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Correlation between the Characteristics of Chronic Kidney Disease Patients Undergoing Hemodialysis and Erythropoietin Stimulating Agent Therapy on Hemoglobin Levels

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ABSTRACT

Background: Chronic Kidney Disease is one of the deadliest diseases in the world with a high prevalence. Hemodialysis is believed to increase the survival of chronic kidney disease patients. This study aims to analyze the relationship between condition factors in patients with chronic kidney disease undergoing hemodialysis and erythropoietin stimulating agent therapy with hemoglobin levels.

Subjects and Method: This research is a quantitative study with a cross-sectional study design carried out at the Madiun City Regional Hospital. Data was taken from June 1, 2022 to June 30, 2022. The population in this study were patients who received hemodialysis services and erythropoietin stimulating agent therapy. The sample was 101 patients with total sampling technique. The independent variables in this study are age, gender, duration of hemodialysis, while the dependent variable is hemoglobin level. Data collection techniques were carried out using patient medical record data. Data analysis used multiple linear regression with Stata 17.

Results: The results of multiple linear regression analysis of the relationship between duration of hemodialysis, gender, age, hemoglobin levels before and hemoglobin levels after chronic kidney disease patients undergoing hemodialysis with erythropoietin stimulating agent therapy show that every 1 month increase in hemodialysis will be followed by an increase in hemoglobin of 0.02g/dL (b= 0.02; 95% CI= 0.01 to 0.03; p=0.018). Every 1g/dL increase in hemoglobin levels before hemodialysis will be followed by hemoglobin levels after hemodialysis of 0.7 g/dL (b=0.7 CI 95% 0.6 to 0.8 p<0.001), gender (b=-0.06; 95% CI= -0.7 to 0.6; p=0.857), and age (b=-0.01; 95% CI= -0.03 to 0.03 p=0.833).

Conclusion: There is a positive relationship between the duration of hemodialysis and hemoglobin levels after chronic kidney disease patients undergo hemodialysis with erythropoietin stimulating agent therapy. There is no statistically significant difference between men and women, age in hemoglobin levels after undergoing hemodialysis with erythropoietin stimulating agent therapy in patients with chronic renal failure.

Keywords: chronic kidney disease, hemodialysis, erythropoietin stimulating agent, hemoglobin

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BACKGROUND

As one of the deadliest diseases in the world, chronic kidney disease (CKD) has a high prevalence with high costs and a poor prognosis along with the increasing number of comorbidities (Dewi et al., 2020). Chronic kidney disease is a direct risk factor for cardiovascular disease, end-stage renal disease and mortality (Almaeen and Hedeab, 2021). CKD is a pathophysiological process that has various types of etiology, which results in progressively decreasing kidney function, thus ending in kidney failure. The role of the kidneys in the body has important functions such as regulating the body's metabolism, endocrine and its contribution to the formation of red blood cells, better known as erythropoiesis. Erythropoiesis will be disrupted, resulting in disruption of red blood cell formation (Amudi and Palar, 2021). In its development, several studies have shown that the prevalence of CKD is increasing in various regions throughout the world.

The increasing prevalence of diabetes and hypertension is also a cause of CKD, which can result in an increase in the prevalence of CKD grades II to V (Aisara et al., 2018). Data related to kidney disease obtained from the results of Basic Health Research (Riskesdas) in 2018. The population aged ≥ 15 years with a diagnosis of chronic kidney failure was 0.13%. Prevalence increases with age, with a sharp increase in the 65 – 74 year age group. The prevalence of men is 0.42% higher than women's 0.35%. The prevalence between urban and rural areas is the same 0.38%, not working 0.48%, working in the self-employed sector 0.35%. The province with the highest prevalence is North Kalimantan at 0.64%, followed by North Maluku, North Sulawesi, Gorontalo and Central Sulawesi at 0.5% each. Meanwhile, East Java Province was the location for this research with a prevalence of 0.29% (Riskesdas, 2018).

