DIAGNOSTIC VALUE OF RETICULOCYTE HEMOGLOBIN AND SOLUBLE TRANSFERRIN RECEPTOR IN DETERMINING THE IRON STATUS OF CHRONIC KIDNEY DISEASE WITH HEMODIALYSIS PATIENTS

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DIAGNOSTIC VALUE OF RETICULOCYTE HEMOGLOBIN AND SOLUBLE TRANSFERRIN RECEPTOR IN DETERMINING THE IRON STATUS OF CHRONIC KIDNEY DISEASE WITH HEMODIALYSIS PATIENTS

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ABSTRACT

Objective: This research aims to find the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the new parameters reticulocyte hemoglobin (Ret-He), and soluble transferrin receptor (sTfR) in determining the iron status of patients with chronic kidney disease with hemodialysis (CKD-HD) who will receive recombinant human erythropoietin (rHuEPO) therapy which requires sufficient iron levels.

Methods: The cross-sectional study was conducted in Hemodialysis (HD) Unit of Dr. M. Soewandhie Regional General Hospital from September 2018 to March 2019. Patients with CKD and anemia who had undergone hemodialysis were recruited in this study. There were two groups: Group 1, patients with iron-deficiency anemia and Group 2, patients without iron-deficiency anemia. Examination on Ret-He and sTfR was performed through comparison with gold standard transferrin saturation and ferritin serum.

Results: The mean±standard deviation of Ret-He is 30.18±2.74 pg, sTfR of male group is 2704.11±1981 mg/l and sTfR of female group is 3837.76±1415 mg/l. The agreement of Ret-He and gold standard was 85.4% (p=0.000) with sensitivity 86.7%, specificity 84.6%, PPV 76.5%, and NPV 91.7%. The agreement of sTfR in male was 92.8% (p=0.002) with sensitivity 100%, specificity 90.9%, PPV 75%, and NPV 100%. As for female, it was 85.1% (p=0.000), with sensitivity 83.3%, specificity 86.75%, PPV 83.3%, and NPV 86.7%. According to sTfR/log ferritin index calculation, the agreement was 100% (p=0.000) for male and 85.1% (p=0.000) for female.

Conclusion: The diagnostic values of the parameters Ret-He, sTfR, and sTfR/log ferritin index were high and therefore can be used to diagnose iron-deficiency anemia in CKD-HD patients who will undergo rHuEPO therapy.

Keywords: Iron-deficiency anemia, Chronic kidney disease with hemodialysis, Reticulocyte hemoglobin, Soluble transferrin receptor.

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INTRODUCTION

Anemia in patients with chronic kidney disease with hemodialysis (CKD-HD) may result in various unfavorable consequences, such as life quality and heart problem that affect the progressivity of the patient' renal failure [1,2]. Anemia in CKD patients is caused by a number of factors, particularly the declining erythropoietin (EPO) production due to damages in kidney structure [3]. However, approximately 25–38% of anemia in patients with CKD is caused by iron deficiency [4]. Iron-deficiency anemia which often occurs in CKD-HD due to loss of blood because trapped of erythrocytes in the dialysis filter and repeated blood collection [5]. The condition of iron deficiency can result in failure in EPO therapy among patients with CKD-HD because recombinant human EPO (rHuEPO) therapy requires sufficient iron reserves as a material for erythropoiesis [5,6]. Monitoring the iron status of patients undergoing EPO therapy is important to detect iron deficiency [7]. Thus, the examination on iron status is necessary to determine the presence of iron-deficiency anemia in patients with CKD-HD before giving rHUEPO to reach the target effectively.

In our country, so far the common examinations for determining iron status use transferrin saturation (TSAT) and ferritin serum. If TSAT is <20% and ferritin serum is <200 ng/ml, it can be determined as absolute iron deficiency, requiring iron transfusion before rHuEPO administration [8]. However, TSAT and ferritin serum examinations are considered relatively unpracticed and expensive, beside transferrin is an acute-phase reactant that will increase by inflammation.

