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OVERVIEW OF IRON STATUS IN CHRONIC KIDNEY DISEASE STAGE 5 PATIENTS UNDERGOING REGULAR HEMODIALYSIS: A LITERATURE REVIEW

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ABSTRACT

Decreased of haemoglobin (Hb) in patients with CKD almost occurs in 80% of cases. The causes are multifactorial, including deficiency of erythropoietin production, a circulating factor that appears to inhibit erythropoietin, shortened red blood cell half-life, increased gastrointestinal blood loss due to thrombocytopenia, folic acid and iron deficiency, and blood loss from hemodialysis or laboratory test samples. This literature evaluation drew its data from full-text English publications published in the preceding up to 2000 until 2022. This study discusses iron status in CKD stage 5 patients undergoing regular hemodialysis. We utilised the databases Sage Pub, Pubmed, and Google Schoolar to create this study. Research shows that serum iron and TIBC levels of patients with CKD who undergo maintenance hemodialysis are better than CKD patients without hemodialysis, but lower than healthy controls and those who undergo kidney transplantation. This figure is different for ferritin.

Keyword: *Chronic Kidney Disease; Hemodialysis; Iron Status*

INTRODUCTION

Chronic kidney disease (CKD) is a term that includes all levels of decreased kidney function from mild, moderate, and severe chronic kidney damage. CKD is a public health problem worldwide. An increase in the incidence and prevalence of renal failure with poor outcome and high costs has occurred in many countries.[1,2] Chronic Kidney Disease (CKD) is more common in the elderly population, younger patients usually have a progressive decline in kidney function, 30% of patients >65 years of age with CKD have stable disease.[1,3]

The number of patients with chronic kidney failure in Indonesia continues to increase and is estimated to grow by around 10% every year.[1,3] Currently, there is no epidemiological study on the prevalence of chronic kidney disease in Indonesia. From data from several nephrology centers in Indonesia, it is estimated that the prevalence of chronic kidney disease is around 100-150 per one million population, respectively.[4,5]

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) reports that one in 10 American adults has chronic kidney disease (CKD) in any stage. Kidney disease is the ninth leading cause of death in the United States. The incidence of CKD in the United States according to those occurring in people aged 20-64 years rose slightly from 2000-2008 and remained <0.5%. The incidence of CKD in people >65 years of age doubled between 2000-2008 from 1.8% to 4.3%.[2]

Decreased of haemoglobin (Hb) in patients with CKD almost occurs in 80% of cases. The causes are multifactorial, including deficiency of erythropoietin production, a circulating factor that appears to inhibit erythropoietin, shortened red blood cell half-life, increased gastrointestinal blood loss due to thrombocytopenia, folic acid and iron deficiency, and blood loss from hemodialysis or laboratory test samples.[6] Although all the factors listed can play a role in the decrease in Hb, erythropoietin deficiency is believed to be the main cause.[7,8]

Patients with chronic kidney disease are at risk for blood loss due to platelet dysfunction. The main cause of blood loss in these patients is from hemodialysis.[7,8] In one study, it was proven that hemodialysis patients could lose an average of 4.6 L/year of blood. Gastrointestinal blood loss, often taken for laboratory tests and folic acid deficiency can also cause anemia. Iron homeostasis appears to be impaired in chronic kidney disease.[9,10]

For reasons that are still unknown (possibly due to malnutrition), transferrin levels in chronic kidney disease are half or one-third of normal levels, eliminating the capacity of the iron transport system. This situation then impairs the ability to remove iron stores from macrophages and hepatocytes in chronic kidney disease. It has been suggested that cytokines have a role in the ACD, with increased iron storage in the reticuloendothelial leading to hyposideremia. Anemia in people with chronic kidney disease may be caused by a variety of reasons.[9–11]

