INTERNATIONAL JOURNAL OF SOCIAL HEALTH
https://ijsh.ph/index.php/rp
Volume 4 Number 2 February 2025 E-ISSN: 2963-3036

Correlation Between Serum Iron with Platelet Count in Patients with End Stage Renal Disease (Esrd) on Hemodialysis at Gunung Jati Cirebon Hospital

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KEYWORDS	ABSTRACT
Chronic Kidney Disease, Esrd, Hemodialysis, Platelet Count, Serum Iron	Chronic Kidney Disease (CKD) is a kidney disorder that occurs gradually and irreversibly, characterized by structural abnormalities or abnormalities in kidney function lasts more than 3 months. CKD stage 5 (also known as ESRD) requires hemodialysis. ESRD on hemodialysis patients are often have iron deficiency. Serum iron levels may reflect changes in platelet counts, but correlation between them is still unclear. To determine the correlation between serum iron with platelet count in patients with ESRD on hemodialysis at Gunung Jati Cirebon Hospital. This is an observational research with a cross-sectional design and retrospective approach. Medical records containing serum iron level and platelet count from January to July 2024 were studied, with a maximum interval of 10 days between each test. Total of 55 samples were obtained. The data were analized using spearman's rho test. In this research, there were 37 (67,72%) patients were iron deficiency and 18 (32,73%) with a normal iron serum. The research also shown that 3 (5,45%) patients had thrombocytopenia, 47 (85,45%) patients had normal platelet count, and 5 (9,10%) had thrombocytosis. Spearman's rho analysis were done resulting a p-value of 0,045 (p<0,05) and rho -0,271 (0,20-0,39). There was a significant correlation with negative affiliation between serum iron and platelet count in ESRD on hemodialysis patients at Gunung Jati Cirebon Hospital. The implication of this research is that low serum iron levels in ESRD patients undergoing hemodialysis can contribute to changes in platelet count, with a significant negative correlation.

DOI: 10.58860/ijsh.v4i2.284

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INTRODUCTION

Chronic Kidney Disease (CKD) is a progressive and irreversible kidney disorder characterized by structural abnormalities or impaired kidney function lasting more than three months (Askenazi et al., 2018). At the most advanced stage, CKD progresses to End-Stage Renal Disease (ESRD), which requires renal replacement therapy such as hemodialysis, peritoneal dialysis, or kidney transplantation. ESRD poses a significant global health burden, with increasing prevalence, incidence, and mortality rates. According to the International Society of Nephrology-Global Kidney Health Atlas (ISN-GKHA), approximately 850 million people worldwide suffer from CKD, accounting for about 9.5% of the global population, with an average mortality rate of 2.4%. In Indonesia, national Basic Health Research (RISKESDAS) data reported a CKD prevalence of 0.38% in individuals aged ≥15 years, nearly doubling from the 2013 estimate of 0.2%. In West Java alone, CKD prevalence reached 0.48%, translating to approximately 131,846 cases.

One of the major complications in ESRD patients undergoing hemodialysis is anemia, which can result from chronic disease or iron deficiency (Fishbane & Spinowitz, 2018). Iron deficiency affects about 50% of non-dialysis-dependent CKD patients and is even more prevalent among ESRD patients on dialysis. Emerging evidence suggests a potential link between iron deficiency and platelet count fluctuations in ESRD patients. Platelets play a crucial role in hemostasis, and both thrombocytosis and thrombocytopenia are observed in ESRD patients. Thrombocytosis may result from factors such as iron deficiency, inflammation, Erythropoiesis-Stimulating Agent (ESA) therapy, or tissue damage. A research by Streja et al. (2016) found that thrombocytosis in hemodialysis patients due to iron deficiency was associated with increased mortality risk. Conversely, thrombocytopenia in ESRD can stem from uremia, severe iron deficiency anemia, sepsis, or heparin therapy, contributing to bleeding risks and increased mortality (Thakar et al., 2021).

Despite existing studies on platelet count variations in ESRD patients, the relationship between serum iron levels and platelet fluctuations remains unclear, particularly in the context of hemodialysis (Kim et al., 2016). Previous research has reported inconsistent findings regarding whether iron deficiency contributes more to thrombocytosis or thrombocytopenia and its subsequent clinical implications. Therefore, there is a critical need for further investigation to elucidate this relationship, as understanding these mechanisms may help optimize anemia management strategies and improve patient outcomes therapy (Liao et al., 2022).

