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Evaluation of serum transferrin receptor level in Children Undergoing Regular Hemodialysis

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ABSTRACT

Background: Patients with chronic kidney disease (CKD) are at risk for anemia as a result of a variety of factors. Blood ferritin levels are an indicator of iron, while blood transferrin receptor (sTfR) levels are an indicator of how much iron is available for cells to use.

Objective: It was the goal of this work to determine the diagnostic value of serum soluble transferrin receptor (sTfR) in children undergoing regular hemodialysis in Pediatric Nephrology Unit in Zagazig University.

Patients and Methods: Our study was applied on 44 children admitted to Pediatric Nephrology Unit at the Pediatric Department in Zagazig University Children Hospital for hemodialysis, during the period from January 2019 to July 2019. Iron profile (serum Iron, ferritin, total iron-binding capacity (TIBC) and serum transferrin) as well as transferrin saturation-sTfRs TfR/log ferritin index was done to all children.

Results: Statistically significant positive association between iron, ferritin, total saturation of transferrin (TSAT) and hemoglobin (Hb) as well as statistically significant negative correlation between TSAT, iron, ferritin and sTfR were found. Anemia of chronic disease (ACD) patients' dialysis time was much longer than that of (Iron deficiency anemia) IDA patients, while hypertension was significantly higher in IDA patients than in ACD patients. The optimal cutoff value for sTfR was (1.75) with a sensitivity of 82% and a specificity of 73.6 %.

Conclusion: STfR is a valuable metric for distinguishing between ACD and IDA, as well as between ACD in patients who get regular hemodialysis. In HD patients, sTfR can be utilized to check iron levels.

Keywords: Regular hemodialysis, Serum transferrin receptor.

INTRODUCTION

Multiple factors contribute to anemia in chronic kidney disease (CKD) patients, including inadequate erythropoietin production, absolute and functional iron shortage as well as long-term inflammation [(1)]. Patients with chronic kidney disease may have anemia as a side effect. The delivery and monitoring of erythropoiesis-stimulating drugs and iron therapy is essential for optimal treatment [(2)].

A target hemoglobin level of 10–12 g/dL in children between the ages of 2 and 19 years, or 9.5–11.5 g/dL in kids younger than 2 years, is suggested according to the National Institute for Clinical Excellence (NICE) Anemia Management in Chronic Kidney Disease recommendations. Numerous iron indicators can be utilized to diagnose iron deficiency anemia in individuals with confounding comorbidities, such as those receiving frequent hemodialysis [(3)].

Ferritin, serum iron total iron-binding capacity (TIBC) or transferrin, and transferrin saturation (TS) are the primary indicators of iron shortage or anemia of chronic disease in humans [(4)]. Although these tests are influenced by chronic disease, the clinical interpretation of data is hindered because of this effect. Iron levels are normally decreased in IDA, but acute phase reactions associated with acute and chronic inflammation may boost ferritin levels. Coexisting iron deficiency and acute or chronic infection or inflammation alters the blood iron, TIBC, and transferrin levels. In individuals with iron deficiency and a concomitant illness or inflammation, these alterations make interpretation problematic [(5)].

When administering erythropoietin-stimulating agents (ESAs) and iron doses, care must be taken not to risk major adverse consequences for the patients [(1)]. To accomplish this goal, a different instrument must be employed. sTfR has been demonstrated to be an indication of iron shortage and is unaffected by concurrent chronic disease or inflammation. sTfR concentrations alone or the sTfR/log ferritin ratio (i.e., the sTfR index) are advised as alternate biomarkers in the presence of high levels of inflammation because they are expected to be less susceptible to inflammation [(6, 7)].

The transferrin receptor is a transmembrane cellular protein that is preferentially produced in cells that need iron, and the soluble form is raised in serum and plasma in situations of iron shortage [(8)].

Ferritin and sTfR levels are two indicators of iron availability for cells. In order to get an accurate assessment of the amount of iron in the body, the sTfR/log ferritin index (sTfR Index) can be calculated using these two measurements. Since iron shortage causes an increase in sTfR and reduction in ferritin concentration, the sTfR index takes advantage of this reciprocal link. When it comes to iron deficiency diagnosis and differentiating between anemia types, sTfR and ferritin levels are helpful. Combining sTfR and ferritin readings as well as the sTfR index computation should enhance anemia classification accuracy, according to some research, severe anemia associated

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with disorders involving active inflammation, in particular [9].