Kidney replacement therapy, which we are more familiar with as hemodialysis, uses a semipermeable membrane which has a function like a nephron so that it can remove metabolic waste products and correct fluid and electrolyte balance disorders in patients with kidney failure (Mailani, 2017). To maintain survival and survival in patients with kidney failure, hemodialysis therapy can help. The survival ability of CKD sufferers undergoing hemodialysis is also influenced by various factors, including the severity of the disease experienced, the condition of various body systems that are disturbed by toxins caused by CKD, regulation of fluid and food intake, and compliance with the hemodialysis schedule (Hasneli, 2017) .

The quality of life of kidney failure patients who receive hemodialysis therapy is decreasing because patients not only face health problems due to chronic kidney disease but also because the therapy lasts a lifetime, resulting in the quality of life of patients undergoing hemodialysis being lower than in patients with congestive heart failure, lung disease, chronic lung, or cancer (Mailani., 2017).

Anemia is one of the most important complications of CKD, which develops early and worsens during long-term disease progression. There is a relationship between lower hemoglobin levels, severity of anemia and decreased kidney function (Al-maeen and Hedeab., 2021). Chronic kidney disease sufferers who experience anemia can reach 80%-90% of patients. The National Health and Nutrition Examination Survey (NHANES) population study states that the incidence of anemia is less than 10% in chronic kidney disease stages 1 and 2, stage 3 is 20-40%, stage 4 is 50-60% and more than 70% in chronic kidney disease stage 5.

That the more severe the level of CKD experienced by the patient, the higher the possibility of experiencing anemia. The main cause of anemia in CKD is most likely a relative deficiency of erythropoietin (EPO) (Kurniawanto et al., 2018).

Anemia generally begins to occur in CKD stage 3 and is almost always found in CKD stage 5. In Indonesia there is no national epidemiological data on anemia in CKD. It can be said to be anemia if the hemoglobin (Hb) level is <14 g/dL (men) or <12 g/dL (women). Contributing factors can cause renal anemia such as iron deficiency, short erythrocyte lifespan, secondary hyperparathyroidism, and inflammatory infections (PERNEFRI., 2011).

Erythropoietin (EPO) is a glycoprotein hormone produced in response to hypoxia in order to increase erythrocyte production. Erythropoietin circulates in plasma and binds to specific receptors on erythrocyte progenitor cells so that they proliferate and differentiate into red blood cells (Faizah et al., 2022).

Erythropoietin Stimulating Agent or erythropoietin stimulant therapy is a therapy that can stimulate the production of the hormone erythropoietin, so it is hoped that hemoglobin production will proceed well and can prevent anemia in patients with chronic kidney disease. Erythropoietin Stimulating Agent therapy is given to maintain hemoglobin levels in chronic kidney disease sufferers undergoing hemodialysis. In general, patients are given Erythropoietin Stimulating Agent therapy if the hemoglobin level is below 10g/dL because chronic anemia is very dangerous for patients with chronic kidney disease (Amudi and Palar., 2021).

Based on the background that has been explained, it is necessary to conduct research on the relationship between factors in the condition of chronic kidney disease patients undergoing hemodialysis and erythronpoietin stimulating agent therapy with hemoglobin levels.

SUBJECTS AND METHOD

1. Study Design

This research is a quantitative study with a cross-sectional study design carried out at the Madiun City Regional Hospital. Data was taken from June 1, 2022 to June 30, 2022.

2. Population and Sample

The population in this study were patients who received hemodialysis services and erythropoietin stimulating agent therapy. The sample was selected by total sampling. The total sample was 101 patients.

3. Study Variables

The independent variables in this study are age, gender, duration of hemodialysis, while the dependent variable is hemoglobin level.

4. Operational definition of variables

The age referred to in this study is the age of chronic kidney disease patients undergoing hemodialysis and erythropoietin stimulating agent therapy.