Based on the above background, this research aims to analyze the relationship between serum iron levels and platelet counts in ESRD patients undergoing hemodialysis therapy. Specifically, it seeks to determine how serum iron fluctuations correlate with platelet count variations among ESRD patients at Gunung Jati General Hospital, Cirebon City. So that the benefit of this research is to provide a more in-depth understanding of the relationship between serum iron levels and platelet counts in ESRD patients undergoing hemodialysis. The results of this study are expected to contribute to the improvement of anemia management in end-stage CKD patients, especially in terms of monitoring iron levels and the risk of hematological disorders related to platelets.

METHOD

The data used in this research consists of secondary data obtained from medical records of ESRD patients who routinely undergo hemodialysis, have been on hemodialysis for ≥ 3 months, are ≥ 18 years old, and have complete serum iron and platelet count data. The laboratory data used were the most recent results recorded between January and July 2024, with a maximum interval of 10 days between examinations of serum iron and platelet count. Data were excluded if the interval between serum iron and platelet count examinations exceeded one day or if patients had a history of blood clotting disorders, anemia due to congenital diseases, cancer, liver cirrhosis, or autoimmune diseases. Additionally, patients experiencing infectious diseases such as malaria, dengue hemorrhagic fever, or sepsis were excluded from the research.

Sampling was conducted using a purposive sampling technique. The sample size was determined using Slovin's formula with a 10% margin of error, resulting in a total of 55 samples. A more detailed explanation regarding the justification for Slovin's formula application, including assumptions and potential limitations, will be provided. The samples were selected from medical records of ESRD patients on hemodialysis who had complete serum iron and platelet count data.

Data analysis was performed in three stages. First, a univariate analysis was conducted to describe the frequency distribution of both independent and dependent variables, specifically serum iron levels and platelet counts. Second, a bivariate analysis was carried out using Spearman's rho test to assess the correlation between serum iron levels and platelet counts. To enhance the validity of the results, additional statistical controls for potential confounding variables, such as medication use that may influence serum iron levels and platelet counts, were considered (Chiu et al., 2021).

Serum iron levels were categorized on an ordinal scale as serum iron deficiency (< 65 µg/dL) and normal serum iron (≥ 65 µg/dL). Platelet counts were also categorized on an ordinal scale into three groups: thrombocytopenia (< 150,000/µL), normal platelet count (150,000–450,000/µL), and thrombocytosis (> 450,000/µL). To ensure the validity and reliability of the data, standard laboratory procedures were followed for serum iron and platelet count measurements. Further details on how validity and reliability were tested will be elaborated, including methods such as inter-rater reliability or repeated measurements (Cole, 2024). Given the retrospective nature of the research, potential biases, such as selection bias and information bias, were considered. Steps were taken to mitigate these biases, including strict adherence to inclusion and exclusion criteria and careful selection of the most recent laboratory data within a reasonable timeframe.

RESULT AND DISCUSSION

In the research, 86 samples met the inclusion criteria, then 31 samples were excluded because 28 samples had a distance of more than 10 days between serum iron and platelet count, 1 sample of lupus, 1 sample of idiopathic thrombocytopenic purpura, and 1 sample of multiple myeloma. In this research, 55 samples were obtained according to the inclusion and exclusion criteria that had been selected.

In the characteristics of the age group, no samples were obtained in the age category 18-24 years, but samples were obtained in the age category 25-34 as many as 7 people (12.73%), age 35-44 as many as 5 people (9.09%), age 45-54 as many as 21 people (38.18%), age 55-64 as many as 13 people (23.64%), age 65-74 as many as 9 people (16.36%). Thus it can be concluded that the distribution of the age group 45-54 years is the most sample group in this research.

Table 1. Distribution of sample characteristics by age group

Age Group (Year)	Frequency (n)	Percentage (%)
18-24	0	0
25-34	7	12,73
35-44	5	9,09
45-54	21	38,18
55-64	13	23,64
65-74	9	16,36
Total	55	100

Based on gender, there were more men than women, namely 35 people (63.64%). While the female gender was 20 people (36.36%).

Table 2. Distribution of sample characteristics based on gender

Gender	Frequency (n)	Percentage (%)
Male	35	63,64
Female	20	36,36
Total	55	100

The univariate variables in this research were serum iron levels and platelet counts. In the characteristics of serum iron levels, out of 55 samples, the category of serum iron deficiency was found to be more than normal serum iron, namely 37 samples (67.27%). While samples with normal serum iron levels were 18 samples (32.73%).