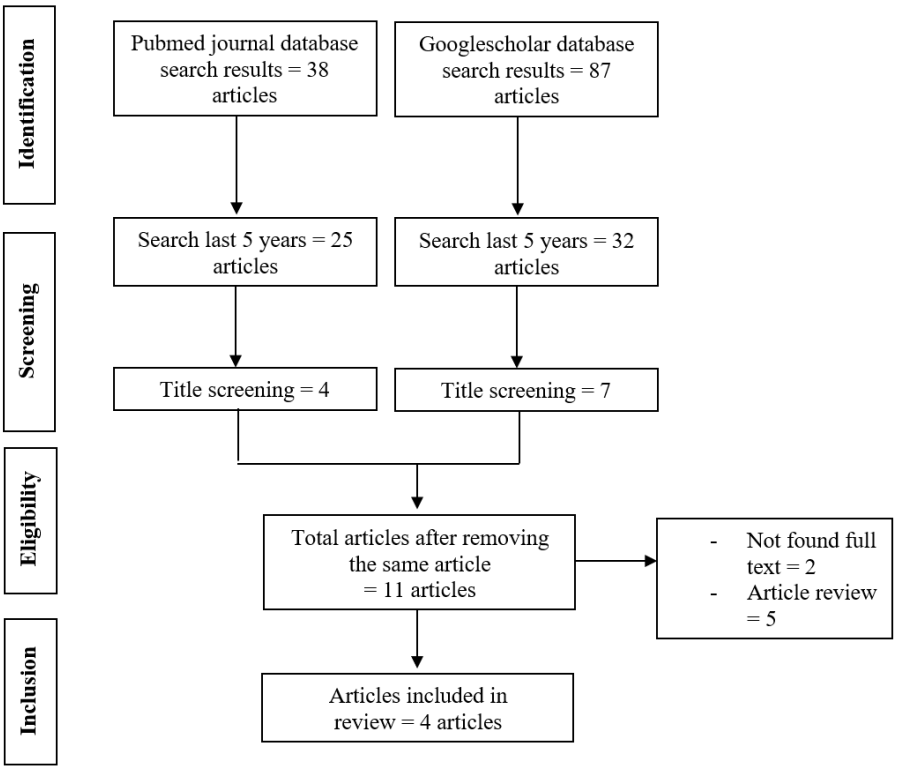

Figure 1. Article search flowchart

The serum ferritin, TSAT, and TIBC are the three most important measures of iron status. Both the serum ferritin concentration and the transferrin saturation are measured and used to target anaemia therapy in patients with chronic kidney disease (CKD). They are also connected with clinical outcomes in patients receiving dialysis treatment.[12]

METHODS

This literature evaluation drew its data from full-text English publications published in the preceding up to 2000 until 2022. This study discusses iron status in CKD stage 5 patients undergoing regular hemodialysis. We utilised the databases Sage Pub, Pubmed, and Google Schoolar to create this study. The PICO (Patient, Intervention, Comparative, and Objective) evaluation of this research comprised patients with CKD stage 5, with the index is iron status and nothing comparison. The article discusses the iron status in CKD stage 5 patients undergoing regular hemodialysis.

The researchers first used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology to add keywords into each database. Among the search phrases used were "iron status" or “ferritin status” and "CKD stage 5". ((("iron"[MeSH Terms] OR "iron"[All Fields] OR (("ferritin s"[All Fields] OR "ferritine"[All Fields] OR "ferritins"[MeSH Terms] OR "ferritins"[All Fields] OR "ferritin"[All Fields]) AND "status"[All Fields])) AND ("CKD"[All Fields] AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "5"[All Fields])) AND ((y_5[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter])). Researchers received four publications, which will be discussed further (Table 1).

