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 for both sTfR and sTfR/log ferritin index were 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 I² 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).
The calculated positive and negative LRs of [1], [10], [34]-
and [39] show that the sTR index is superior overall when compared with sTR. The LR graph is plotted using overall combined true positive rate (TPR) and false positive rate (FPR) of sTR and sTR index and is shown in Fig. 4, where the red point shows sTR and the blue point shows sTR index values. It can also be confirmed from LR graph that the sTR index is superior overall when compared with sTR.

The analysis for overall sensitivity and specificity of sTR and sTR index is also performed. The forest plots of the sensitivity and specificity for both sTR and sTR index are shown in Figs. 5 and 6, respectively. The overall pooled sensitivity of sTR and sTR index is 81% (CI = 79%-84%) and 85% (CI = 83%-87%) respectively (for sTR: Chi-square = 177.92, p < 0.0001, I² = 94.4%; for sTR index: Chi-square = 143.15, p < 0.0001, I² = 93%). The overall pooled specificity of sTR and sTR index is 84% (CI = 82%-86%) and 93% (CI = 91%-94%) respectively (for sTR: Chi-square = 132.16, p < 0.0001, I² = 92.4%; for sTR index: Chi-square = 84.83, p < 0.0001, I² = 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
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 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


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


