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# Role of Soluble Transferrin Receptor and Transferrin Receptor-Ferritin Index to Detect Iron Deficiency Anemia in Regular Hemodialysis Patients

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**Keywords:** Regular hemodialysis; Iron deficiency anaemia; sTfR; TfR-F index

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**Abstract**

**BACKGROUND:** Several iron indicators can be used to detect iron deficiency anaemia (IDA) where confounding comorbidities occurred such as patients with regular hemodialysis.

**AIM:** This study was aimed to determine the diagnostic value of serum transferrin receptor (sTfR) and transferrin receptor-transferrin index (TfR-F index) and to combine these two markers in detecting IDA in regular hemodialysis anaemic patients.

**METHODS:** There were 70 patients recruited consecutively. IDA was diagnosed based on TS < 20% and ferritin level < 200 ng/L and functional iron deficiency when TS < 20% and ferritin > 200 ng/L. TfR-F index calculated as sTfR/log ferritin.

**RESULTS:** Correlation of ferritin to iron level was changed when its correlation adjusted by confounding inflammation (CRP level > 10). The correlation strength of ferritin to iron serum before adjusted was r = 0.37 with p = 0.02 but became r = 0.65 with p = 0.023 after adjusted to CRP > 10. In inflammation (CRP > 10), ferritin mild-moderately correlated with iron but became moderately strong when there was no inflammation (CRP < 10). AUC for sTfR was 0.77 with p = 0.028 (95% CI 0.55-0.99), and for TfR-F index has larger AUC 0.85% with p = 0.004 (95%CI 0.69-1.00), hence TfR-F index more superior than sTfR. sTfR and sTfR-F index were not correlated with CRP with p > 0.05, and sTfR and TfR-F index mean level was different between IDA and ACD patients although not statistically significant.

**CONCLUSION:** When sTfR and the TfR-F index used in combination to detect IDA, we found the largest AUC on ROC 0.98 (95% CI 0.94-1.00).

## Introduction

Anaemia is a well-known problem in chronic kidney disease (CKD) especially end-stage renal disease who need regular hemodialysis (RH) leading to higher morbidity and mortality rate. Anaemia affects 49-55% of patient with CKD and more prevalent once diseases become more advanced. Moreover, in the population-based survey, anaemia is an essential indicator of iron deficiency [1], [2], [3]. Although many conditions contributing to anaemia in CKD patients such as the diminished production of erythropoietin stimulating agent (ESA), blood loss due to bleeding disorders and frequent laboratory test, impaired of iron absorption and iron retention within reticuloendothelial [4], every anaemia should be defined of its original causes to be well managed. ESA according to KDOQI is one of many important treatment options for anaemia in CKD patients, and to achieve a maximal response, iron status should be determined. Unresponsiveness to ESA treatment is defined when iron availability in time for erythropoiesis deficient, therefore iron management is an essential element for anaemia in CKD patients. There were two major iron disorders in this group of patients' absolute iron deficiency and functional iron deficiency. These two different iron deficiency (ID) might be hard to

distinguish since definitive tools for each of those conditions is lacking [5], [6].

Several iron indicators can be used to detect iron deficiency anaemia (IDA) in a setting where confounding comorbidities co-occur such as patients with RH. The most available iron indicators for IDA in the complicated area are transferrin saturation (TS) and ferritin level [4], [7]. But these two indicators have been known affected by inflammation where hemodialysis itself, an inflammation condition through uremic toxin, underlying diseases, hemodialysis process, making their interpretation hindered by physiologic factors and cause failure to detect ID status [8], [9]. The best diagnostic tool to identify IDA in CKD is still iron stained bone marrow aspiration (BMA) but because BMA is invasive, could not be used as a standard of care in daily practice. Therefore more convenient non-invasive and reliable enough method to detect iron status is needed. Recently two markers emerged, e.g., soluble transferrin receptor (sTfR) and the ratio of sTfR/log ferritin (TfR-F index) as a new promising indicator that can differentiate IDA with others especially anaemia of chronic disease (ACD). These two markers not entirely influenced by concurrent chronic disease as well as inflammation [4], [10], [11], [12].