Table 3. Distribution of sample variables based on serum iron levels

Serum Iron Level	Frequency (n)	Percentage (%)
Serum iron deficiency (<65µg/dl)	37	67,27
Normal serum iron (≥ 65µg/dl)	18	32,73
Total	55	100

In the characteristics of platelet count, out of 55 samples, there were 3 samples with thrombocytopenia category (5.45%), normal platelet levels of 47 people (85.45%), and thrombocytosis of 5 people (9.10%). Thus, in this research, most samples were obtained with normal platelet counts.

Table 4. Distribution of sample variables based on platelet count

Platelet Count	Frequency (n)	Percentage (%)
Thrombocytopenia (< 150,000/µL)	3	5,45
platelets (150,000-450,000/µL)	47	85,45
Thrombocytosis (>450,000/µL)	5	9,10
Total	55	100

In the bivariate analysis between serum iron levels and platelet counts in ESRD patients on hemodialysis at Gunung Jati General Hospital, 37 samples were found to have serum iron deficiency. Of the 37 samples (67.3%), 1 sample (1.8%) was found with thrombocytopenia, 31 samples (56.4%) with normal platelet levels, and 5 samples (9.1%) with thrombocytosis. While samples with normal serum iron levels were found in 18 samples (32.7%), where samples with thrombocytopenia were 2 samples (3.6%), normal platelets were 16 samples (29.1%), and there were no thrombocytosis samples.

Table 5. Correlation test analysis between serum iron levels and platelet counts

Radar Serum Iron		Platelet Count			Total	*p-value*	r*
		Thrombocytopenia	Normal Platelets	Thrombocytosis			
Serum Iron Deficiency	n	1	31	5	37	0,045	- 0,271
	(%)	(1,8%)	(56,4%)	(9,1%)	(67,3%)		
Normal Serum Iron	n	2	16	0	18		
	(%)	(3,6%)	(29,1%)	(0%)	(32,7%)		
Total	n	3	47	5	55		
	(%)	(5,5%)	(85,5%)	(9%)	(100%)		

**Spearman's rho* test

In the results of bivariate analysis using the Spearman's rho test, a p-value of 0.045 (p <0.05) and an r value of -0.271 (0.20-0.39) were obtained, so it was concluded that there was a significant negative relationship with a weak level of strength.

In this research, the majority of ESRD patients on hemodialysis experienced serum iron deficiency (67.27%). These results are similar to research conducted by Prasetyorini T, et al (2024), which found that CKD patients undergoing hemodialysis both in pre-hemodialysis and post-hemodialysis, more often had decreased serum iron levels (55.6% and 57.1%) than normal serum iron. Increased hepsidin, bleeding, chronic inflammation, or ESA therapy in CKD patients on hemodialysis can be factors that affect this condition. This was proven in a research conducted by Vaseekaran S.K (2023) where there was an increase in the median value of hepsidin levels in CKD patients compared to the healthy population, with the mean value of hepsidin levels in stage 5 CKD patients being 600-750ng/ml. Increased hepsidin levels are caused by decreased renal excretory function and chronic inflammation, which will inhibit intestinal iron absorption and the release of iron reserves in hepatocytes, cells, or macrophages, thus reducing the availability of iron for erythropoiesis. The research also found a significant negative relationship between hepsidin and hemoglobin levels in CKD patients with functional iron deficiency.

Research conducted in CKD patients on hemodialysis found variations in platelet counts. in this research, normal platelet counts were more common in CKD patients on hemodialysis. This is in accordance with research conducted by Baaten C, et al (2021) which states that 14 studies reported the majority of CKD patients with normal platelet counts, 5 studies with thrombocytopenia, and 1 research with thrombocytosis. In a research conducted by Abdelrahim A, et al (2023), the mean value of platelet counts in CKD patients on hemodialysis was 268 ± 100 x103 which indicates that the average CKD patient on hemodialysis has a normal platelet count. This may be due to the compensatory mechanism to keep the platelet count within normal limits or due to routine monitoring of heparin administration during the hemodialysis process.

In CKD patients, thrombocytopenia can be found. According to research conducted by Latiwesh OB, et al (n.d.), CKD patients undergoing hemodialysis have a lower platelet count than CKD patients who have not undergone hemodialysis therapy ($p<0.005$). This may be due to the utilization of platelets through continuous activation due to shear stress in extracorporal circulation and exposure to dialysis membrane in repeated hemodialysis that induces aggregation, secretion, and formation of platelet-leukocyte aggregates; or due to reduced platelet production by megakaryocytes. The use of heparin can also cause thrombocytopenia, as stated in the research of Pintaningrum, et al (2021) which concluded that heparin therapy in CKD patients during hemodialysis caused thrombocytopenia or known as Heparin-Induced Thrombocytopenia.

