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Research Article

The Correlation between Serum Iron Level and Transferrin Saturation with Reticulocyte Hemoglobin Equivalent (RET-He) in Routine Hemodialysis

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ABSTRACT

Introduction: Iron deficiency often occurs in patients with chronic kidney disease (CKD) stage 5 undergoing routine hemodialysis (CKD-5D). Reticulocyte hemoglobin equivalent (RET-He) is a more stable substance and is not influenced by acute and chronic conditions. RET-He examination as a new and easy parameter is needed besides serum iron levels and transferrin saturation in patients with chronic kidney disease (CKD) patients undergoing routine hemodialysis (CKD-SD). This study aimed to determine the correlation between serum iron levels and transferrin saturation with RET-He in CKD-5D.

Methods: This was a cross-sectional study in the hemodialysis unit of Hasan Sadikin General Hospital Bandung, Indonesia. Blood sampling was performed using the Sysmex automatic hematology tool with 35 parameters. The statistical test used Pearson correlation and Unpaired T-test. The correlation was considered significant when p<O.05 with a 95% confidence interval.

Results: There were 181 patients with CKD-5D, 137 patients had complete data, and 97 patients who fulfilled inclusion and exclusion criteria taken randomly as study subjects. Average of age was 48±13 years, male 53 (54.6%), median of HD duration 36 (12-168) months, hemoglobin 9.1 (4.7—13.7) gr/dL, serum iron (SI) 54 (14—166) pg/dL, total iron-binding capacity (TIBC) 234 (137—429) pg/dL, Trasnferrin saturation (Tsat) 22.2 % (10.1—75. l) and RET-He 31.7 (19.3—37.5) pg/cell. Serum iron was correlated with RET-He (t-=0.348; p<O.OOl) and Tsat was correlated too (r=O.454; p<O.OOl).

Conclusions: There was a significant correlation between SI and Tsat levels with RET-He in CKD-5D patients.

Keywords: CKD-SD, Anemia, Iron deficiency, Transferrin saturation, RET-He

INTRODUCTION

In the world, chronic kidney disease (CKD) has high prevalence about 5-10%, leading cause of death as the 12th and the seventh sequence causes of disability, as a chronic disease. A progressive decline in kidney function leads to complications, such as anemia, malnutrition, atherosclerosis, mineral and bone disorder in chronic kidney disease (MBD-CKD), neuropathy, and decrease quality of life. These complications will be more severe in patients with CKD stage 5 undergoing routine hemodialysis (CKD-5D). [1-3] The incidence rate in Indonesia also increases annually. In 2013, there were 15,128 new patients and 9,396 active patients. This amount increased to 17,193 new patients and 1 11689 active patients in 2014.[4] According to data from the Indonesian Renal Registry ORR) in 2015, there were 211050 patients diagnosed with end-stage kidney disease (ESKD) with routine hemodialysis and in 2007 there is an increased four times compared to of

4,977 patients with the highest cause of death 44% due to cardiovascular disease in Indonesia.5

Iron deficiency often OCCUrs in patients with CKD5D.[6] The causes of iron deficiency anemia in patients with routine hemodialysis (HD) are blood loss during dialysis, occult blood loss, increased tendency for bleeding, frequent blood sampling for laboratory examination and increase iron consumption by erythropoiesis-stimulating agent (ESA) or erythropoietin (EPO).[7]

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The typical markers for absolute iron deficiency in CKD are ferritin < 100 ng/ml in non-HD or nonperitoneal dialysis (PD) and < 200 ng/ml in routine HD or transferrin saturation <20%.Serum ferritin levels and low rates transferrin saturation is common in most patients with impaired renal function. [10]

The latest parameter of reticulocyte hemoglobin equivalent (RET-He) is useful for diagnosing iron deficiency anemia (IDA).[T I] RET-He, in coniunction with standard blood cell counts and iron parameters, could enable the diagnosis to be more rapidly and accurately.11,12 RET-He examination uses a new hematologic analyzer tool, but there was not been much-published data on these parameters.[12] RET-He examination could be an alternative to examine the functional iron deficiency anemia That is faster, easier and cheaper. This study aimed to determine the correlation between serum iron levels and transferrin saturation with RET-He in patients with CKD-5D.