sTfR is a monomer glycoprotein that detached from transmembrane TfR protein after truncated and lost their first 100 amino acid then released into the blood became sTfR. While TfR-F index is calculated from rationing sTfR over logarithm of ferritin, there was a close linear relationship between TfR-F index and iron store. Their value may be negative in the condition where iron is in a deficit state to maintain normal haemoglobin level [13]. The Clinical role of sTfR in identifying IDA patients has been studied in numbers of researches. Majority of these studies support the value of sTfR to detect ID and be able to differentiate IDA from ACD [14], [15], [16], [17]. However, Fussaro et al. showed sTfR was not much better than TS or ferritin to detect ID in patients with CKD [18]. Data from thalassemia population revealed sTfR is a diagnostic tool with moderate accuracy to detect IDA patient, as well as in sickle cell anaemia sTfR level reflecting more to erythropoietic activity than to ID [19], [20]. Punnonen et al. presented that TfR-F index has higher sensitivity and specificity to distinguish IDA from ACD and this ratio has corroborated by several other studies [4], [21], [22]. However a recent meta-analysis by Infusino et al. claimed that sTfR has better clinical performance than TfR-F index in identifying IDA [23].

This study aim was to determine the diagnostic value of sTfR and TfR-F index and to combine these two markers in detecting IDA in RH anaemic patients.

## Material and Methods

This observational cross-sectional study was performed to determine the diagnostic value of sTfR and TfR-F index to detect IDA in RH anaemic patients at Sanglah Hospital Bali. There were 70 patients recruited consecutively and agreed to sign an informed consent approved by the Institutional Review Board of Sanglah hospital by the ethical principles of the Declaration of Helsinki. IDA was diagnosis based on TS < 20% and ferritin level < 200 ng/L and functional ID when TS < 20% but ferritin > 200 ng/L [24], [25], [26]. Medical history, physical examination, conventional haematology parameters including CBC, Iron serum, Total iron binding capacity (TIBC), ferritin serum, haemoglobin level, CRP, sTfR were studied. sTfR was measured using Biovender Human ELISA kit on RD 1940 11100. TfR-F index calculated as sTfR/log ferritin [4], [21].

**Table 1: Characteristics of study subjects**

| Characteristics | Number (mean or %) |
|---|---|
| Gender | |
| Male | 40 (57.1) |
| Female | 30 (42.9) |
| Age (year), median (min-max) | 51 (23-60) |
| BMI (kg/m$^2$), mean ± SD | 21.35 ± 2.14 |
| Hemoglobin (gram/dl), mean ± SD | 7.77 ± 1.24 |
| MCV (fl), mean ± SD | 88.45 ± 6.07 |
| MCHC (%), mean ± SD | 30.41±2.01 |
| MCH (pg), mean ± SD | 27.22±2.58 |
| RDW (%), mean ± SD | 14.65±2.09 |
| SI (μg/dl), median (min-max) | 58.67 (11.52-316.80) |
| TIBC (μg/dl), median (min-max) | 175.00 (91.00-701.00) |
| Ferritin (ng/ml), median (min-max) | 795.65 (24.35-3944.00) |
| Transferrin saturation (%), median (min-max) | 34.67 (4.93-99.62) |
| CRP (mg/L), median (min-max) | 24.82 (1.00-92.09) |
| sTfR (μg/ml), median (min-max) | 0.61 (0.16-4.23) |
| IDA, n (%) | 6 (8.57) |
| ACD, n (%) | 18 (25.7) |
| TfR-F index, median (min-max) | 0.28 (0.05-3.05) |

BMI: Body Mass Index; MCV: Mean Corpuscular Volume; MCHC: Mean Corpuscular Hemoglobin Concentration; MCH: Mean Corpuscular Hemoglobin; RDW: Red Cell Distribution Width; SI: Serum Iron; TIBC: Total Iron Binding Capacity; CRP: C-Reactive Protein; sTfR: Soluble Transferrin Receptor; IDA: Iron Deficiency Anemia; ACD: Anemia of Chronic Disease; TfR-F index: TfR/log ferritin ratio.