RESULT

Rafi (2007) evaluated the accuracy of two commonly used tests, transferrin saturation (TSAT) and serum ferritin levels, in assessing and monitoring body iron stores. They studied 24 regular hemodialysis patients receiving regular erythropoietin therapy over a 12-month period. According to the TSAT and serum ferritin readings, patients were categorised as normal, deficient, undetermined, or overloaded. Iron status could be assessed in 16 (67%) patients using TSAT and serum ferritin; 12 (50%) had acceptable (or normal) iron status, three (12.5%) had iron deficiency, and one (4.2%) had iron excess.[13]

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	HD Duration	Result
Rafi, 2007[13]	Saudi Arabia	Cross sectional	24 patient with HD regular	12 month	Iron serum: 79.79 ± 53.68 ng/mL, total iron binding capacity (TIBC) 236 ± 56 ng/ml, serum ferritin 344 ± 197 ng/ml, and transferring saturation (TSAT) 33.63 ± 22.57 %.
Malysko, 2006[14]	Poland	Cross sectional	104 patient with HD regular	36 month	Iron serum: 81.38 ± 14.12 ng/mL, TIBC: 249.8 ± 71.41 ng/ml, TSAT: 33.84 ± 23.50%, ferritin: 709.1 ± 375. ng/ml.
Rambod, 2008[15]	USA	Cross sectional	789 patient with HD regular	60 month	Iron serum: 56.88 ± 18.13 ng/ml, TIBC : 231 ± 52 ng/ml, ferritin: 217 ± 152 ng/ml, TSAT: 23,1 ± 4,2 %
Tarek, 2014[16]	Saudi Arabia	Cross sectional	54 patient with HD regular	No data	Iron serum: 80.26 ± 11.04 ng/ml, TIBC : 232.48 ± 32.14 ng/ml, ferritin: 698.80 ± 74.04 ng/ml

Iron status was unknown in the remaining eight patients; six had elevated blood ferritin but low TSAT (functional iron deficiency), and two had elevated TSAT levels but low serum ferritin. Serum ferritin has a very poor sensitivity for identifying iron overload on its own. In conclusion, when TSAT and serum ferritin are combined, they have a poor sensitivity for identifying iron deficiency in CKD patients on HD. When TSAT and serum ferritin readings diverge, they become unreliable for directing iron treatment, and this pattern of data is often indicative of functional iron shortage.[13]

Table 2. Differences between serum iron, TIBC, ferritin and TSAT between studies

Author	Iron serum	TIBC	Ferritin serum	TSAT
Rafi, 2007[13]	79.79 ± 53.68 ng/mL	236 ± 56 ng/ml	344 ± 197 ng/ml	33.63 ± 22.57 %
Malysko, 2006[14]	81.38 ± 14.12 ng/ml	249.8 ± 71.41 ng/ml	709.1 ± 375. ng/ml	33.84 ± 23.50%
Rambod, 2008[15]	56.88 ± 18.13 ng/ml	231 ± 52	217 ± 152 ng/ml	23,1 ± 4,2 %
Tarek, 2014[16]	80.26 ± 11.04 ng/ml	232.48 ± 32.14 ng/ml	698.80 ± 74.04 ng/ml	No data