Recently, there are new parameters in automatic blood cell hematology analyzer, i.e., reticulocyte hemoglobin (Ret-He). Some researchers found that Ret-He is an early sign of iron-deficiency anemia unaffected by inflammation and can assess iron availability for erythropoiesis in the bone marrow and therefore can diagnose iron-deficiency anemia earlier in patients with CKD-HD [9]. It is also highly efficient in predicting intravenous iron therapy response in patients with CKD-HD. Ret-He measurement can be performed simultaneously during the routine examination of complete blood count (CBC) without any additional cost and more blood sample, making it more reliable than TSAT (serum iron [SI]: Total iron-binding capacity [TIBC]) or ferritin [10,11].

Soluble transferrin receptor (sTfR) is a new parameter that is sensitive, functioning specifically as the early sign of iron deficiency and is a part of transferrin receptor of erythroblast and other cells in the bone marrow, unaffected by inflammation or infection factor. In iron-deficiency anemia, erythroblast in the bone marrow will increase the presentation of transferrin receptor membrane, and likewise, in patients receiving rHuEPO where erythropoiesis increases, transferrin receptor in erythroblast will be increased and will be released to the circulation in the form of sTfR [12]. In the mixed condition with anemia of chronic disease (ACD), sTfR will secondarily increase toward the existing iron-deficiency due to ACD [13]. It is expected to help to detect iron-deficiency anemia in patients with CKD-HD.

METHODS

Design of this study is cross-sectional, conducted in the hemodialysis unit of Dr M. Soewandhie Regional General Hospital from September 2018 to March 2019. CKD-HD with anemia patients undergoing hemodialysis was involved in this study with the following criteria: Adult patients with CKD above 21 years old, undergoing hemodialysis, and hemoglobin value of <13.5 g/dL for male and <12 g/dL for female. It has been declared passing the ethical clearance by the Ethics Committee of Medical Research Faculty of Medicine Universitas Airlangga.

There were 41 CKD-HD with anemia patients involved in this study. Blood sample was collected for the examination of complete blood count (CBC), SI, TIBC, ferritin, Ret-He, and sTfR. Hemoglobin (Hgb) and Ret-He were examined using flow cytometry with Sysmex XN 1000 B3 (Sysmex Corporation, Japan) machine. SI and TIBC examinations were performed using the kinetic method with the Dimension EXL (Siemens Healthineers Global) machine. Ferritin serum examination was performed using enzyme-linked fluorescent assay method with the mini VIDAS (BioMerieux) instrument. sTfR examination was performed using enzyme-linked immunoassay (ELISA) method with ELISA HumaReader (HUMAN Diagnostics Worldwide) instrument. Calibration and quality control were performed on all parameters in accordance with the recommendation from each manufacturer.

The patients were divided into two groups: Group 1, patients with iron-deficiency anemia based on the criteria of TSAT <20 and ferritin serum <200 ng/mL; and Group 2, patients with no iron-deficiency anemia, who does not meet those criteria. To whom Ret-He and sTfR examination was performed and then compared with TSAT and ferritin serum as the gold standard in this study. The statistical analysis was performed using Chi-square and Kappa measure of agreement tests.

RESULTS

The characteristics of the sample consisted of sex, age, Hgb level, SI, TIBC, Ret-He, and sTfR. The number of patients involved in this study was 41. There were 14 (34.1%) males and 27 (65.8%) females (Table 1).

The agreement Ret-He and sTfR in diagnosing iron-deficiency anemia based on gold standard is shown in Table 2. There were 15 (36.6%) patients with iron-deficiency anemia and 26 (63.4%) patients non-iron-deficiency anemia based on gold standard parameter. Based on Ret-He, there were 17 (41.5%) patients with iron-deficiency anemia and 24 (58.5%) patients non-iron-deficiency anemia. Diagnosis according to the sTfR with cutoff of 4.639 mg/L for male and 4.496 mg/L for female, there were 4 (28.6%) male patients and 12 (44.4%) female patients with iron-deficiency anemia, while the patients were without iron-deficiency anemia there were 10 (71.4%) for males and 15 (55.6%) for females.