Statistical analysis was performed using SPSS software for windows with p-value < 0.5 indicating statistical significance. ROC (receiver operating curve) was performed, and the AUC (area under the curve) was calculated to assess the power of sTfR and TfR-F index to detect IDA in RH anaemic patients. The AUC is a measure of test accuracy, with the largest area under curve indicating the better test. The optimal cut-off value of sTfR and TfR-F index were determined using ROC curve for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), the accuracy of the test. The closer the curve to the upper left corner of the plot the more accurate the test was. In this study, the cut-off value was selected to the point where sensitivity slightly overwhelming specificity by the goal of sTfR and TfR-F index to screen more IDA patients. Multiple regression analysis was performed to compare the AUC area of sTfR, TFR index and when sTfR and TfR-F index were combined. Person's correlation analysis was also performed to evaluate the possible

connections of each parameter especially main iron indicators to inflammation marker.

## Results

Out of 70 patients enrolled in this study, 40 (57.1%) were male, and 30 (40.2%) were female. A total of 6 patients (8.57%) and 18 patients (25.7%) were with IDA and ACD, respectively. Characteristics of the study subjects are presented in Table 1.

Correlation of serum ferritin with serum iron is depicted in Table 2. It could be seen that the strength was altered due to the existence of inflammation (CRP).

**Table 2: Partial correlation between serum ferritin and iron**

| | CRP < 10 (No Inflammation) | | CRP < 10 (With Inflammation) | |
|---|---|---|---|---|
| | Correlation coef | p | Correlation coef | p |
| Ferritin | 0.648 | 0.23 | 0.321 | 0.016 |

CRP: C-Reactive Protein.

In Table 3, no correlation observed between new indicators chosen with inflammation (CRP), although these new iron indicators (STFR and TFR index) differed between IDA and Non-IDA (Table 4). However, the difference was not significant ($p > 0.05$).

**Table 3: Correlation of STFR and TFR index with CRP**

| Variable | Correlation coef | p |
|---|---|---|
| sTfR | -0.129 | 0.287 |
| TfR-F index | -0.76 | 0.531 |

sTfR: Soluble Transferrin Receptor; TfR-F index: TfR/log ferritin ratio.

Our study revealed that AUC (area under curve) for sTfR was 0.77 with $p = 0.028$ (95% CI 0.55-0.99). The cut-off value, at its maximum sensitivity of 83.3% and specificity of 67.2%, was 0.71. The TfR-F index has larger AUC, which is 0.85, with $p = 0.004$ (95% CI 0.69-1.00).

**Table 4: Mean difference between IDA with Non-IDA**

| | IDA (n = 6) | Non-IDA (n = 64) | p |
|---|---|---|---|
| sTFR | -0.0946 | 0.2368 | 0.474 |
| TfR-F index | -0.0124 | 0.6772 | 0.141 |

sTfR: Soluble Transferrin Receptor; TfR-F index: TfR/log ferritin ratio.

The cut-off value, at its best sensitivity of 83.3% and specificity of 81.2%, was 0.33. The TfR-F index was superior compared to sTfR, as seen in Figure 1A. When sTfR and TfR-F index were used in combination to determine the existence of IDA in regular hemodialysis patients (Figure 1B), it was found that they carry the largest AUC, which is 0.98 (95% CI 0.94-1.00).

A) B)

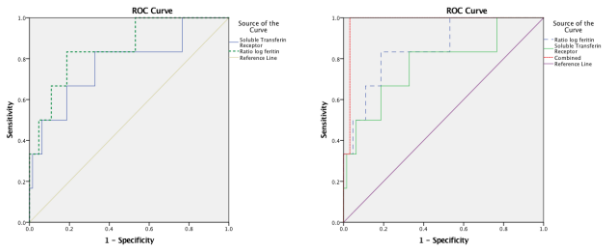


*Figure 1: A) The receiver operating curve (ROC) of sTfR and TfR-F index to detect IDA in RH patients. B) The receiver operating curve (ROC) of sTfR and TfR-F index combination to detect IDA in RH patients*

## Discussion

CKD is a steady, gradual progressive chronic disease where kidney functions finally diminished, and this group of patients will mostly require RH with a higher mortality rate when compared to the general population [27], [28]. Data from 5 European countries in DOPP study found that the prevalence of anaemia in RH patients was 49% (by the year 1989-1999) – 55% (by the year 2000) [29]. Among three main type of anaemia in CKD population which are decreased ESA production due to kidney disorders, anaemia of chronic disorder and IDA, IDA in CKD population in term of clinical practice posed substantial challenges [30]. There was numerous and multifactorial process contributed including occult bleeding, chronic bleeding, defect in iron absorption because of inflammation, frequent laboratory testing, massive ESA treatment with supraphysiologic erythropoiesis. The annual blood loss estimated to be 1.5-3 gram [1], [30]. Besides absolute ID where iron storage is severely reduced or absent in bone marrow, however patient on RH also have the functional ID that partly related to ESA treatment and ACD due to inflammatory state of its underlying pathologic [31]. This functional ID markedly defines by sufficient iron store on body tissue but lack of iron availability for erythropoietic processed [5], [6], [32].