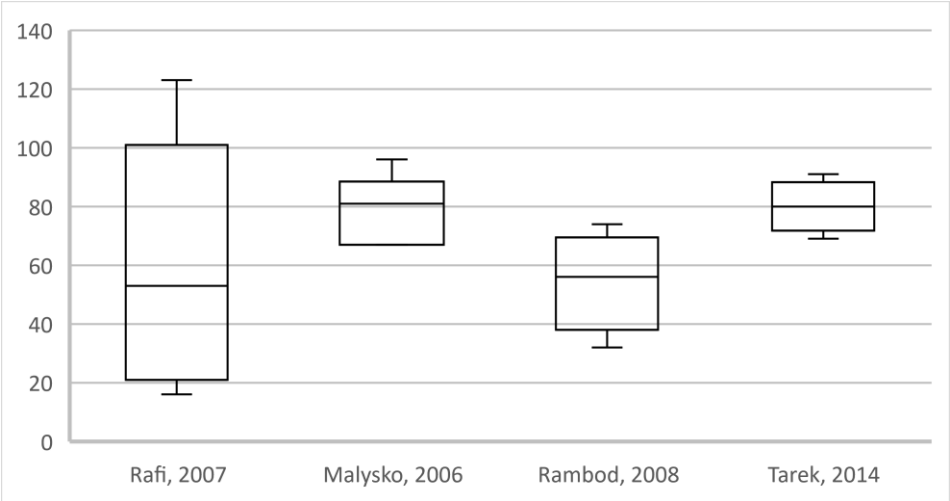

Figure 2: Serum iron block-pot

Another study showed that patients with serum Iron: 81.38 ± 14.12 ng/mL, TIBC: 249.8 ± 71.41 ng/ml, TSAT: 33.84 ± 23.50%, ferritin: 709.1 ± 375. Ng/mL. The rate was higher in those without hemodialysis, but lower than in those who received a kidney transplant.[14] Another study showed that patients with serum iron serum: 80.26 ± 11.04, TIBC : 232.48 ± 32.14, ferritin: 698.80 ± 74.04, TSAT. The rate was higher in those without hemodialysis, but lower than control. Although the difference is not significant.[16]

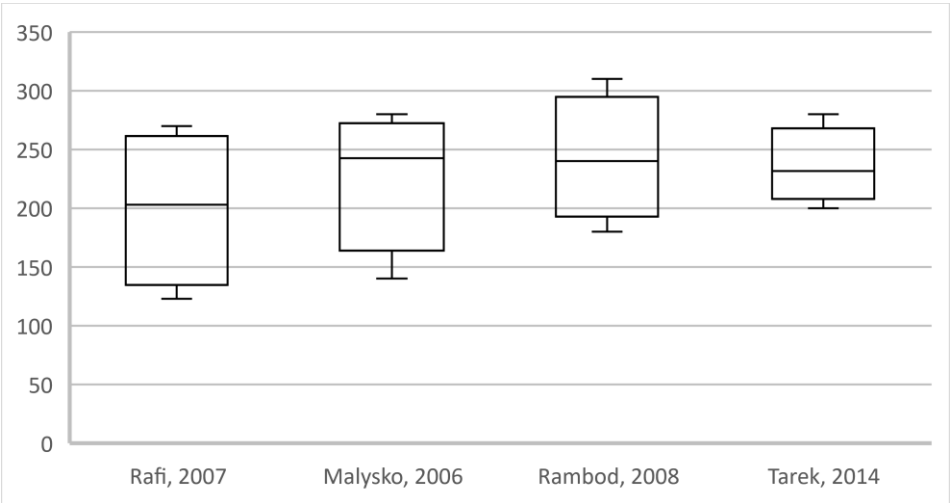

Figure 3: TIBC block-pot

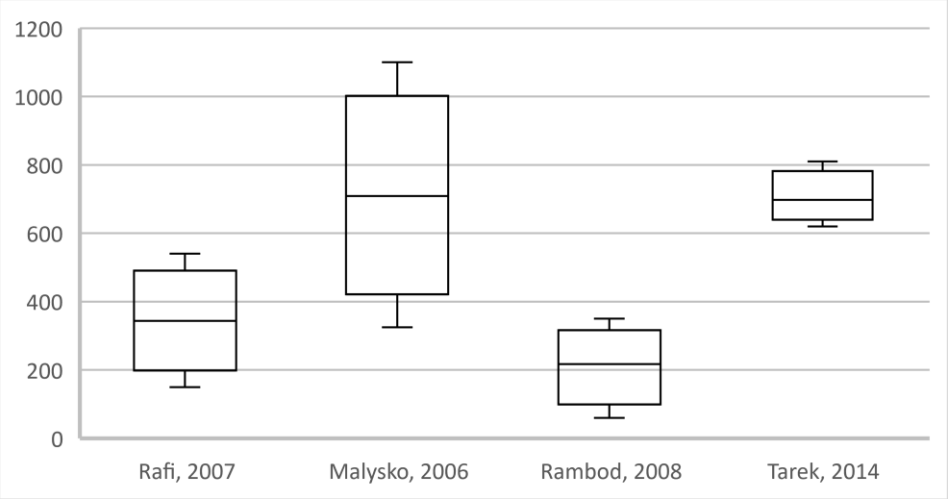

Figure 4: Ferritin block-pot

Rambod study also conducted that serum iron levels: 56.88 ± 18.13, TIBC: 231 ± 52, ferritin: 217 ± 152, and TSAT: 23.1 ± 4.2%. In people with MHD, high levels of ferritin, especially in conjunction with low ISAT, are linked to inflammation. Strategies that separate inflammation from iron metabolism may help people with chronic kidney disease manage their anaemia better. Inflammation can have a negative effect on iron metabolism and make it more difficult for people to respond to iron treatment.[15] Previous studies have shown that iron and TIBC levels in patients with CKD undergoing hemodialysis are low, while ferritin levels are in the high group.