The gender referred to in this study is the gender of chronic kidney disease patients undergoing hemodialysis and erythropoietin stimulating agent therapy.

The duration of hemodialysis referred to in this study is the duration of hemodialysis for chronic kidney disease patients undergoing hemodialysis and erythropoietin stimulating agent therapy.

Hemoglobin levels are a marker for patients experiencing anemia and ESA therapy is given to increase and maintain hemoglobin levels. The hemoglobin level referred to in this study is the increase in hemoglobin levels after chronic kidney disease patients underwent hemodialysis with erythropoietin stimulating agent therapy.

5. Study Instruments

The data collection technique used is patient medical record data.

6. Data analysis

Data analysis was carried out using multiple linear regression with Stata 17.

RESULTS

1. Sample Characteristics

The results of the analysis in Table 1 show that the majority of research subjects were over 45 years old, namely 81 (80.2%) and the remaining 20 subjects (19.8%) were under 45 years old. Based on gender, the majority of research subjects were male, namely 63 (62.4%) and 38 (37.6%) female. The results of the study showed that the majority of hemo-dialysis duration was more than 12 months, namely 70 (69.3%) and less than 12 months were 31 subjects (30.7%). Meanwhile, the hemoglobin levels of patients with chronic kidney disease before and after undergoing hemodialysis and erythropoietin stimulating agent therapy in this study experienced a decrease in the majority, namely 33 subjects (32.7%) and 68 subjects (67.3%) experienced an increase.

The results of the analysis in Table 2 above show that the youngest age is 30 years, the oldest is 77 years with an average age of 53.3 years. The minimum duration of hemodialysis is 1 month, the maximum is 84 months with an average duration of hemo-dialysis of 34.8 months. The hemoglobin level before hemodialysis with erythropoetin stimulating agent therapy was a minimum of 0 and a maximum of 18g/dL with an average of 9.3g/dL. Meanwhile, the hemoglobin level after hemodialysis with erythropoietin stimulating agent therapy was a minimum of 0 and a maximum of 17.3g/dL with an average of 9.5g/dL.

Table 1. Sample Characteristics (categorical data)

Variable	Category	n	(%)
Age	< 45 years	20	19.8
	≥ 45 years	81	80.2
Gender	Male	63	62.4
	Female	38	37.6
Duration of	< 12 months	31	30.7
Hemodialysis	≥ 12 months	70	69.3
Hemoglobin levels	Increase	33	32.7
	Decrease	68	67.3

Table 2. Sample Characteristics (continuous data)

Variable	N	Mean	SD	Min	Max
Age	101	53.3	10.6	30	77
Duration of Hemodialysis	101	34.8	25.2	1	84
Hemoglobin levels (Pre)	101	9.3	2.6	0	18
Hemoglobin levels (Post)	101	9.5	2.5	0	17.3

Table 3. Multiple Linear Regression Analysis

Independent variable	Regression coefficient (b)	CI 95%		p
		Lower Limit	Upper Limit	
Constanta	2.7	0.7	4.7	0.009
Duration of hemodialysis	0.02	0.01	0.03	0.018
Hemoglobin levels (pre)	0.7	0.6	0.8	<0.001
Gender	- 0.06	-0.7	0.6	0.857
Age	- 0.01	- 0.03	0.03	0.833

Independent variable	Regression coefficient (b)	CI 95%		p
		Lower Limit	Upper Limit	
N observation = 101 Adjusted R^2 = 63% P < 0.001				

2. Multiple Linear Regression Analysis

Table 3 shows that there is a positive relationship between the duration of hemodialysis and hemoglobin levels after chronic kidney disease patients underwent hemodialysis with erythropoietin stimulating agent therapy. This relationship is statistically significant, after controlling for the influence of confounding factors, namely hemoglobin levels before hemodialysis, gender and age. Every additional 1 month of hemodialysis will be followed by an increase in hemoglobin of 0.02g/dL (b=0.02 CI95% 0.01 to 0.03 p=0.018).