Table 3 indicates the agreement of Ret-He toward gold standard in determining iron-deficiency anemia, i.e. 85.4% (p=0.000), with true positive (TP) and true negative (TN) were 31.7% and 53.7%, respectively. The agreement of sTfR in male was 92.8% (p=0.002) with TP and TN of 21.4% and 71.4% respectively. In female, it was 85.1% (p=0.000), with TP and TN were 37% and 48.1%, respectively. In the calculation of sTfR/log ferritin index, the agreement in male was 100% (p=0.000) with TP and TN of 21.4% and 78.6%, respectively, while in female it was 85.1% (p=0.000), with TP and TN were 40.7% and 44.4%, respectively.

Table 4 indicates that result of agreement Ret-He and gold standard in detecting iron-deficiency anemia is 85.4% (p=0.000), with sensitivity of 86.7%, specificity of 84.6%, positive predictive value (PPV) of 76.5%, and negative predictive value (NPV) of 91.7%, with area under curve (AUC) of 0.887 (Fig. 1). The agreement result of sTfR in male was 92.8% (p=0.002) with sensitivity, specificity, PPV, and NPV of 100%, 90.9%,

Table 1: Characteristics of the subjects

Characteristic	Mean±SD	Total
Sex		
Male		14 (34.1%)
Female		27 (65.8%)
Age range	46.6±8.4 years old	
Hgb (g/dl)	9.20±1.54	41
SI (µg/dl)	55.41±28.42	41
TIBC (µg/dl)	227.20±80.55	41
TSAT (µg/dl)	33.74±40.79%	41
Ferritin serum (ng/ml)	472.25±199.00 ng/ml	41
Ret-He (mg/l)	30.18±2.74 pg	41
sTfR (mg/l)	L: 2704.11±1981 P: 3837.76±1415	41

SI: Serum iron, TIBC: Total Iron-binding capacity, TSAT: Transferrin saturation, Ret He: Reticulocyte hemoglobin, sTfR: Soluble transferrin receptor

Table 2: Category of subjects based on the standard criteria

Category	Total (frequency %)		
	TSAT and ferritin	Ret-He frequency	sTfR frequency
Iron deficiency	15 (36.6)	17 (41.5)	M 4 (28.6) F 12 (44.4)
No iron deficiency	26 (63.4)	24 (58.5)	M 10 (71.4) F 15 (55.6)

TSAT: Transferrin saturation, Ret-He: Reticulocyte hemoglobin, sTfR: Soluble transferrin receptor. Iron deficiency limit: TSAT <20%, Ferritin <200 ng/ml, Ret-He ≤29.05 pg, sTfR male >4.639 mg/l, female >4.496 mg/l

Table 3: Diagnostic tests of Ret-He and sTfR towards TSAT and ferritin

	TSAT and ferritin	
	Total (frequency %)	
	Iron-deficiency anemia	Non iron-deficiency anemia
Ret He cut off=29.05 pg		
Iron-deficiency anemia	13 (31.7)	4 (9.8)
Non iron-deficiency anemia	2 (4.9)	22 (53.7)
Kappa test	*p=0.000 (85.4)	
sTfR (male)		
cut off=4.639 mg/l		
Iron-deficiency anemia	3 (21.4)	1 (7.1)
Non iron-deficiency anemia	0 (0.0)	10 (71.4)
Kappa test	*p=0.002 (92.8)	
sTfR (female)		
cut off=4.496 mg/l		
Iron-deficiency anemia	10 (37)	2 (7.4)
Non iron-deficiency anemia	2 (7.4)	13 (48.1)
Kappa test	*p=0.003 (85.1)	
sTfR/log ferritin (male)		
cut off=2.053 mg/l		
Iron-deficiency anemia	3 (21.4)	0 (0.0)
Non iron-deficiency anemia	0 (0.0)	11 (78.6)
Kappa test	*p=0.000 (100)	
sTfR/log ferritin (female)		
cut off=1.965 mg/l		
Iron-deficiency anemia	11 (40.7)	3 (11.1)
Non iron-deficiency anemia	1 (3.7)	12 (44.4)
Kappa test	*p=0.000 (85.1)	