Our present study found that 6 (8.6%) patient with IDA using TS < 20% and ferritin < 200 ng/L, and 18 (25.7%) with functional ID based on KDOQI, Pernefri, and Bahrainwalla et al., [3], [24], [26]. It is generally believed that ID should clinically determine whether an absolute iron deficiency or functional iron deficiency is. However, this separation is often practically impossible to delineate. One clue to hold that help determined functional ID related to inflammation is retrospectively by observing ESA treatment responses of intravenous iron with or without concomitant raise of ESA dose and decreased ferritin level [32]. It is well known that TS and ferritin

are not proper iron indicators in the setting of inflammation because of the confounding effect of immune response to inflammation could compromising the true role of TS and ferritin. Ferritin is a positive acute phase protein where its level increased begin early during inflammation reach its peak in a week. From an experimental longitudinal study on serum ferritin, reported that ferritin level reaches its maximal after 3 days and gradually returned to the normal level in the next 10 days [1]. The confounding effect of inflammation can mislead conclusion whether over or underestimate of ID prevalence. According to BRIDA (Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia) project to assess the effect of inflammation on ferritin level to estimate ID, one should consider regression correction factors. The study performed on 29765 pre-school children and 25731 women of reproductive age using CRP and a1-acid glycoprotein (AGP) as a marker of inflammation reported that regression correction changes the estimated prevalence of ID in pre-school by median + 25 percentage points when ferritin serum was used [33]. BRIDA project suggested the need to determine marker of inflammation when assessing iron indicators status even at the population level [34], e.g., CRP for acute inflammation (rapid onset within hours) or AGP (late rising in 24 hours and lasted 4-5 days) for chronic inflammation [35]. The precise underlying pathophysiologic how inflammation influence and change iron indicators are yet to be defined. Inflammation and iron status (nutrition in a broad sense) are well connected in a way bidirectionally such that nutrition disorders can compromise immune function. Also, inflammation through immune response released acute phase protein ferritin and also hepcidin in order to withhold iron that certain microbe growth desperately depends on [1]. Disorder of iron metabolism happened because acute phase protein ferritin, transferrin, hepcidin have their ability to disturb the distribution of iron in every cell of the human body. Whether acute inflammation resulted from infection or injury, or chronic inflammation causes metabolic disturbance through releasing cytokines, and this can affect the regulation and production of the acute hepatic protein that contributed to the disorder of iron metabolism. Besides, several studies support the notion that during inflammation iron absorption on gastrointestinal also is compromised [33], [36].

In this study, we found that the correlation of ferritin to iron level was changed when its correlation adjusted by confounding inflammation (CRP level > 10). The correlation strength of ferritin to iron serum before adjusted was r = +0.37 with p = 0.02 but became r = +0.65 with p = 0.023 after adjusted to CRP > 10. In the setting of inflammation (CRP > 10), ferritin mild-moderately correlated to iron but became moderately strong when there was no inflammation (CRP < 10) where ferritin level truly represents tissue iron storage. In the future, knowledge about inflammation biomarkers should fill the gaps whether specific causes of inflammation (e.g., infection, injury, arthritis, malignancy, obesity, autoimmune diseases) also have their influence on each and specific iron indicators status. For example, the liver disease where ferritin is produced may directly cause a higher level of ferritin without followed by an increased level of inflammation biomarkers [33].