There is a positive and statistically significant relationship between hemoglobin levels before and hemoglobin levels after chronic kidney disease patients undergoing hemodialysis with erythronpoietin stimulating agent therapy, after controlling for the influence of confounding factors, namely duration of hemodialysis, gender and age. Every 1g/dL increase in hemoglobin levels before hemodialysis will be followed by hemoglobin levels after hemodialysis of 0.7 g/dL (b=0.7 CI 95% 0.6 to 0.8 p<0.001).

There was no statistically significant difference between men and women in hemoglobin levels after undergoing hemodialysis with erythropoietin stimulating agent therapy in patients with chronic kidney disease (b=-0.06 CI 95% -0.7 to 0.6 p=0.857).

There was no statistically significant relationship between age and hemoglobin levels after chronic kidney disease patients underwent hemodialysis with erythropoietin stimulating agent therapy (b=-0.01 CI 95% -0.03 to 0.03 p=0.833).

DISCUSSION

1. The relationship between duration of hemodialysis and hemoglobin levels after chronic kidney disease patients undergo hemodialysis with erythropoietin stimulating agent therapy.

The results of the study showed that the majority of hemodialysis duration was more than 12 months, namely 70 subjects (69.3%) and less than 12 months, there were 31 subjects (30.7%). Meanwhile, according to the description of the characteristics of the research sample, they had undergone at least 1 month of hemodialysis and a maximum of 84 months with an average duration of hemodialysis of 34.8 months.

Based on the results of the analysis, it was found that there was a positive relationship between the duration of hemodialysis and hemoglobin levels after chronic kidney disease patients underwent hemodialysis and erythropoietin stimulating agent therapy as indicated by the statistically significant results, namely that every 1 month increase in hemodialysis will be followed by an increase in hemoglobin of 0.02g/dL in total. Statistically significant p<0.001, which has controlled for confounding factors, namely hemoglobin levels before hemodialysis, gender and age. Based on the results of the analysis, it was found that there was a positive relationship between the duration of hemodialysis and hemoglobin levels after chronic kidney disease patients underwent hemodialysis with

erythropoietin stimulating agent therapy, which was indicated by the statistically significant results, namely that every 1 month increase in hemodialysis would be followed by an increase in hemoglobin of 0.02-g/dL. statistically significant (p<0.001), which has controlled for confounding factors, namely hemoglobin levels before hemodialysis, gender and age. The results of this study are in line with research by Puspita et al (2019) which shows that there is a significant difference between the frequency of hemodialysis twice and three times a week on the difference in hemoglobin levels of chronic kidney failure patients pre and post hemodialysis, so it can be explained that the number of hemodialysis frequencies is intended to The patient does not experience uremia and fluid overload disorders as well as complications caused by kidney damage. The more frequent the frequency of hemodialysis, the better the patient's quality of life (Puspita et al., 2019).

In another study by Retni and Ayuna (2021), it was found that 12 respondents underwent hemodialysis ≤ 1 year, 3 people suffered from anemia and 9 people did not suffer from anemia, while 18 respondents underwent hemodialysis > 1 year, 18 people suffered from anemia. This shows that There is a relationship between the length of time chronic kidney failure patients undergo routine hemodialysis and the incidence of anemia in the hemodialysis room at Prof. Hospital. Dr. H. Aloei Saboe Gorontalo City. This condition is one of the reasons for administering erythropoietin stimulating agent therapy or erythropoietin stimulant therapy which is a therapy to stimulate the production of the hormone erythropoietin so that hemoglobin production occurs well and can prevent anemia in chronic kidney disease patients who are undergoing hemodialysis (Amudi and Palar., 2021). Correction of anemia with erythropoietin stimulating agent therapy can slow the progression of chronic kidney disease, reduce the incidence of morbidity and mortality and improve quality of life.

