Blood Transfusion, Serum Total Iron Binding Capacity and Iron in Hemodialysis Patients Margono Soekarjo Hospital

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Abstract: In the final stages, chronic kidney disease (CKD) patients require renal replacement therapy like hemodialysis (HD). Packed Red Cell (PRC) transfusion is an anaemia management therapy that can increase serum Total Iron Binding Capacity (TIBC) and iron levels. This study analyzed blood transfusions, TIBC serum and iron serum levels in hemodialysis patients with repeated transfusions at Margono Soekarjo Hospital to assess the value of TIBC in the iron excess and deficiency diagnosis. An observational analytic design with cross-sectional findings was used. We investigated 85 hemodialysis patients; (73.3% men and 26.7% women aged 20 to 70 years) visited hemodialysis clinics from January 2018 to 2020. Correlation studies showed a linear relationship between the number of blood transfusions and the level of iron serum in hemodialysis patients (value *P*: 0.0001), a positive correlation between the number of blood transfusions and TIBC serum concentration (value *P*: 0.04); the significant relationship between TIBC serum and iron serum (value: 0.003). The prevalence of excess iron was 10.6%, and 2.3% in iron deficiency. Non-iron therapy patients with a maximum of one transfusion with iron therapy, patients with transfusions who are not on iron therapy, and patients on oral iron therapy were compared. The Kruskal-Wallis test showed that iron levels varied significantly between groups (*P* value: 0.0001). TIBC serum is not a reliable marker of excess iron. For patients with regular transfusions, periodical checking of TIBC and iron serum is recommended.

1 INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with a high prevalence and an increasing incidence every year. CKD is the 27th cause of death in the world in 1990 and increased to 18th in 2010. According to (Hall 2016), globally, the prevalence of CKD is 13.4% for stage 1-5 patients and 10.6% for stage 3- patients 5 (Hall et al., 2016; Urrechage et al., 2013). In Malaysia, 18 million people, an estimated 1800 new kidney failure cases per year. The Ministry of Health (2017) reports that CKD's prevalence reaches 12.5% in Indonesia's adult population. In Central Java, CKD's prevalence reached 0.3% of Central Java's population (Depkes, 2017)

CKD patients with hemodialysis generally have low Hb levels, and anaemia is not uncommon. The indication for transfusion in CKD patients is anaemia with a Hb level <7 g / dL. CKD anaemia occurs due to erythropoietin (EPO) deficiency, decreased intestinal iron absorption, iron deficiency, and iron loss during HD. During hemodialysis, there is frequent hemodynamic instability and decreased oxygen perfusion to body tissues due to a sudden decrease in blood volume during blood filtration. CKD also decreases catecholamine hormones' sensitivity because the damaged kidneys cannot clear the blood vessels' hormone. The results in a decrease in heart rate. Combining these two things will reduce the stroke volume, resulting in hypoperfusion of organs (McGuire et al., 2018). Hemoglobin is the

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blood's oxygen carrier. If the levels decrease, there can be a decrease in the oxygenation of the body's organs. Anaemia with a Hb level that is too low (<7 g / dL) puts CKD patients at high risk for doing HD because the patient's hemodynamic function becomes increasingly unstable, so it is too risky to do HD (Hider et al., 2013; Kdigo, 2012).

One of the treatments for anaemia in CKD is by transferring Packed Red Cell (PRC) components so that the patient's Hb level increases. In the body, after one erythrocyte life cycle, iron is released from heme. If it is excess, iron will be stored in the endoplasmic reticulum tissue as ferritin and hemosiderin, but the body does not have an active iron secretion system. As the amount of PRC transfused increases, the serum iron accumulates. The results in less transferrin, which is not bound by iron. Simultaneously, levels of non-transferrin bound iron (NTBI) increased. It can cause excess iron (Gao et al., 2014).

Chronic renal failure is often associated with Renal anaemia due to iron-restricted erythropoiesis (Hall et al., 2016; Urrechaga E., 2013). Kidneys secrete erythropoietin, a protein that is involved in erythropoiesis. The secretion of erythropoietin decreases when kidneys are damaged, resulting in renal anaemia (Depkes, 2017). Because iron is also required for erythropoiesis, iron deficiency may also cause anaemia (Depkes 2017; McGuire et a., 2018). The principal means to treat renal anaemia in most settings are Blood transfusion, erythropoietin (EPO), and iron therapy (Hider et al., 2013; Kdigo, 2012). Renal anaemia correction in chronic renal failure patients could carry a risk for iron overload (Gao et al., 2014; Thavarajah et al., 2019) and increase the risk of adverse events such as hypertension, congestive heart failure, myocardial infarction, and vascular access thrombosis (Depkes, 2019; Milic et al., 2016). Correction of renal anaemia to be done by blood transfusions and iron therapy. Although transfusions are considerably safer nowadays (Bozhuizen et al., 2019), transfusion reactions must be prevented as a risk in blood transfusion therapy (Robinson et al., 2017; Tanhehco et al., 2012; Gao et al., 2014). These risks include transmission of infectious agents (robinson et al., 2017; Alla et al., 2016; Rerambiah et al, 2014), the development of alloimmunization (Tagny et al., 2013; Baby et al., 2010) and iron overload (Esther et al., 2018). The present study aimed to evaluate iron status in patients with renal failure undergoing hemodialysis and assess the value of Total Iron Binding Capacity (TIBC) in diagnosing iron overload and iron deficiency in an RSUD Prof Dr. Margono Soekarjo Hospital.