METHOD

This was a cross-sectional study. This study was received approval and recommendation from The Ethics Commitlee Medical Research of Faculty of Medicine, Universitas Padiadiaran, Bandung, Indonesia, and permission from the director of Hasan Sadikin Hospital Bandung, Indonesia (ethical approval No: LB.04.01/A05/EC/161/V/2017). This study was conducted in hemodialysis installation, Hasan Sadikin Hospital, Bandung, Indonesia. Inclusion criteria were CKD-5D patients twice a week at least for 3 months, age of > 18 years, complete data, and willing to participate in this study by signing informed consent. Exclusion criteria were patients that fulfill the inclusion criteria but having other severe comorbidities such as sepsis, malignancy, hospitalization, iron therapy, transfusion in past a month, seve hypoalbuminemia (albumin <2.5 mg/dL) and patients stopped during the study. Blood sampling was performed, which about 7 ml consisted of 3 ml for routine blood examination including RETHe and 4 ml for blood chemistry examination. The examination using Sysmex automatic hematology tool with 35 parameters. Blood chemistry examination were serum iron (St), total iron-binding capacity (TIBC), and calculation of Sl divided by TIBC as Transferrin saturation (Tsat).

The statistical test used Pearson correlation when normally distributed and Rank Spearman Analysis when not normally distributed. To find out the difference of mean, unpaired T-test or Mann Whitney U was used when not normally distributed. The correlation was considered significant when p<O.05 with a 95% confidence interval.

RESULTS

There were 181 patients CKD-5D- The completed data were 139 patients and only 97 patients who fulfilled inclusion and exclusion criteria and were willing to sign informed consent (Fig. 1). In this study, there were 53 (54.6%) male patients and 44 (45.4%) female patients, with an average of age 48 ± 13 years. The median duration of HD in this study was 36 (12—168) months. Most of the subiect's education was senior high school 38 (39.2%), elementary school 24 (24.7%), and iunior high school (15.5%), and also there was 1patient with the highest educational (PhD)- The most common etiology of CKD was hypertension 60 (61.9%) patients, followed by primary glomerulopathy 14 (14.4%) patients and diabetic kidney disease (DKD) 13 (13.4%) patients (Table 1).

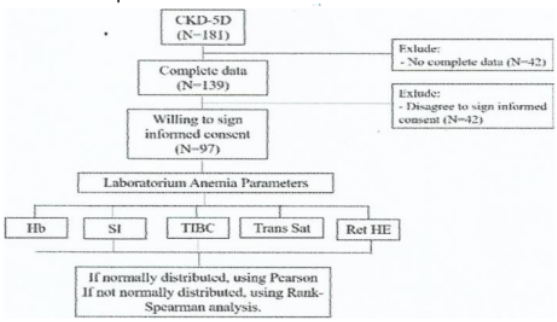

Fig.l: Flowchart of Participants

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Table 1: The characteristic data of the subjects CKD-SD patients

Variables	Number (%) n=97)	Median or Mean + SD
Sex	53 (54.6)	
Male	44 (45.4)	
Female		
Age (years)		48 + 13
Education	24 (24.7)	
Elementary School	15 (15.5)	
Junior High School	38 (39.2)	
Senior High School	8 (8.2)	
Diploma	11 (1 1.3)	
Bachelor	1 (1 .0)	
PhD		
CKD etiology	60 (61.9)	
Hypertension	14 (14.4)	
Glomerulopathy	13 (13.4)	
Diabetic Kidney Disease	6 (6.2)	
Pyeionephrifis	2 (2.1)	
Polycystic Kidney Disease	1 (1.0)	
Nephritic Lupus	1 (1.0)	
Obstruction nephropathy		
Duration of Hemodialysis (months)		36 (12-168)
Hemoglobin level (mg/dL)		9.1 (4.7—13.7)
Serum Iron (gg/dL)		54 (14—166)
TIBC (ug/dL)		234 (137-429)
Transferrin saturation (%)		22.2 (10.1-75.1)
RET-He level (pg/cell)		31.7 (19.3-37.5)

Notes: CKD-5D=chronic kidney disease stage 5 undergoing routine hemodialysis; SD=Standard Deviation; CI=Confidence Interval; CKD=Chronic Kidney Disease; TIBC=total iron binding capacity; RET-He=Reticulocyte hemoglobin equivalent.