The frequency of hemodialysis that is routinely undertaken will have an effect on the inflammatory process in patients with kidney failure. More frequent hemodialysis will reduce plasma IL-6 levels and the need for exogenous erythropoietin. The mechanism for reducing the need for exogenous erythropoietin is due to better control of inflammation, which is manifested by a decrease in plasma IL-6 levels (Dwitarini et al., 2017).

2. Relationship between hemoglobin levels before and hemoglobin levels after chronic kidney disease patients undergoing hemodialysis with erythropoietin stimulating agent therapy

The description of the characteristics of this research sample shows that the average hemoglobin level before hemodialysis and erythropoietin stimulating agent therapy was 9.3g/dL. Meanwhile, the average hemoglobin level after hemodialysis and erythropoietin stimulating agent therapy was 9.5g/dL.

The results of the analysis of the relationship between hemoglobin levels before and hemoglobin levels after chronic kidney disease patients underwent hemodialysis and erythropoietin stimulating agent therapy in this study showed a positive and statistically significant relationship, namely every 1g/dL increase in hemoglobin levels before hemodialysis will be followed by hemoglobin levels after hemodialysis of 0.7g/dL is statistically significant p<0.001 and has been controlled for confounding factors, namely duration of hemodialysis, gender and age. The results of this analysis are in line with previous research by Puspita et al (2019), namely that there was an

increase in hemoglobin levels and erythroncyte index in patients with chronic kidney failure pre and post hemodialysis in the two and three times a week therapy frequency groups.

The increase in hemoglobin levels is due to slow re-equilibrum of intravascular volume in the first 24-48 hours after hemodialysis. Several liters of fluid, which often exceeds the total plasma volume, from the blood compartment can move to the dialysate compartment through the ultrafiltration process, so that the volume of plasma fluid in the blood is reduced as a result causing changes in intravascular volume and can increase blood viscosity after hemodialysis which can be identified by an increase in levels. An increase in hemoglobin levels after undergoing hemodialysis can occur due to a significant improvement in erythropoiesis. This is due to the removal of uremic toxins (erythroid suppressors) during dialysis so that it can increase the response of erythropoietin in producing red blood cells. An increase in hemoglobin levels after hemodialysis occurs in patients who undergo adequate hemodialysis. In the hemodialysis process, the process of removing residual metabolic waste or certain toxins from the blood circulation is carried out, which can cause hemoconcentration, namely an increase in the number of red blood cells resulting from a decrease in plasma volume so that hemoglobin levels will increase (Putri and Astuti., 2020).

Based on data from this study, patients were given erythropoietin stimulating agent therapy after hemoglobin levels fell below 10g/dL to correct erythropoietin deficiency as well as iron supplementation to correct and prevent iron deficiency caused by continuous blood loss and the associated increased iron requirements. with the initiation of erythropoietin therapy because chronic anemia is very dangerous for patients with chronic kidney disease so that hemoglobin levels can be increased or at least maintained.

Also in line with the results of research conducted by Dwitarini et al. (2017), there was a significant difference in hemoglobin levels before and after undergoing hemodialysis in patients with chronic kidney disease at Sanglah General Hospital, Denpasar, Bali, namely that hemoglobin levels after hemodialysis were higher compared to hemoglobin levels before hemodialysis.

Another study conducted by Ayesh et al. (2014) showed that the average hemoglobin increased significantly in chronic kidney disease patients who underwent adequate hemodialysis compared to patients who underwent inadequate hemodialysis. The mean levels of erythropoietin stimulating agent were lower in patients with adequate hemodialysis compared to patients with inadequate hemodialysis. Adequate hemodialysis plays an important role in correcting anemia in kidney failure patients by increasing the activity of erythrocyte glucose-6-phosphate dehydrogenase (G6PD). Erythrocyte G6PD as the main enzyme in the hexose monophosphate shunt (HMP). HMP plays a significant role in the antioxidant reactions of red blood cells. If there is a decrease in G6PD activity, it will cause hemolysis, which plays a role in the pathogenesis of anemia in patients with kidney failure.