DISCUSSION

Previous studies have shown that iron and TIBC levels in patients with CKD undergoing hemodialysis are low, while ferritin levels are in the high group. In chronic inflammatory disorders such as chronic infections, cancer, and autoimmune diseases, anaemia of chronic disease (ACD) is the most common type of anaemia seen in hospitalised patients. ACD is associated with a low serum iron concentrations inside the case of excessive reticuloendotelial iron stores; it is a hypoproliferative anaemia. It has been suggested that cytokines have a role in the ACD, with increased iron storage in the reticuloendothelial leading to hyposideremia.[9–11]

Anemia in people with chronic kidney disease may be caused by a variety of reasons. Exogenous iron and erythropoietin acquisition through biologically unregulated mechanisms cause erythropoiesis and iron homeostasis to be compromised as a result of a complex chain of events that includes a defined as the ratio insufficiency of erythropoietin, systemic inflammatory, blood loss, decreased iron absorption and utilisation, and decreased iron absorption and consumption (blood transfusions and medicinal erythropoietin and iron administration).[17]

While in IDA, the amount of iron stored in the body determines how much iron is available for use, in function iron deficiency (iron limited erythropoiesis), the amount of iron available is determined by the pace at which iron is mobilised from the reserves. Iron deficiency or functional iron deficiency may be difficult to diagnose in people with acute or chronic inflammatory disorders. Recombinant human erythropoietin (rHuEpo) has been approved for the treatment of anaemia associated with renal illness.[9–11]

That treatment leads in functional iron shortage as a consequence of inadequate iron reserves to support the increased erythropoiesis caused by the therapy. When it comes to dialysis patients, iron shortage is the most common reason for a poor response to erythropoietin. Noncompliance, gastrointestinal side effects, poor absorption, and medication interaction are all factors that limit the effectiveness of long-term orally given iron treatment; intravenous iron compounds are used to treat dialysis patients who become iron deficient.[10,11]

Iron deficiency can be caused by blood loss and poor gastrointestinal absorption (antacids given in hyperphosphatemia also bind iron in the intestine). In addition, the hemodialysis process can cause a loss of 3-5 grams of iron per year. Normally, we lose 1-2 mg of iron per day, so iron loss in dialysis patients is 10-20 times more. The life span of erythrocytes in patients with renal failure is only about half of that of normal erythrocytes.[10,11]

This increase in erythrocyte hemolysis appears to be due to abnormalities in the plasma chemical environment and not to defects in the blood cells themselves. Hemolysis in terminal renal failure is moderate. In chronic hemodialysis patients, the lifespan of erythrocytes measured using Cr showed a variation from normal red blood cells that lived but the mean survival time was reduced by 25-30%.[10,11]

Tsukamoto shown that mean iron content in residual blood was 1,247.3 ± 796.2 μg (mean ± SD) and the median was 1,002 μg (95% CI 377.6-3,461.6 μg), indicating 160.8 mg (95% CI 58.9-540.0 mg) iron loss annually when hemodialysis

was performed 156 times a year. Fifty milliliter whole blood for monthly blood test and another 2 ml of whole blood lost by paracentesis at every dialysis session contains 228.6 and 118.9 mg iron at 11 g/dl hemoglobin, respectively.[18]

Therefore, an annual total iron loss due to hemodialysis comes to 508.3 mg (95% CI 406.4-887.5 mg). Five hundred milligram of annual iron supplementation might be sufficient to maintain iron status in hemodialysis patients, which is less than the dose recommended as 1,000-2,000 mg a year. Further study will be required to verify this iron supplementation dosage with recent hemodialysis procedure.[18]