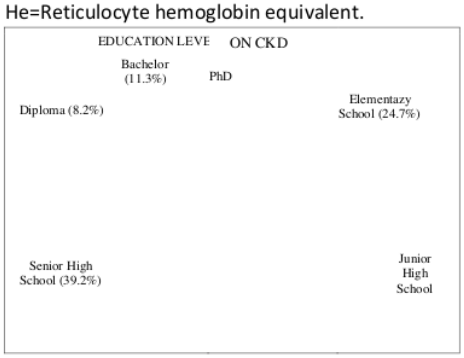

Fig.2: Chronic kidney disease patients by education level (n=97). This study mostly used the median, not the mean data, by Kolmogorov Smirnov calculation. The data were not normally distributed using median with range and that normally distributed using the mean with standard deviation. The results of study

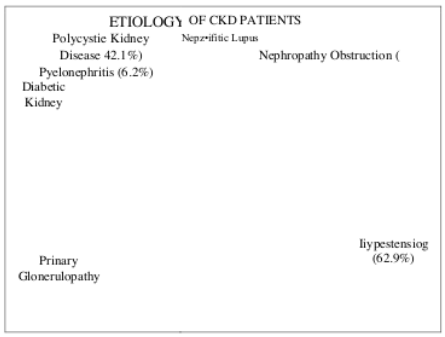

Fig.3: Chronic kidney disease patients by etiology (n=97).

found that median of anemia parameters were hemoglobin level 9.1 (4.7—13.7) gr/dLt Sl 54 (14-166) ug/dL, TIBC 234 037-429) ug/dL,

Transferrin saturation (Tsat) 22.2% (10.1—75.1) and median RET-He level 31.7 (19.3—37.5)

pg/cell (Table 1 The proportion by education according to age, duration of HD, hemoglobin and etiology can see in Fig. 2 and Fig. 3. There level, Sl, TIBC, Tsat, and RET-He (Table 2). was no difference between men and women

Table 2: The characteristic data by sex of CKD-SD patients

Variables	Sex (n=97) (Median or Mean+SD)		P value*
	Male (n=53)	Female (n=44)	
Age (years) Duration of HD months	46.68 + 10.29 48 (12-120	46.66 + 13.34 36 (12-¯ 168)	0.446 0.303
Hemoglobin gr/dL	9.1 (7-12.7)	9.2 4.7-13.7)	0.656
Sl (µg/dL)	57 (14—166	53.5 (22-165)	0.865
TIBC Transferrin saturation (%	243.1 (137-429) 24.1 (10.2-75.1)	234.8 062-356) 20.4 (10.1-73.6)	0.386 0.496
RET-He (pg/ceil)	32.4 (19.3-37.5)	31.1 (23.1-35.5)	0.132

Notes: CKD-5D=chronic kidney disease stage 5 undergoing routine hemodialysis; SD=standard deviation; HD=hemodialysis; Sl=serum iron; RET-He=Reticulocyte hemoglobin equivalent.

*Statistical test using unpaired t test (normally distributed) and Mann Whitney U test (not normally distributed), significant when p<0.05.

The statistical analysis of the correlation between the RET-He level with the duration of HD, hemoglobin, Sl, TIBC, and Tsat was performed using Rank-Spearman analysis because the data was not normally distributed. This study found a significant correlation statistically between RET-He and Sl (r=0.348; p<0.001) and Tsat (r=0.454; p<0.001) (Table 3).

Table 3: Bivariate correlaäon between RET-HE with the duration of HD, hemoglobin, serum iron, and transferrin saturation in CKD-SD patients

Variables	RET-He (n=97)	
	Correlation coefficient (r)	P value*
Duration of HD (months)	-0.066	0.519
Hem lobin gr/dL	-0.040	0.696
Sl (ug/dL) TIBC	0.348 -0.052	 0.615
Transferrin Saturation	0.454	

Notes: CKD-5D= chronic kidney disease stage 5 undergoing routine hemodialysis; HD=hemodialysis; Sl=serum iron; RET-He=Reticulocyte hemoglobin equivalent,

*Statistical test using Rank-Spearman analysis (Because all data is not normally distributed), significance when p<0.05.

There was a significant correlation between RETHe levels with serum iron and transferrin saturation as seems on the figure in linear regression. It suggested that Sl was low and RETHe level would be low. Similarly, when the transferrin saturation level was high, the RET-He level was high too (Fig. 4).