Thrombocytosis may also occur in these patients. Thrombocytosis was found more in CKD patients on hemodialysis with serum iron deficiency. This is in accordance with a research conducted by Liao R, et al (2022) where there was an increase in the number of platelets in CKD patients on hemodialysis with serum iron deficiency. According to the theory of Karpatkin, et al (1972), this can occur due to disruption of the inhibitor compartment, where iron can directly or indirectly prevent the process of thrombopoiesis above normal through an unknown mechanism.

In this research, the results of the analysis using Spearman's rho test, obtained a p-value of 0.045 ($p <0.05$) which shows there is a significant relationship with an r value of -0.271 (0.20-0.39) which shows a relationship with a weak level of strength. The relationship obtained is negative so that the lower the serum iron level, the higher the platelet count and vice versa.

In the general population, iron deficiency is often associated with an increase in platelet count. In a research conducted by Voudoukis E, et al (2016) on 198 samples of Inflammatory Bowel Disease (IBD) patients, the relationship between platelet count and iron deficiency anemia parameters in IBD patients was found. Similar results were also shown in a research conducted by Patel G, et al (2022) on 294 patients with iron deficiency anemia in a large tertiary care center, Northwestern India, where a significant and negative relationship was found between platelet count and serum iron with a p-value of 0.006 and an r value in the Pearson test of -0.255. In this research, 59.9% of iron deficiency anemia patients with normal platelet counts, 33.7% with thrombocytosis and 6.4% with thrombocytopenia were found. The relationship between iron deficiency anemia and thrombocytosis is still not completely clear, but some studies suggest that iron stimulates an increase in platelet count secondarily by increasing the rate of production of precursor cells towards megakaryocytes, accelerating megakaryocyte maturation, stem cell shunt due to inhibition of erythropoiesis which increases platelet production, or EPO therapy which has a synergistic effect on TPO thereby increasing platelet production.

The results in this research are also similar to research conducted by Liao R, et al (2022) with a retrospective cohort method on 1,167 ESRD patients on hemodialysis in the nephrology department of western china hospitals from 2012-2017. In this research, the results showed that there was a weak negative significant relationship between serum iron levels and platelet counts ($\rho = -0.1466$, $P < .001$).

The relationship is weak due to several factors and conditions that can affect serum iron levels and platelet counts in samples. In this research, the percentage of iron deficiency patients with normal platelet counts was 56.4%. Serum iron deficiency in CKD patients on hemodialysis can be caused by several factors. Chronic inflammation in CKD is one of the factors that can increase the production of hepsidin hormone in the blood so that there is a decrease in iron levels in the plasma. The decrease in serum iron will increase the number of platelets in the plasma. Chronic inflammation can also increase platelet count through activation of proinflammatory cytokines. The increase in platelet count can be within the normal range or above normal, depending on the level of decrease in serum iron levels or compensatory mechanisms by the human body. Until now, no studies have been obtained regarding the range of serum iron levels that can cause thrombocytosis in patients on hemodialysis. EPO deficiency is also often found in CKD patients on hemodialysis. EPO has a synergistic effect on TPO, where a decrease in EPO can cause a decrease in MEP production so that the production of megakaryocytes can be normal or decreased. The administration of iron replacement therapy can also normalize platelet counts, and be a strategy to reduce the risk of thromboembolism in CKD patients on hemodialysis.

CONCLUSION

Based on the results of this research, the majority of ESRD patients undergoing hemodialysis at Gunung Jati General Hospital, Cirebon City, had serum iron deficiency (67.27%), while most had normal platelet counts (85.45%). A significant negative correlation was found between serum iron levels and platelet counts (p-value 0.045, r = -0.271), although the correlation was weak. These findings highlight the potential role of serum iron levels in influencing platelet counts in ESRD patients undergoing hemodialysis. Clinically, this suggests the need for careful monitoring of iron supplementation and platelet levels to optimize patient management and minimize potential hematological complications. For future research, it is recommended that serum iron and platelet count examinations be conducted simultaneously to improve accuracy. Additionally, further studies with stronger research designs are needed to explore other contributing factors influencing this correlation, including their impact on platelet function and clinical outcomes in ESRD patients undergoing hemodialysis.

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