It was the goal of this work to determine the diagnostic value of serum soluble transferrin receptor (sTfR) in children undergoing regular hemodialysis in Pediatric Nephrology Unit in Zagazig University.

PATIENTS AND METHODS

Forty-four children who were admitted to Pediatric Nephrology Unit for hemodialysis at Zagazig University Hospitals between January 2019 and July 2019, served as the subjects for this cross sectional trial.

Ethical considerations:

As long as all parents of participants signed informed consent forms and submitted them to Zagazig University's Research Ethics Committee, the study was allowed (ZU-IRB#6280). We followed the World Medical Association's ethical code for human experimentation, the Helsinki Declaration.

Inclusion criteria: Hemodialysis for more than 6 months, no iron supplement uptake for 3 weeks prior to sampling, erythropoietin therapy with a fixed dose for at least 3 months and no erythropoietin administration for at least 86 hours before sample donation.

Exclusion criteria: Patients unable or unwilling to give informed consent, presence of hemorrhage. presence of acute hepatic disease.

This is what all of the participants in this research had to go through:

History: The patient's age, sex, gender, and history regarding causes of chronic renal failure, duration of dialysis (Years), size of filter, and frequency of dialysis. Number of blood transfusion/months. Urine output, conservative management, and medications.

Clinical examination: Weight of children, height, body mass index (BMI), blood pressure.

Laboratory evaluation: Blood samples were taken at the time of sepsis suspicion. Skin was rubbed with antiseptic and 4 cm of blood was taken: 1 cm of blood was collected in a test tube containing 20 mcg of EDETA for CBC, 2 cm of blood was collected in a plain test tube for CRP and serum creatinine, 1 cm of blood was injected into culture bottle.

1. **Complete Blood Count:** Analysis by sysmex 21-kx cell counter for hemoglobin (Hb), RDW, hematocrit value, platelet count, and white blood cell (WBC) count was performed on the blood specimens. Results of CBC were interpreted using Hematological scoring system by **Rodwell *et al.* [10].**
2. **Quantitative C- reactive protein (CRP):** 1 cm of blood was taken, blood was collected in a plain test tube, left to clot, then centrifuged for 10 minutes at 1500 rpm, Turbox plus was used to separate and analyze serum. Above 6 mg/l, results were deemed positive.
3. **Kidney function tests: Urea and creatinine.**
4. **Liver function tests: Total bilirubin, direct bilirubin, total protein, albumin, ALT and AST.**
5. **Serum calcium and serum phosphorus levels.**
6. **Parathyroid hormone (PTH) levels.**
7. **C-reactive protein.**

Determination of serum ferritin concentration [11]:

An enzyme linked immunosorbent assay kit (RAMCO LABORATORIES, INC., USA) was used to measure the serum ferritin levels in accordance with the manufacturer's recommendations.

1- Calculated by using this formula, the transferrin saturation index (TSI): The total iron-binding capacity (TIBC) divided by the iron concentration and multiplied by 100. There was no doubt that TSI > 16 percent was a correct value [12].

2- Body iron store (BIS): In order to compute the BIS range (2.13-2.79) mg/kg, we used the formula comparing the STFR and ferritin concentrations [13].

3- In order to determine the soluble transferrin receptor index (sTfR/logF), the following equations were used: Taking the logarithm of ferritin concentration and multiplying it by 100, we get the serum receptor concentration [14].

4- Immunoenzymatic assay of human soluble transferrin receptor (sTFR) [15]: An enzyme-linked immunosorbent test kit (BioVendor ELISA, China) was used to measure the level of human sTfR, following the manufacturer's instructions.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). The independent t-test (t) and the Mann-Whitney (MW) tests were employed to compare parametric and non-parametric quantitative data, respectively, in the analysis of the differences between the groups. Proportions were compared using the Chi-square test (X^2). The diagnostic and prognostic utility in newborn sepsis were evaluated using Receiver Operating Characteristics (ROC) analysis. P value 0.05 was considered statistically significant (S). It was judged highly significant (HS) when the P value was 0.001 and non-significant (NS) when the P value was >0.05.