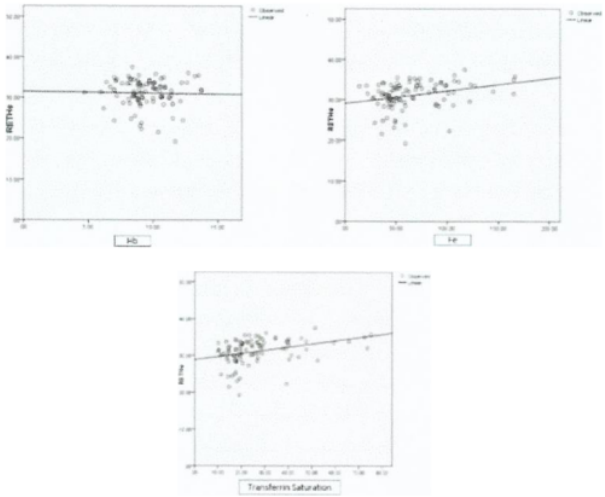

Fig.4: Regression chart between RET-He level and hemoglobin (Hb) level, serum iron (Fe), and transferrin saturaäon. (Note: RET-He = reticulocyte hemoglobin equivalent)

The Tsat value in this study had value <20% of deciency anemia. While the cut off point of RET42 patients (43.3%). Tsat cut off point < 20% He was < 29 pg/cell was defined as functional indicates the presence of functional iron iron deficiency anemia. (Table 4).

Table 4: Correlation between RET-He and transferrin saturation in CKD-5D patients

Transferrin saturation	RET-He (n=97 %)			p*
	< 29 pg/cell	29 pg/cell	TOTAL	
< 20%	14 (14.4)	28 (28.9	42 (43.3)	0.004t
> 20%	5 (5.2)	50 (51.5)	55 (56.7)	
TOTAL	19 (19.7)	78 (80.4)	97 (100)	

Notes: RET-He=Reticulocyte hemoglobin equivalent; CKD-5D=chronic kidney disease stage 5 undergoing routine hemodialysis.

*Statistical test using Chi Square, significance when p<O.05.

DISCUSSION

This was a cross-sectional study with CKD-5D patients with anemia according .to KDiGO 2012. The CKD-5D patients often developing anemia, including iron deficiency anemia.10,13,14 The baseline characteristic in this study including sex, age, duration of HD, etiology of CKD, hemoglobin, serum iron (Sl), TIBC, Transferrin saturation and RET-He. There were 53 (54.6%) male patients and 44 (45.4%) female patients. The average patient's age in this study was 48 + 13 years. The result was not much different from those reported from the IRR (Indonesian Renal Registry) data that the average age group of patients on routine HD is 45-64 years.[5] Education levels were mostly good, there were more than half are iunior high school (75.3%).

In this study, the most common etiology of CKD was hypertension (61.9%). This result were higher than reported by IRR 2015 that the etiology of CKD-5D in Indonesia is mostly hypertension (44%) followed by diabetes (22%),[5] which was different from this study who found lesser diabetes (13.4%). Reports from The United States and European data showed that the most common etiology of CKD is diabetic kidney disease.15,16 The duration of hemodialysis in the study ranged from 1 to 168 months with a median of 36 months (3 years).

The hemoglobin levels in this study were low because the subiects were mostly anemia or under normal hemoglobin levels as the KDIGO 2012 criteria for anemia on CKD patients. The mean hemoglobin level in this study was 9.47 + 1.76 gr/dL. Analysis with Kolmogorov Smirnov's calculations showed the data were not normally distributed, and the medians were 9.1 (4.7—13.7) gr/dL.

The hemoglobin level was higher than the KDIGO standard which is 9.0 g/dL as the limit for 9,13,18

EPO (erythropoietin) administration for CKD-5D patients. [13] This suggested that the average hemoglobin level of the study subjects was a good category for the initiation of EPO administration. Hemoglobin level is a parameter of anemia condition and has an impact on general condition that low hemoglobin level increases the morbidity and mortality especially in patients CKD-5D.[9,17] One of the anemia that occurs in CKD-5D patients is iron deficiency anemia. [17] In this study, the median level of Sl was 54 (14-166) gg/dL. This level was still within normal limits, but in CKD-5D the functional iron value was more important clinically. For the determination of functional iron anemia, TIBC examination was required. The TIBC levels in this study were 234 (137—429) ug/dL. Tsat was obtained from Sl divided by TIBC calculation as one of iron deficiency anemia parameters. In this study, Tsat values were 22.2% (10.1—75.1), which was above the limits of iron deficiency anemia (20%) [9,13] This indicated the possibility of CKD-5D patients in this study was not from functional iron deficiency condition. But it should be understood that transferrin is a negative acute phase reactant, which plays a role in calculating transferrin saturation and is not reliable in chronic conditions.19-23 So, determination of functional iron deficiency anemia using Tsat becomes less valid.23