2 MATERIALS AND METHODS

We investigated 85 hemodialysis patients (73.3% male and 26.7% female aged 22 to 73 years) who attended Prof. Dr. Margono Soekarjo Hemodialysis Center Hospital from January 2018 to January 2020, using cross-sectional studies. Patients were divided into four (4) groups; (1) patients with none or single transfusion without iron therapy; (2) patients with none or single under iron therapy; (3) polytransfused patients without iron therapy; (4) polytransfused patients with iron therapy. Blood samples were taken before the hemodialysis session. 3 mL of venous blood was collected in straight tubes. The collected blood samples were then centrifuged (3000 rpm for 15 minutes. Iron and TIBC in the serum used Cobas c501 to interpret. Table 1 shows TIBC and iron concentration ranges in the serum and interpretation of the results. Characteristics data and research variables showed in the form of descriptive analysis. The independent variables are including blood transfusion and iron serum. The independent variable of this study is TIBC.

We used the Spearman test to assess the correlation between the number of transfusions, iron, and TIBC levels. The strength of TIBC and iron serum concentrations compatibility was assessed based on the Kappa coefficient (κ) that was calculated using the formula $\kappa = (Po - Pe)/1 - Pe$, where Po is the relative observed agreement among assessor and Pe is the theoretical probability of chance agreement. The groups' discrepancy was analyzed using the Kruskal-Wallis multiple comparison test Dunn's post-test to assess therapeutic effectiveness. P value below 5% was considered as significant. Regarding ethics, the health research ethics committee of RSUD Prof Dr. Margono Soekarjo Number 420/01030/I/2020 approved the study. Besides, all patients consented to participate in the study.

3 RESULTS

It can be seen in Table 1 that the distribution of iron and TIBC levels and their interpretation in the study sample population. Univariate analysis can be seen in Table 2. It is found that most gender is male. The most blood group is the patient with blood group B, and the most age group is the patient aged 51-60 years. Figure 1 shows that the number of PRC units received by CKD patients undergoing HD by repeated transfusions is 2 - 14, with a maximum average of 4

kolf. Correlation between transfusion, TIBC, and Iron levels are shown here.

Table 1. TIBC and Iron range in the serum and interpretations.

	Iron deficiency	Normal	Iron overload
Serum TIBC	>400µg/dL	245-400µg/dL	<245µg/dL
Serum Iron	<35µg/dL	35-140µg/dL	>140µg/dL

Data showed a positive and significant correlation between the number of transfusions and TIBC levels (Spearman r: 0.65; P value: 0.0001). Although it was weak, the correlation between the number of transfusions and iron serum levels was positive and significant (Spearman r: 0.32; P value: 0.03).

Table 2. Research Characteristics

Characteristics		**N=85**	**%**
Gender	Male	53	73.3
	Female	32	26.7
Blood type	A	25	33.3
	B	28	33.3
	AB	10	11.1
	O	22	22.2
Age (year)	22 – 30	6	7.1
	31 – 40	5	5.8
	41 – 50	29	34.1
	51 – 60	37	43.5
	61 – 70	6	7.1
	> 70	2	2.4

Further correlation analysis showed a significant relationship between TIBC and iron serum concentration (Spearman r: 0.32; P value: 0.003). However, the observed Spearman r coefficient suggested that the correlation between TIBC serum and iron serum concentrations is weak, although significant. Next is the correlation between TIBC and Iron serum in excess iron cases. Table 3 shows the distribution of patients according to TIBC and their iron levels in this study. The prevalence of excess iron based on TIBC serum was 46.06%. The prevalence of excess iron was 15.7% when it was assessed based on the iron serum levels. The prevalence of excess iron based on TIBC and the iron concentration in serum was 10.6%. The prevalence of iron deficiency based on TIBC serum was 17.4%, while iron deficiency based on iron serum concentration was 8.9%. The prevalence of iron deficiency in both TIBC and iron concentration is 3.3%.