RESULTS

The mean age was 11.9 years ranged from 4 to 16 years, 56.8% of them were females. Mean of body mass index (BMI) was 17.2 ranged from 10.5 to 22 **(Table 1).**

Table (1): The demographics of the patients being studied

Demographic data	Case group (n=44)	
	Mean ± SD Median (Range)	
Age (years)	**11.9±3.8 (4-16)**	
Weight (Kg)	**29.6 ±10.3** **29.9 (12.5-47)**	
Height (cm)	**137±12.5** **105 (85-148)**	
BMI (kg/m^2)	**17.2±2.9** **15.5 (10.5-20)**	
Variable	**Numbers (44)**	**%**
Sex **Male** **Female**	 **19** **25**	 **43.2** **56.8**

Duration of dialysis among studied patients ranged from 1 to 15 years with mean of 4.4 ± 3.5 years and duration of dialysis session ranged from 2.5 up to 4.5 hours and duration of illness before dialysis ranged from 1.5 to 6.5 years. 56.8% of patient have a duration of dialysis more than 24 months, 31.8% presented with pallor and only 13.6%. Need urgent blood transfusion for treatment of anemia. Most of cases were anuric (61.4%) and 81.8% were hypertensive on antihypertensive drugs **(Table 2).**

Table (2): Data among the studied patients

Variables	Case group (n=44)	
	Mean ± SD Range	
Duration of dialysis (years)	4.4 ± 3.5 (1-15)	
Duration of dialysis session (hours)	3.6±0.52 (2.5-4.5)	
Duration of illness (before dialysis)	4±2.5 (1.5-6.5)	
Systolic blood pressure (mm Hg)	118.8 ± 14.7 (90-140)	
Diastolic blood pressure (mm Hg)	77.3 ± 10.6 (50-90)	
	Numbers (44)	**%**
Duration of dialysis ≤24 months > 24 months	 19 25	 43.2 56.8
Urine output Polyuric Oliguric Anuric	 9 8 27	 20.4 18.2 61.4
Pallor Yes No	 14 30	 31.8 68.2
Receive blood transfusion Yes No	 6 38	 13.6 86.4
Hypertensive patient (with medication)	36	81.8

Statistically significant positive association between iron, ferritin, TSAT and Hb as well as statistically significant negative correlation between TSAT, iron, ferritin and sTfR were found **(Table 3)**

Table (3): Correlation between Soluble transferrin receptor and log ferritin index with iron indices and C-reactive protein (CRP) among studied patients

Variable	STfR		Log ferritin index	
	r	P	r	
Iron (µg/dL)	-0.532	0.008 S	-0.423	0.01 S
Ferritin (ng /mL)	-0.343	0.04 S	-0.342	0.04 S
TSAT (%)	-0.921	0.001 HS	-0.723	0.002 S
TIBC (µg/dL)	0.432	0.02 S	0.611	0.001 HS
HB(g/dL)	-0.795	0.001 HS	-0.8	0.001 HS
Reticulocyte Hb	0.213	0.342 NS	0.312	0.532 NS
CRP	-0.09	0.534 NS	-0.096	0.522 NS

Patients with IDA had statistically significant shorter duration of dialysis than patients with ACD and statistically significant as regard hypertension. But regarding other clinical data there was no statistically significant difference **(Table 4).**

Table (4): Comparison between patients with iron deficiency anemia (IDA) and anemia of chronic disease (ACD) in clinical data

Variable	IDA (5) Mean ± SD	ACD (39) Mean ± SD	MW*	P
Duration of dialysis (years) Median	2.2±1.3 2	4.7±3.6 4	3.01*	**0.008 S**
Duration of dialysis session (hours) Median	3.3±0.44 3	3.6±0.53 4	1.5*	**0.145** NS
Variables	F(5) %	F(39) %	X^2	**P**
Received blood transfusion	0 0.0	6 15.4	0.891	**0.345 NS**
Hypertensive	3 60	33 84.6	1.81	**0.179** NS