*Significant (p<0.05), TSAT: Transferrin saturation, Ret-He: Reticulocyte hemoglobin, sTfR: Soluble transferrin receptor. Iron deficiency limit: TSAT <20%, ferritin <200 ng/ml, Ret He ≤29.05 pg, sTfR male >4.639 mg/l, female >4.496 mg/l, sTfR/log ferritin male 2.053, sTfR/log ferritin female 1.965

Table 4: Diagnostic value of Ret-He and sTfR toward gold standard

Parameters	Agreement with gold standard (%)	Significance	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative positive value (%)	Area under curve (%)
Ret-He	85.4	*0.000	8.67	84.6	76.5	91.7	0.887
sTfR							
Male	92.8	*0.002	100	90.9	75	100	0.97
Female	85.1	*0.000	83.3	86.7	83.3	86.7	0.84
sTfR/log ferritin							
Male	100	*0.000	100	100	100	100	1.00
Female	85.1	*0.000	91.2	80	78.6	92.3	0.89

*Significant (p<0.05), Ret-He: Reticulocyte hemoglobin, sTfR: Soluble transferrin receptor

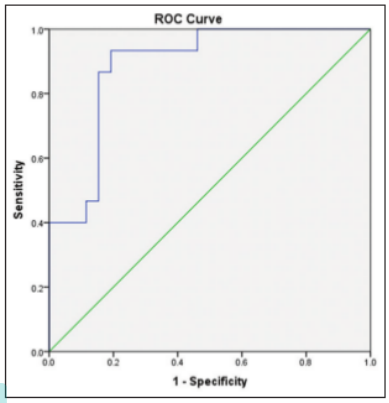

Fig. 1: Receiver operating characteristic curve for reticulocyte hemoglobin parameter in diagnosing iron-deficiency anemia in patients with chronic kidney disease with hemodialysis. The Y-axis represents sensitivity or true positive. The X-axis represents 1-specificity or false positive. The area under curve is 0.887

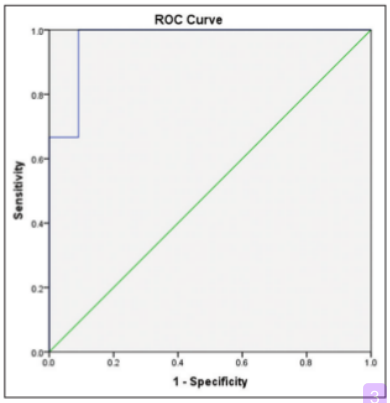

Fig. 2: Receiver operating characteristic curve for soluble transferrin receptor parameter (male) in diagnosing iron-deficiency anemia in patients with chronic kidney disease with hemodialysis. The Y-axis represents sensitivity or true positive. The X-axis represents 1-specificity or false positive. The area under curve is 0.970

75%, and 100%, respectively, with AUC of 0.97 (Fig. 2). In female, it was 85.1% (p=0.000), with sensitivity, specificity, PPV, and NPV of 83.3%, 86.75%, 83.3%, and 86.7%, respectively, with AUC of 0.84 (Fig. 3). In the calculation of sTfR/log ferritin index, the agreement in male was 100% (p=0.000) with sensitivity, specificity, PPV, and NPV of 100%,

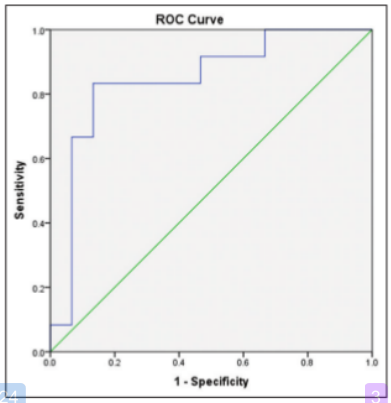

Fig. 3: Receiver operating characteristic curve for soluble transferrin receptor parameter (female), in diagnosing iron-deficiency anemia in patients with chronic kidney disease with hemodialysis. The Y-axis represents sensitivity or true positivity. The X-axis represents 1-specificity or false positive. The area under curve is 0.844

100%, 100%, and 100%, respectively. Meanwhile, in female, in female was 85.1% (p=0.000) with sensitivity, specificity, PPV, and NPV of 91.2%, 80%, 78.6%, and 92.3%, respectively.