Using sTfR and TfR-F index to identify IDA in RH anaemic patient, we found that our results also corroborated several other studies that confirmed sTFR and TfR-F index have a significant role to detect IDA in the setting of confounding inflammation such as regular hemodialysis. We found AUC for sTfR was 0.77 with p = 0.028 95% CI 0.55-0.99, and for TfR-F index has larger AUC 0.85% with p = 0.004 95%CI 0.69-1.00. A prospective multicenter study to differentiate IDA and ACD conducted by Skikne et al., using sTfR and TfR-F index, reported that sTfR has AUC 0.74% with p < 0.0001 95%CI 0.66-0.83, and TfR-F index has larger AUC of 0.87% with p < 0.0001 hence more superior than sTfR in detecting IDA in the setting of inflammation. Bone marrow iron stained as golden standard was not used, but established opinion and practice for diagnosis and classification of anaemia were followed. Another study also found sTfR and TfR-F index value are useful parameters in assessing iron status in CKD patients. However, they were best in complementing to existing indices of serum ferritin and TS. TfR-F index also showed more superior than sTfR in distinguishing IDA and ACD [37]. The study using bone marrow iron staining as the golden standard for IDA which only pure no stained iron was considered IDA, meanwhile +1 to +6 iron staining considered non-IDA [4]. Study on inflammatory bowel disease and regular hemodialysis on ESA treatment also reported that TfR-F index is more accurate at distinguishing between IDA and ACD [26], [28], [38], [39]. The superiority of TfR-F index over sTfR was not so surprising since this index was derived from two elements that reciprocally associated (sTfR increased, and ferritin decreased) affected by ID. Moreover, especially in RH patients, ID was partly related to inflammation status that can increase ferritin level [4], [37].

TfR-F index has been found to have close, linear relationships with stored iron expressed as per kg body weight. This finding resulted from the experimental study that performs repeated phlebotomy of 14 healthy subjects where sTfR and ferritin were measured consecutively in serial [22]. A longitudinal study of 129 anaemic hospital patients observed that TfR-F index increased in IDA but not in ACD patient [21]. Peterson et al. reported that TfR-F index was decreased in ACD, but increased in IDA and patient with mixed IDA and ACD [40]. These studies again supported TfR-F index was a useful tool to detect IDA in the complicated area [41]. However, a recent meta-analysis by Infusino et al. showed that

the TfR-F index was no better than sTfR in detecting IDA in the presence of confounding condition [23].

sTfR is a soluble fragment of membrane-bound TfR that truncated from nearly all cells mostly from erythroblast and reticulocyte, has become easier to perform in the past 10 years and can be measured quantitatively. It is sensitive to represent iron availability during the erythropoietic process in bone marrow and other tissue as well as represent tissue iron status. sTfR increased in absolute ID and during stimulated erythropoietic either post ESA treatment or other condition such as thalassemia, sickle cell anaemia, hemolytic anaemia. In the situation where marrow activity is depressed due to hypoplasia, chemotherapy-induced marrow depressed, sTfR concentration decreased [10], [17], sTfR level can range from 8 times below normal to 20 times above the normal level [1]. A study in Pakistan reported sTfR in RH patients could differentiate between iron replete and iron deplete [42]. sTfR also represent iron availability during erythropoiesis activity supported by a study of Yin et al., through GEE model, sTfR was found significantly associated with the time point when hemodialysis was performed, meaning iron availability in time for undergoing erythropoietic process making sTfR an important marker of erythropoietic [43].

Our study also found out sTfR, and the TfR-F index was not correlated with CRP with $p > 0.05$, and sTfR and TfR-F index mean level was different between the patient with ADB and ACD although not statistically significant due to low power (small samples size). When sTfR and TfR-F index use in combination to detect IDA, we found the largest AUC on ROC 0.98 95%Ci 0.94-1.00. These findings also other studies claimed that sTfR less influenced by inflammation and can be used to determine IDA in the situation where inflammation and infection co-exist. The limitation of our study was not using iron stained bone marrow as a golden standard to determine IDA patient due to inconvenience and invasiveness. STFR was measured by Biovender Human sTfR ELISA kit on RD 194011100, not the one that WHO recommended [44]. There is no international reference standard exist for sTfR assay. It is impossible to compare single threshold value that would be accurate for all commercial kits and chemical device [14]. Since every available commercial kit is method-dependent, and this difference may cause by the disparity of TFR preparation used as standard and raise antibodies [14], [16], [45].

In conclusion, this study conclusion was sTfR, and TfR-F index proved to be important tools to determine IDA in RH anaemic patients and TFR index has superior accuracy than sTfR. When sTfR and TfR-F index used in combination, their diagnostic value reaches the best.

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