Differences in most of iron indices were found to be statistically significant between the two groups **(Table 5).**

Table (5): Comparison between patients with iron deficiency anemia (IDA) and anemia of chronic disease (ACD) regarding iron indices

Variable	IDA(5) mean ± SD	ACD (39) mean ± SD	t-test\ MW*	P
Hb	8.3±0.64	9.3±0.97	2.23	**0.031 S**
Iron **Median**	30.5±5.5 32	103±6.7 90	3.61*	**<0.001 HS**
TIBC **Median**	236.2±11.1 198	218.3±45.96 213	0.296*	**0.711 NS**
T.SAT **Median**	15.8±3.6 17	46.9±9.9 40	4.2*	**<0.001 HS**
Log ferritin index **Median**	1.16 ± 0.27 1.22	1.8 ± 0.34 1.9	4.84	**<0.001 HS**
Ferritin **Median**	162.1 ± 9.7 110	1176.5 ± 46.3 859	3.082*	**0.002 S**
sTfR **Median**	5.2 ± 0.97 5.3	2.7 ± 0.2 3.3	3.3*	**0.001 HS**
Ret Hb	23.4 ± 0.95	32.4 ± 2.81	7.1	**0.001 HS**

When determining the optimal cutoff value for sTfR, we used the receiver operating curve (ROC), which showed that the test had an IDA detection sensitivity of 82% and a specificity of 73.6 percent **(Table 6).**

Table (6): Diagnostic performance of soluble transferrin receptor in detection of IDA in the study group

Variable	Cutoff	AUC	P	Sensitivity	Specificity	Accuracy
sTfR	1.75	0.794	**0.01**	82%	73.6%	76.9%

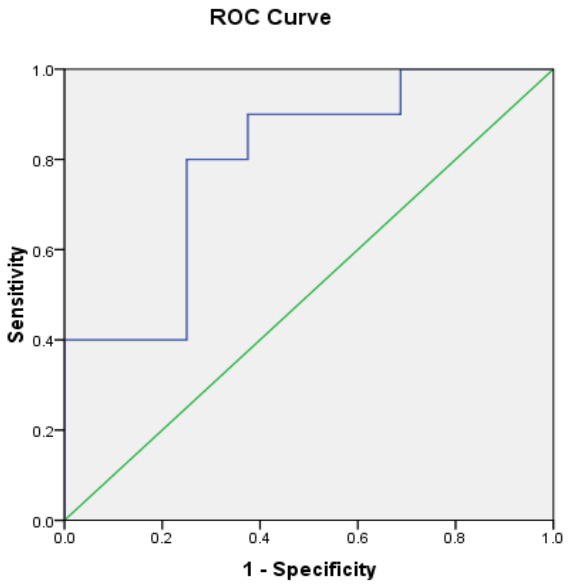

Figure (1): ROC curve of soluble transferrin receptor for detection of IDA in studied group

DISCUSSION

Acinetobacter species are Gram-negative aerobic bacteria that produce catalase but not oxidase. Hemodialysis patients frequently have anemia. ACD and IDA are the most frequent kinds of anemia, although others can occur as well. A fundamental challenge in clinical practice has always been distinguishing between these two forms of anemia, particularly in conditions like chronic inflammatory illness, where both anemias might coexist [(3)].

Perl's reaction is the gold standard approach for measuring iron status, however it is intrusive and uncomfortable for the patients. As a result, a variety of tests have been developed to provide a non-invasive, sensitive way to determine one's bodily iron status [(16)]. Iron levels can be assessed using serum sTfR, which has been found to be useful when inflammatory conditions are present; however, there has been no consensus on where the antibody comes from and how to standardize it [(17)].

Patients on regular hemodialysis are more likely to suffer from anemia. ACD and IDA are the most frequent kinds of anemia, however others might occur. A fundamental challenge in clinical practice has always been distinguishing between these two forms of anemia, particularly in conditions like chronic inflammatory illness, where both anemias might coexist [(17)].