DISCUSSION

The determination of irons status in patients with CKD-HD is very important, especially as preparation of patients who will receive rHuEPO therapy which requires sufficient iron and to treat the condition of anemia itself. The condition of iron deficiency can result in failure of EPO therapy in patients with CKD-HD [14,15]. Therefore, the examination on iron status is necessary to determine the presence of iron-deficiency anemia in patients with CKD-HD before rHuEPO administration. Monitoring the iron status in patients receiving EPO with iron regiment therapy is also important to avoid the side effect of excessive iron treatment [8,16].

The establishment of Ret-He criteria in determining iron-deficiency is closely related to the used of cutoff value. In this study, it was statistically obtained that Ret-He cutoff value of 29.05 ng/mL has the best diagnostic value, closed with the study by Wirawan in 2017 which results in the cutoff of 29.0 ng/mL [17]. In this study, it was obtained that if the category of iron-deficiency is only based on the Ret-He level, there were 17 (41.5%) patients with iron-deficiency anemia and 24 (58.5%) patients without iron-deficiency anemia. If compared to the gold standard, the result compatibility of Ret-He with the gold standard in determining iron-deficiency was 85.4% with p=0.000 (<0.05) and sensitivity, specificity, PPV, and NPV of 86.7%, 84.6%, 76.5%, and 91.7% with AUC 0.887, respectively.

A study by Toki *et al.* in 2016 obtained that Ret-He in detecting iron-deficiency anemia with cutoff of 30.9 pg has the sensitivity of 68%, specificity of 91%. Ret-He is also positively correlated with SI (r=0.654), TSAT (r=0.666), and ferritin (r=0.604), with AUC of 0.902, howevwer has negatively correlated with TIBC (r=-0.617) and sTfR (r=-0.655) [18]. It is in line with this study, which obtained sensitivity of 86.7%, specificity of 84.6%, with cutoff of 29.05 pg and AUC of 0.887 (p=0.000). This study shows that Ret-He diagnostic value in detecting iron-deficiency anemia is good, especially in mixed patients with chronic diseases such as CKD-HD.

Brugnara *et al.* (2006) study results Ret-He in patients with chronic dialysis, if compared with the conventional parameters (SI <40, TSAT <20%, ferritin serum<100 ng/ml, Hgb <11 g/dL) has sensitivity of 93.3%, specificity of 83.2%, and receiver operating characteristic of 0.913 (p<0.0001) [19]. The sensitivity and specificity obtained in this study are 86.7% and 84.6%. This difference perhaps due to the difference in cutoff. The study conducted by Lankhorst and Wish in 2010 stated that the use of cutoff of ≤32 pg to administer iron intravenous or to diagnose iron-deficiency anemia in CKD patients will improve therapy utility and will be beneficial in reducing EPO needs in the long-term compared to using cutoff of ≤29 pg [20].

Mast *et al.* study results that Ret-He is actually better for iron therapy monitoring only rather than for absolute iron deficiency diagnosis. However, this study found that Ret-He diagnostic value is quite good for determining whether intravenous iron therapy before EPO administration is necessary for patients with CKD-HD [15].

Some other studies stated that to diagnose absolute iron-deficiency anemia in patients with CKD; the interpretation will be better when using the combination of Ret-He level toward the ratio of sTfR/log ferritin [16,21]. However, in this study results that single Ret-He examination only, the compatibility of iron-deficiency anemia diagnosis and gold standard is good enough, i.e., 85.4% (p=0.000). Some researchers in their studies even found that Ret-He represents measurement of Hgb and reticulocyte and directly correlated with the presence of iron in the bone marrow, implying that Ret-He parameter is the gold standard in iron deficiency diagnosis and can replace iron examination with blue in bone marrow, as well as soluble transferrin index that is known as the gold standard [22].