A study including thirteen pools of blood from hemodialysis and nonhemodialysis patients, researchers discovered intermethod differences of up to 150 ng/ml when they compared six routinely used ferritin tests. A study of 60 stable hemodialysis patients found that the intraindividual variability for ferritin was between 2 and 62 percent when assessed during an initial two-week period, and between 3 and 52 percent when examined over a six-week period.[19]

Serum Ferritin adequately reflects iron stores in bone marrow of HD patients and also functions as an acute phase reactant. Despite the ferritin values ranging from approximately 80-480 ng/mL, the iron stores were absent on bone marrow aspiration in ESRD patients starting dialysis and may have functional iron deficiency (FID). Indian patients with CKD have evidence of iron overload similar to those in developed countries.[12,20]

Despite the accumulation of tissue iron and elevated serum ferritin which occurs in HDCKD patients on iv iron therapy, the hemoglobin levels continue to be low, which point to the prevalence of FID anemia seen in CKD patients. We have examined the accumulation of tissue iron and elevated serum ferritin in HDCKD and NDCKD patients receiving iv and oral iron therapy respectively. The serum iron levels were correlated with tissue iron and ferritin levels to gauge the occurrences of functional and absolute iron deficiency.[12,20]

Blood ferritin levels are a proxy for iron storage, and current recommendations for treating anaemia in hemodialysis patients recommend that serum ferritin concentrations be maintained at levels more than 200 ng/ml at all times. Patients on chronic hemodialysis were studied to assess the interassay differences and short-term intraindividual variability of serum ferritin levels, with the goal of demonstrating how these variations may influence treatment choices.[19]

Levels of saturated and unsaturated iron binding capacity (UIBC, TIBC) as alternative markers of transferrin saturation and hypo pigmentation, there was evaluate iron overload along with Hb and any elevated due to increased inflammation which inhibits hepcidin.[21] In chronic renal failure, a significant reduction in TIBC and ferritin levels is associated with a chronic inflammatory disease or tumours, as well as proteinuria.[22]

Inverse connection between ferritin and transferrin levels implies that increased ferritin synthesis may compensate for lower levels of iron-bound transferrin, which decreases the amounts of iron status present in the bloodstream. Ferritin levels in hemodialysis patients should be checked on a regular basis to ensure that they do not become iron deficient and that their ferritin value does not continue to rise.[22]

Long-term hemodialysis may produce erythropoietin deficit due to faulty iron supplies, while faulty iron supplies can cause iron deficiency due to faulty iron supplies When the transferrin binding capabilities of iron medications are exceeded, as well as when the quantity of non-transferrin reactive iron in the plasma rises, undesirable consequences might occur.[22]

Anemia or status iron make a signifficant impact for patient with CKD. Patients getting inappropriately low ESA given dosages under the bundled payment system were shown to have a greater risk of mortality if their haemoglobin level was lower (<10 g/dL) for a longer period of time. An elevated serum ferritin level of <300 ng/mL was linked with a greater risk of all-cause and cardiovascular mortality, whereas an elevated serum ferritin level of more than 800 ng/mL was associated with a higher risk of all-cause and infectionrelated death.[23]

Death from any cause and cardiovascular disease were shown to be lower in those who had TSAT values between 30 and 50 percent, according to the research. On the basis of the findings of the AIM-HD study, we recommend that patients with prevalent hemodialysis avoid having a low haemoglobin value and maintain a ferritin level between 300 and 800 ng/mL and a TSAT level between 30 and 50 percent, as well as prompt IV iron supplementation in patients with prevalent hemodialysis receiving the restricted ESA doses but prompt IV iron supplementation.[23]

CONCLUSION

Research shows that serum iron and TIBC levels of patients with CKD who undergo maintenance hemodialysis are better than CKD patients without hemodialysis, but lower than healthy controls and those who undergo kidney transplantation. This figure is different for ferritin.

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