There are two types of iron deficiency anemia that affect hemodialysis patients on recombinant human erythropoietin (rHuEPO) therapy: functional and absolute. Since these two illnesses are so similar, it might be difficult to tell them apart [(18)].

In our study 44 hemodialysis patients with a mean age of 11.9±3.8 years ranged from 4 to 16 years were examined. 56.8% of them were females. Mean of body mass index was 17.2 ranged from 10.5 to 22. In a study done by **Vázquez-López *et al.*** [(19)], they enrolled 1239 children, their age ranged from 1–16 years, of whom 620 (50%) were female.

sTfR levels have been used in earlier studies to detect iron insufficiency in individuals with end-stage renal disease. When there is a decrease in intracellular iron, the synthesis of TfR increases so that iron uptake into the cell may rise. The mean sTfR values in this investigation were 4.4 1.3 g/ml, which was higher than the standard reference value. Also, same finding has been put up by **Gupta *et al.*** [(20)]. **Zhong and Hu** [(21)] found that sTfR levels were higher than normal level. This indicates that the formation of sTfR increases during hemodialysis, and the abnormally elevated sTfR can affect iron metabolism and cause iron deficiency.

sTfR levels are inversely associated with hemoglobin and hematocrit levels in our study. This came in agreement with **Majeed *et al.*** [(18)]. sTFR levels

have been shown to be adversely connected to hemoglobin (p-values less than 0.01), according to the researchers. **Gupta *et al.*** [20] have found the same findings. In disagreement with our study, studying in Taiwan discovered a positive association between sTfR and hematocrit [22]**. Lorenzo *et al.*** [23] also found a link between them.

Each of ferritin, iron, and TSAT had a statistically significant negative connection with sTfR. A statistically significant negative correlation between sTfR values, as proposed by **Tarng and Huang** [24] who studied the relationship between sTfR and SF/TSAT.

Zhong and Hu [21] found, after further analysis of the iron deficiency anemia during hemodialysis and its correlation with sTfR, that serum ferritin levels were negatively correlated with sTfR levels and concluded that sTfR to be appropriate indicator of iron deficiency anemia.

sTfR levels were shown to be inversely linked with ferritin, iron, and TSAT, however this correlation was statistically insignificant [18]. To the contrary, the findings of **Beerenhout *et al.*** [25] revealed no connection between sTfR and SF.

In the current study, there was statistically significant difference between the two groups in log ferritin index. This came in agreement with **Skikne *et al.*** [26] who found that there was statistically significant difference between the ACD and IDA groups in log ferritin index ($P < 0.0001$).

A person's iron storage is measured by serum ferritin levels, whereas the availability of iron to cells is measured by serum sTfR levels. In order to get an accurate assessment of the amount of iron in the body, the sTfR/log ferritin index (sTfR Index) can be calculated using these two measurements [27].

The sTfR index thus exploits the reciprocal relationship between two variables altered by iron shortage, a rise in sTfR and a reduction in the ferritin concentration. It has been suggested in some studies that using sTfR and ferritin measurements and the sTfR index calculation to accurately classify anemia, particularly in anemia accompanied by active inflammation, improves the ability to accurately classify anemia, particularly in anemia accompanying diseases with active inflammation [28]**.** According to previous studies, using the sTfR index may increase the accuracy of anemia classification when inflammation is present [29, 30]**.**

In the current study, the diagnostic performance of sTfR was used for detection IDA in hemodialysis patients, receiver operating curve (ROC) was used to define the best cutoff value of sTfR, which was (1.75) with sensitivity 82% and specificity 73.6%. This came in agreement with several studies that have reported the clinical usefulness of sTfR in the diagnosis of IDA in children [31, 32] and adults [33], with AUC values usually ≥ 0.80. In disagreement with our study, some studies have concluded that TfR has only limited value for detecting iron depletion and that they are not good indicators of early stages of ID [32]**.**

When it comes to distinguishing between anemia caused by iron shortage and anemia caused by inflammation, sTfR is superior to serum ferritin [1]**.** We found that sTfR can be used to diagnose functional iron insufficiency, regardless of the concurrent storage status of iron, as demonstrated in a previous work by **Suominen and colleagues** [30].