When iron-deficiency anemia criteria are only based on sTfR, the obtained compatibility with the gold standard in male is 92.8% with sensitivity, specificity, PPV, and NPV of 100%, 90.0%, 75%, and 100%, respectively, while in female it was 85.1% with sensitivity, specificity, PPV, and NPV of 83.3%, 90.9%, 83.3%, and 86.7%, respectively. It is in spite of the arguments from several researchers that the combination of sTfR index and ferritin serum will work better compared to sTfR alone [23,24], particularly in mixed cases to differentiate between pure and mixed iron-deficiency anemia.

In this study's calculation of sTfR/log ferritin index, the obtained agreement toward gold standard was 100% in male. Meanwhile, when the only sTfR was used, the conformity ability was 92.8% with sensitivity, specificity, PPV, and NPV of 100%, 100%, 100%, and 100%, respectively. As for female, the conformity ability in sTfR/log ferritin was 85.1%, the same as when using only sTfR, with sensitivity, specificity, PPV, and NPV of 91.2%, 80%, 78.6%, and 92.3%, respectively. This indicates that the use of sTfR/log ferritin ratio has the diagnostic value, even slightly higher than using sTfR only.

Marković *et al.* (2005) study obtained diagnostic efficiency for iron-deficiency anemia of 0.884 using sTfR only, 0.638 when using ferritin serum only, and 0.820 when using sTfR/ferritin index [21]. This indicates that the efficiency of sTfR/ferritin index is not better than the measurement of sTfR only. This corresponds with this study that results in the diagnostic ability of sTfR as a gold standard is good, i.e., 92.8% in male and 85.1% in female. Matsuda *et al.* (2002) obtained that sTfR examination can be used to differentiate iron-deficiency anemia from other anemia, such as chronic disease anemia, aplastic anemia and myelodysplastic syndrome, and iron-deficiency anemia in CKD [15]. In this study, it is used to diagnose iron-deficiency anemia in patients with CKD-HD.

The criteria of iron deficiency anemia in CKD-HD in this study based on Indonesian Nephrology Association 2011, i.e., TSAT of <20% and ferritin serum of <200 ng/ml [8]. Meanwhile, Braga *et al.* stated that sTfR is indeed more sensitive in detecting iron-deficiency anemia when using bone marrow as the gold standard, but it is stated that the meta-analysis requires a further study [25].

Regarding to the diagnostic value of sTfR results, it can be concluded that sTfR is good enough as a parameter to diagnose iron-deficiency anemia, in line with the previous study by Latif *et al.*, which obtained a significantly higher sTfR mean value in patients with iron-deficiency anemia (4.81±1.64 µg/mL) compared to those with chronic disease anemia (2.89±1.4 µg/mL), as well as compared to the normal control group (2.96±0.78 µg/mL) [4]. Braga *et al.* study resulted that sTfR can indicate the functional iron status as well as differentiating it with absolute iron deficiency, which sTfR level drastically increase in the absolute iron deficiency [25]. Using sTfR/log ferritin formula, if the result is >2, it implies an overlapping between iron-deficiency anemia and chronic disease anemia, but the ratio of <1 implies only chronic disease anemia [13]. The sTfR/log ferritin ratio cutoff obtained in this study was 2.053 with AUC of 1.000 in male and cutoff of 1.965 with AUC of 0.894 in female. This indicates that the sTfR/log is a very good parameter for diagnosing iron-deficiency anemia in CKD-HD. Thus, this result confirms the previous study by Adhiatma *et al.* that resulted if the sTfR/log ferritin >2 indicates an overlapping between iron-deficiency anemia and chronic disease anemia (CKD-HD) [13].

CONCLUSION

There is a significant agreement result between Ret-He, sTfR, and sTfR/log ferritin with the gold standard (TSAT and ferritin serum) in assessing CKD-HD with iron-deficiency anemia patients. Therefore, it can be used to examine the iron status in CKD-HD patients who will receive rHuEPO therapy.

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