Table 3. Patients Distribution according to their TIBC and iron levels in serum

Total Iron Binding Capacity				
	Iron deficiency	normal	Iron Overload	Total
Iron Deficiency	3	5	7	15
Normal	15	19	26	60
Iron Overload	1	5	8	14
Total	19	29	41	89

Cohen's Kappa (κ) formula used in this study with 0.14 κ coefficient. As a result, the correlation between TIBC and iron levels in the serum was considered weak or inadequate. Regarding transfusion, TIBC, and Iron serum, a comparison was made on patients in groups 1 and 2 to patients in groups 3 and 4. The "Kruskal-Wallis test" showed that TIBC levels varied significantly between the groups (P value: 0.0001). Besides, "Dunn's Multiple Comparison Test" also showed that (1) on patients without iron therapy, TIBC level was significantly higher in polytransfused patients than patients with none or single transfusion (P value: 0.0001), (2) on patients under iron therapy, the TIBC level was significantly higher in polytransfused patients than on patients who had none or single transfusion (P value < 0.05), (3) polytransfused patients on iron therapy had significantly higher levels of TIBC compared to patients who had none or one transfusion and without iron therapy (P value: 0.001), and (4) polytransfused patients who were not on iron therapy had significantly higher levels of TIBC compared to patients who had none or single transfusion and who were under iron therapy (P value < 0.05).

Table 4. Discrepancy between groups

Groups	f	p
1	20	< 0.001
2	21	
3	22	
4	22	

Comparing the same groups of patients for their serum iron concentrations, the "Kruskal-Wallis test" showed no significant differences between the groups (table 4).

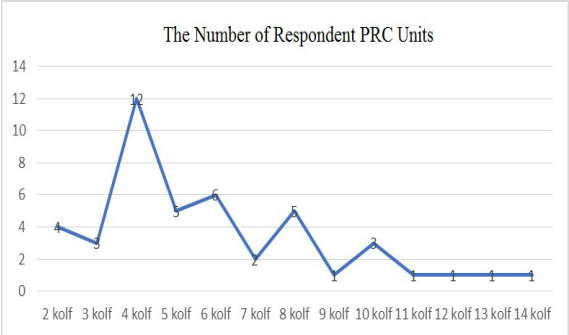

Figure 1 Distribution of data on the number of respondent PRC units

4 DISCUSSION

The present study aimed to evaluate iron status in patients with renal failure undergoing hemodialysis and assess the value of TIBC in the diagnosis of excess iron and iron deficiency. In developing countries such as Indonesia, TIBC serum level in patients is often used as a marker for excess or deficiency iron diagnosis in hemodialysis patients. This is because iron-binding capacity is the transferrin's capacity to bind with iron. When iron stores are depleted, the transferrin levels increase in blood. As only one-third of transferrin is saturated with iron, so the transferrin present in serum has an extra binding capacity (67%). It is called unsaturated iron-binding capacity (UIBC). TIBC is the total of iron serum and UIBC. Iron status in hemodialysis patients monitored using serum TIBC may rarely be performed by hemodialysis service personnel because confounding factors such as acute, chronic inflammation, and malnutrition can cause different TIBC serum value interpretation (Gujja et al., 2010).

This study showed an intense positive linear relationship between the number of blood transfusions with TIBC serum levels. It also indicated a weak association between the number of blood transfusions and iron concentrations in the serum. The compatibility level between TIBC and iron levels in the serum was low. The data suggest that multiple transfusions increase TIBC serum substantially and at lower iron serum levels. We found that in hemodialysis patients, TIBC serum is strongly overestimated iron level. TIBC serum also overestimates iron deficiency cases, but on a lower level. In this study, the prevalence of excess iron based on TIBC serum was 42.3, whereas the prevalence of excess iron based on iron serum levels was 21.2%. The prevalence of iron deficiency based on TIBC serum and iron serum was, respectively, 17.4% and 10.6%. Based on the data, 65% of patients had moderately high TIBC serum levels, and 67% of patients with very high TIBC levels had their iron serum level within the normal range. High TIBC serum is not a reliable marker of excess iron (Petkova et al., 2019; Pfeiffer et al., 2017). Because the use of TIBC serum as a marker for excess iron or deficiency could lead to (1) holding iron therapy in patients that need it and (2) giving iron treatment to patients who do not require it, accurate assessment of the body iron load is essential to prevent iron toxicity and to manage iron chelation therapy. Although we did not assess liver iron concentration (LIC) by magnetic resonance imaging (MRI), based on the published report (Depkes, 2017; Milic et al., 2018; Hoffbrand et al., 2012).

The Anemia monitoring due to retention in dialyzers was not possible in this study. This study also did not monitor the nutritional intake and diet consumed by patients. The type of food consumed by the patient can affect iron serum levels. Red meat is the most effective food (40%) absorbed by the intestine because it is a heme iron source. Consumption of vitamin C also increases the absorption of iron in the intestines.

Meanwhile, intake containing calcium and tannins inhibits iron absorption, thereby reducing serum iron levels. Therefore, this can be a confounding factor in this study. The suggestion is to do similar research by controlling for confounding factors such as nutritional intake, Erythropoiesis Stimulating Agents (ESAs) therapy. Future research will use the cohort method to see the disease's course and the effect of transfusion on iron levels in a more usual manner. We would suggest patients under regular transfusion therapy to do TIBC and iron serum measurement periodically in these countries.

5 CONCLUSIONS

TIBC serum is not a reliable marker of excess iron. For patients with regular transfusions, periodical checking of TIBC and iron serum is recommended.

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