The AUC (area under the curve) for sTfR was found to be 0.7, with a sensitivity of 82% and a specificity of 73.6 % in the current investigation, which used the receiver operating curve (ROC). To put it another way, **Suega *et al.*** [3] discovered that sTfR had an AUC (area under the curve) of 0.77. At its highest sensitivity of 83.3 percent and its highest specificity of 67.2 percent, the cutoff value was 0.71. Preliminary results from a prospective multicenter trial to distinguish IDA and ACD using TfR and the sTfR-F index [26], found that sTfR had an area under the curve (AUC) of 0.74 percent, with 95% confidence interval (CI) of 0.60–0.83.

CONCLUSION

STfR is a valuable metric for distinguishing between ACD and IDA, as well as between ACD in patients who get regular hemodialysis. In HD patients, sTfR can be utilized to check iron levels. In these patients, sTfR is beneficial in improving anemia evaluation.

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REFERENCES

1. **Gaweda A (2017):** Markers of iron status in chronic kidney disease diagnosing iron deficiency. Hemodial Int., 21(1): 21–27.
2. **Akel M, Shamas K, Sakr F *et al.* (2017):** Evaluation of the management of anemia in hemodialysis patients in Lebanon**.** J Nephropharmacol., 6(2): 68–73.
3. **Suega K, Kandarini Y, Tubung J (2019):** Role of soluble transferrin receptor and transferrin receptor-ferritin index to detect iron deficiency anemia in regular hemodialysis patients.Macedonian Journal of Medical Sciences, 7(1):97-102.
4. **Ganz T (2013):** Systemic iron homeostasis. Physiol Rev., 93(4): 1721–1741.
5. **Babitt J, Lin H (2012):** Mechanisms of anemia in CKD. J Am Soc Nephrol., 23(10): 1631–1634.
6. **Northrop-Clewes C, Thurnham D (2013):** Biomarkers for the differentiation of anemia and their clinical usefulness. J Blood Med., 4:11–22.
7. **WHO (2007):** Assessing the iron status of populations: including literature reviews: report of a joint World Health Organization/Centers for Disease Control and Prevention Technical Consultation on the Assessment of Iron Status at the Population Level. 2nd ed. Geneva (Switzerland): WHO; 2007. https://apps.who.int/iris/handle/10665/75368
8. **Formanowicz D, Formanowicz P (2012):** Transferrin changes in haemodialysed patients. Int Urol Nephrol.,

44: 907–919.