3. Relationship between gender and hemoglobin levels after chronic kidney disease patients undergoing hemodialysis with erythropoietin stimulating agent therapy

Researchers found that the largest population of 101 research subjects was male, namely 63 subjects or 62.4% and 38 (37.6%) female.

Based on the results of the analysis, it shows that there is no statistically significant difference between men and women in hemoglobin levels after undergoing hemodialysis and erythropoietin stimulating agent therapy with a significance value of 0.857 > 0.05. Gender as a variable can provide differences in incidence rates for men and women. The incidence of kidney failure in men is twice as high as in women, because men predominantly often suffer from systemic diseases (diabetes mellitus, hypertension, glomerulonephritis, polycystic kidney disease and lupus), as well as a family history of inherited diseases (Levey et al., 2007).

Salman et al. (2016) from their study in Malaysia also found that the percentage of chronic kidney disease patients who were male was higher than that of chronic kidney disease patients who were female. According to Pranandari and Supadmi (2015), clinically men have a risk of developing chronic kidney failure 2 times greater than women, because men's lifestyle is more at risk of developing chronic kidney disease due to smoking habits and alcohol consumption which can cause stress. on the kidneys so that the kidneys work harder (Pranandari and Supadmi., 2015). In line with data from the 11th report of the Indonesian renal registry in 2018, 57% of chronic kidney disease sufferers undergoing hemodialysis were men compared to 43% women.

4. Relationship between age and hemoglobin levels after chronic kidney disease patients undergo hemo-dialysis with erythropoietin stimulating agent therapy

In this study, researchers found that the largest population of 101 research subjects was over 45 years old, namely around 81 subjects (80.2%) and the remaining 20 subjects (19.8%) were under 45 years old. The description of the characteristics of the research sample shows that the youngest age is 30 years, the oldest is 77 years with an average age of 53.3 years.

The results of the analysis showed that there was no statistically significant relationship according to the age of chronic kidney disease patients and hemoglobin levels after undergoing hemodialysis with erythropoietin stimulating agent therapy at the Madiun City Regional Hospital, which was indicated by a significance value of 0.833 > 0.05.

This research is in line with the analysis carried out by Retni and Ayuba in 2021, namely the results of the chi-square statistical test obtained a Fisher exact value of 0.517 (α>0.05) which shows that there is no relationship between age and the incidence of anemia in patients with chronic renal failure who undergo routine hemodialysis in the hemodialysis room at RSUD Prof. Dr. H. Aloei Saboe Gorontalo City. Retni and Ayuba are of the opinion that there is no relationship between age and anemia in chronic kidney failure patients undergoing routine hemodialysis in the Hemodialysis Room at Prof. Hospital. Dr. H. Aloei Saboe Gorontalo City because both those aged ≤ 35 years and those aged > 35 years generally suffer from anemia. The cause of anemia itself can be caused by many factors and can be experienced by people of all ages. In accordance with the opinion of Sudoyo et al (2014), that in chronic kidney failure the glomerular filtration rate decreases progressively up to 50% of normal, there is a decrease in the ability of the kidney tubules to reabsorb and concentrate urine, a decrease in the ability to empty the bladder completely, thus increasing the risk of infection. and obstruction and decreased fluid intake have an impact on the risk of damage including decreased secretion of the hormone erythropoietin as a hormone that

plays a role in the formation of red blood cells.

Likewise, previous research conducted by Garini in 2018 gave results that as you get older, hemoglobin levels increase. Even if we look at the lowest hemoglobin levels, they are found in the elderly. In the elderly, the risk of anemia is very high.

AUTHORS CONTRIBUTION

Dwi Trisnawati Zainal as the main researcher chose the topic, searched for, collected and analyzed research data. Didik Tamtomo and Bhisma Murti review and research documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study.

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