "Diagnostic significance of serum soluble transferrin receptors in various anemic diseases: the first multi-institutional joint study in japan," *Haematologia*, vol. 32, pp. 225–238, 2002.
[30] Z. Javier, A. Victor, and M. Alfonso et al., "Meta-disc: a software for meta-analysis of test accuracy data," *BMC Med Res Methodol*, vol. 6 , pp. 31, 2006.
[31] J.B. Brad et al., "Comparing diagnostic tests: a simple graphic using likelihood ratios," *Stat. Med,* vol. 19, pp. 649–663, 2000.
[32] M. Markovic, S. Majkic, and V. Subota, "Usefulness of soluble transferrin receptor and ferritin in iron deficiency and chronic disease," *Scand J Clin Lab Invest*, vol. 65, pp. 571–576, 2005.
[33] G. Sema, E. Nilgun, and A. K. Mehmet et al., "Soluble transferrin receptor and soluble transferrin receptor-ferritin index for evaluation of the iron status in elderly patients," *Tohoku J Exp Med*, vol. 202, pp. 135–142, 2004.
[34] J. L. Eun, O. E. Eun, and P. Yeon-Joon et al., "Soluble transferrin receptor (stfr), ferritin, and stfr/log ferritin index in anemic patients with nonhematologic malignancy and chronic inflammation," *Clin. Chem*, vol. 48, pp. 1118–1121, 2002.
[35] O. Pantelis, E. K. Ioannis, and M. Ippokratis et al., "Soluble transferrin receptor-ferritin index in the evaluation of anemia in inflammatory bowel disease: a case-control study," *Ann Gastroenterol*, vol. 24, pp. 108–114, 2011.
[36] L. Vazquez, C. Amparo, L. Francisco et al., "The usefulness of serum transferrin receptor for discriminating iron deficiency without anemia in children," *Haematologica*, vol. 91,pp. 264–265, 2006.
[37] P. Geon, P. Young, and J. Sook et al., "Soluble transferrin receptor-ferritin index and estimated body iron in iron-deficiency anemia in select chronic diseases," *Ann Hematol*, vol. 88, pp. 913–915, 2009.
[38] M. Markovic, S. Majkic, and S. Ignjatovic et al., "Reticulocyte haemoglobin content vs. soluble transferrin receptor and ferritin index in iron deficiency anaemia accompanied with inflammation," *International journal of laboratory hematology*, vol. 29, pp. 341–346, 2007.
[39] M. P. Leers, J. F. Keuren, and W. P. Oosterhuis, "The value of the thomas-plot in the diagnostic work up of anemic patients referred by general practitioners," *International journal of laboratory hematology*, vol. 32, pp. 572–581, 2010.