9. **Berlin T, Meyer A, Rotman-Pikielny P *et al.* (2011):** Soluble transferrin receptor as a diagnostic laboratory test for detection of iron deficiency anemia in acute illness of hospitalized patients. Isr Med Assoc J., 13:96-98.
10. **Rodwell R, Leslie A, Tudehope D (1988):** Early diagnosis of neonatal sepsis using a hematologic scoring system. The Journal of Pediatrics, 112(5): 761–767.
11. **Jacobs A, Lawrie H, Entwistle C *et al.* (1972)**: Gastric acid secretion in chronic iron-deficiency anemia. Lancet, 2: 190-192.
12. **Kamer B, Dółka E, Pasowska R *et al.* (2012):** The usefulness of soluble transferrin receptor (sTfR) in differentiating anemia occurring in young children. Folia Histochemica et Cytobiologica, 50(3):473-9.
13. **Cook J (2003):** Evaluation of the iron status of a population. Blood, 48:449–455.
14. **Dimitriou H, Stiakaki E, Markaki E *et al.* (2000):** Soluble transferrin receptor levels and soluble transferrin receptor/log ferritin index in the evaluation of erythropoietic status in childhood infections and malignancy. Acta Pædiatr., 89: 1169–1173.
15. **Fernández-Real J, Moreno J, López-Bermejo A *et al.* (2007):** Circulating soluble transferrin receptor according to glucose tolerance status and insulin sensitivity. Diabetes Care, 30: 604-608.
16. **Mahdavi M, Makhlough A, Kosaryan M *et al.* (2011):** Credibility of the measurement of serum ferritin and transferrin receptor as indicators of iron deficiency anemia in hemodialysis patients. Eur Rev Med Pharmacol Sci., 15: 1158-62.
17. **Al-Rubaie H, Al-Bayaa I, Al-Amiri Y (2019):** The value of soluble transferrin receptor and soluble transferrin receptor-ferritin index in discriminating iron deficiency anemia from anemia of chronic disease in patients with rheumatoid arthritis. The Open Rheumatology Journal, 13(1): 1-5.
18. **Majeed A, Hameed A, Aftab I *et al.* (2016):** Soluble serum transferrin receptor (STFR) levels in hemodialysis patients. Annals of King Edward Medical University, 22(4): 117-112.
19. **Vázquez-López M, López-Ruzafa E, Ibáñez-Alcalde M *et al.* (2019):** The usefulness of reticulocyte haemoglobin content, serum transferrin receptor and the sTfR-ferritin index to identify iron deficiency in healthy children aged 1–16 years. European Journal of Pediatrics, 178(1): 41-49.
20. **Gupta S, Uppal B, Pawar B (2009):** Is soluble transferrin receptor a good marker of iron deficiency anemia in chronic kidney disease patients? Indian J Nephrol., 19:96-100.
21. **Zhong G, Hu P (2018):** Correlation of serum hepcidin and transferrin receptor contents with iron deficiency and micro-inflammatory response in patients with hemodialysis. Journal of Hainan Medical University, 24(1): 33-36.
22. **Chiang W, Tsai T, Chen Y *et al.* (2002):** Serum soluble transferrin receptor reflects erythropoiesis but not iron availability in erythropoietin-treated chronic hemodialysis patients. Clin Nephrol., 58 (5):363-9.
23. **Lorenzo J, Rodriguez M, Martin S *et al.* (2001):** Assessment of erythropoiesis activity during hemodialysis therapy by soluble transferrin receptor levels and ferrokinectic measurement. Am J Kidney Dis., 37:550-6.
24. **Tarng D, Huang T (2002):**Determinants of circulating soluble transferrin receptor level in chronic haemodialysis patients. NDT., 17 (6): 1063-69.
25. **Beerenhout C, Bekers O, Kooman J *et al.* (2002):**A comparison between the soluble transferrin receptor, transferritin saturation and serum ferritin as markers of iron state in hemodialysis patients. Nephron, 92: 32-35.
26. **Skikne B, Punnonen K, Caldron P *et al.* (2011):** 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. American Journal of Hematology, 86(11):923-7.
27. **Beguin Y (2003):**Soluble transferrin receptor for the evaluation of erythropoiesis and iron status. Clin Chim Acta, 329: 9–22.
28. **Margetic S, Topic E, Ruzic D *et al.* (2005):**Soluble transferrin receptor and transferrin receptor-ferritin index in iron deficiency anemia and anemia in rheumatoid arthritis. Clin Chem Lab Med., 43(3): 326-31.
29. **Matsuda A, Bessho M, Mori S *et al.* (2002):** Diagnostic significance of serum soluble transferrin receptors in various anemic diseases: The first multi-institutionaljoint study in Japan. Haematologia, 32: 225–238.
30. **Suominen P, Mottonen T, Rajamaki A *et al.* (2000):** Single values of serum transferrin receptor and transferrin receptor ferritin index can be used to detecttrue and functional iron deficiency in rheumatoid arthritis patients with anemia. Arthritis Rheum., 43:1016–1020.
31. **Davidkova S, Prestidge T, Reed P *et al.* (2016):**Comparison of reticulocyte hemoglobin equivalent with traditional markers of iron and erythropoiesis in pediatric dialysis. Pediatr Nephrol., 31:819–826.
32. **Uijterschout L, Domellöf M, Vloemans J *et al.* (2014)** The value of Ret-Hb and sTfR in the diagnosis of iron depletion in healthy, young children. Eur J Clin Nutr., 68: 882–886.
33. **Urrechaga E, Borque L, Escanero J (2013):** Erythrocyte and reticulocyte indices in the assessment of erythropoiesis activity and iron availability. Int J Lab Hematol., 35:144–149.