The markers for functional iron deficiency in CKD are ferritin level > 1 OOng/ml in non HD/PD and >200ng/ml in routine HD or transferri% saturation Diagnosis of iron deficiency anemia or functional iron deficiency is depended by patients with acute or chronic inflammation because most of the biochemical markers for iron metabolism are strongly influenced by acute phase reactions.22,24-26 In this study, most of the subiects had anemia of chronic disease (ACD) and anemia associated with chronic kidney disease (CKD). Ferritin serum is a positive acute phase reactant and as an indicator of iron storage instead of iron supply, whereas transferrin is a negative acute phase reactant, which plays a role in calculating transferrin saturation under chronic conditions.[24,27] This study examined levels of RET-He as an indicator of functional iron deficiency anemia.

The results showed the RET-He levels were 31.5 (21.5-37.5) pg/cell. The RET-He examination used a Sysmex Automatic Machine with 35 parameters.11,28 Currently RET-He has been widely used to assess functional iron deficiency anemia?[9] RET-He examination is still not routinely used in CKD patients, especially CKD-5D to assess the status of functional anemia because currently, ferritin and Tsat are used both from KDIGO 2012 and Indonesian Society of Nephrology consensus. Some reports mention the similarily of results between CHr (reticulocyte hemoglobin content) and RET-He, the difference is the checker tool. CHr using ADVIA (Siemens) and RET-He using Sysmex.30,31 RET-He measurements provide useful information in diagnosing anemia, iron-deficient erythropoiesis, and functional iron deficiency and response to iron therapy during recombinant human erythropoietin (r-HuEPO) administration.32 The cut-off value that defines erythropoiesis deficiency is 29 pg.33,34 RET-He can replace CHr without reducing sensitivity and specificiW'. Patients who analyzed the inequalities between RET-He and CHr in terms of diagnostic showed an agreement of 449 out of 474 patients (94.4%).RET-He may replace CHr as a parameter determining iron deficiency.33,35 The result based on the bivariate calculation between RET-He and the existing variables, ie. duration of HD, hemoglobin level, serum iron (Sl), TIBC, and transferrin saturation (Tsat). The significant statistic correlated positive results were iron (Sl) (r=O.348; p<0.001) and Tsat (r4).454; p<O.001) (Table 3).

The correlation between RET-He with Sl and Tsat were significant because both of them were parameters of iron measurement. This show that RET-He correlated with the iron level in the blood, but to determine functional iron deficiency, currently it is better to use RET-He. RET-He is not affected by acute or chronic conditions whereas iron can not determine functional iron deficiency because Ferritin and Tsat are the parameters used to deterrnine in the acute phase reactant.22,23 In acute inflammatory conditions, ferritin may increase up to 3000% and decrease by UP to 30/0-0 22,24 Because of that, the RET-He examination can be used as the indicator of functional iron deficiency, which results were not far from Tsat and iron level but specific and not associated with acute and chronic response. This examination is also an easier and cheaper technology than the parameters that exist so far. The compatibility between RET-He and TSat is significant is still lower than kappa value = 0.3 (Table 4). [24] The problem is not all the examination site have Siemens ADVIA (CHr) or Sysmex (RET-He) as the

examination tools. The limitation of this study has only performed in one center with limited subjects of patients on routine hemodialysis.

CONCLUSIONS

The examination of RET-He was correlated statistically with Sl (r=0.348; p<O.001) and TSat (r=0.454; p<O.001). There was a weak significant correlation between RET-He and transferrin saturation (kappa=O.3). This suggest that the RET-He examination was reliable as an indicator of functional iron deficiency anemia than TSat and iron because it did not depend on acute or chronic response conditions. Also, RET- and cheaper technology than the parameters that have been used to diagnose functional iron deficiency anemia. Further study to compare RET-He, ferritin, and transferrin saturation as a diagnostic tool for diagnosing functional iron deficiency anemia by assessing its sensitivity and specificity is needed especially with larger sample size.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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