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Correlation between Erythropoietin Resistance Index and Mortality in Regular Hemodialysis Patients at H. Adam Malik General Hospital Medan

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ABSTRACT

Introduction: One of the functions of the kidneys is the production of erythropoietin, a signaling molecule that stimulates the production of red blood cells, in response to reduced oxygen levels in the blood. In chronic kidney disease, there is a disturbance in the production of erythropoietin. Several previous studies have linked the index of erythropoietin resistance to mortality in patients with chronic kidney disease. The study aimed to correlate between erythropoietin resistance index (ERI) and Mortality in regular hemodialysis patients.

Method: Observational analytic study with a cross-sectional method to assess the relationship between ERI and mortality in all regular hemodialysis patients at H Adam Malik Medan. The ERI was used to evaluate erythropoietin EPO by comparing the dose of EPO to the hemoglobin level. The data were tested statistically with the Chi-Square method.

Results: The average study subjects suffered from anemia with Hb levels of 8.21 g/dL, serum iron levels of 63.22 mcg/dL, and increased total iron-binding capacity (TIBC) levels with an average value of 190.2 mcg/dL, low ferritin levels of 195.59 mcg/L and serum transferrin (TSAT) 19.2%, and of 2.94 g/dL. Albumin levels, transferrin saturation, and ERI were associated with the mortality rate of patients undergoing regular hemodialysis (p=0.021; p=0.011; p=0.012).

Conclusion: There is a relationship between the index of erythropoietin resistance and the mortality rate of patients undergoing regular hemodialysis

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ABSTRAK

Pendahuluan: *Salah satu fungsi ginjal adalah produksi erythropoietin, molekul pensinyalan yang merangsang produksi sel darah merah, sebagai respons terhadap berkurangnya kadar oksigen dalam darah. Pada penyakit ginjal kronis, ada gangguan dalam produksi erythropoietin. Beberapa penelitian sebelumnya telah menghubungkan indeks resistensi eritropoietin terhadap mortalitas pada pasien dengan penyakit ginjal kronis. Penelitian ini bertujuan untuk mengkorelasikan antara indeks resistensi eritropoietin (ERI) dan mortalitas pada pasien hemodialisis reguler.*

Metode: *Penelitian analitik observasional dengan metode cross-sectional untuk menilai hubungan antara ERI dan mortalitas pada semua pasien hemodialisis reguler di H Adam Malik Medan. ERI digunakan untuk mengevaluasi EPO eritropoietin dengan membandingkan dosis EPO dengan kadar hemoglobin. Data diuji secara statistik dengan metode Chi-Square.*

Hasil: *Rata-rata subjek penelitian menderita anemia dengan kadar Hb 8,21 g/dL, kadar serum besi 63,22 mcg/dL dan peningkatan kadar total iron-binding capacity (TIBC) dengan nilai rata-rata 190,2 mcg/dL, rendah kadar feritin 195,59 mcg/L dan kadar serum transferin (TSAT) 19,2%, dan kadar albumin 2,94 g/dL. Tingkat albumin, saturasi transferin, dan ERI dikaitkan dengan tingkat kematian pasien yang menjalani hemodialisis reguler (p = 0,021; p = 0,011; p = 0,012).*

Kesimpulan: *Terdapat hubungan antara indeks resistensi eritropoietin dengan angka kematian pasien yang menjalani hemodialisis reguler*

Kata kunci: *Indeks Resistensi Eritropoietin, Hemodialisis, Mortalitas*

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1 Introduction

Chronic kidney disease (CKD) is an umbrella term for heterogeneous disorders that affect the structure and function of the kidneys. Variation in disease expression is partly related to cause and pathology, severity, and progression. Chronic kidney disease is described as irreversible, slow evolution, and progressive. Another important aspect is the presence of pathological abnormalities indicating a higher risk of complications and death, especially related to cardiovascular.[1,2]

The Kidney Disease Improvement Global Outcomes (KDIGO) defines CKD as a decrease in kidney function as indicated by a glomerular filtration rate (GFR) of less than 60 mL/minute per 1.73 m^2, or markers of kidney damage, or both, with a minimum duration of 3 months. Some indicators of kidney damage are albuminuria, renal imaging changes, hematuria/leukocyturia, persistent hydro electrolytic disturbances, histological changes on kidney biopsy, and previous

kidney transplantation. Albuminuria was defined as the presence of more than 30 mg of albumin in the urine in 24 hours or more than 30 mg/g of albumin in an isolated urine sample adjusted for urine creatinine. Due to the central role of GFR in the pathophysiology of complications, the disease is classified into five stages based on GFR: greater than 90 mL/min per 1.73 m^2 (stage 1), 60-89 mL/min per 1.73 m^2 (stage 2), 30-59 mL/min per 1.73 m^2 (stage 3), 15-29 mL/min per 1.73 m^2 (stage 4), and less than 15 mL/min per 1.73 m^2 (stage 5).[2,3]

The prevalence of all stages of CKD varies between 7-12% in various regions of the world. The prevalence of CKD Stage 3 - Stage 5 in adults varies worldwide, with values reported as 1.7% in China, 3.1% in Canada, 5.8% in Australia, and 6.7% in the United States. In Europe, prevalence ranges from 2.3% in Germany, 2.4% in Finland, 4.0% in Spain to 5.2% in the UK. The variability in these figures is a worthy point for further study and may be due to different reasons.[4] According to Basic Health Research in 2013, the prevalence of chronic kidney failure based on a doctor's diagnosis in Indonesia was 0.2 percent and increased to 0.38 percent in 2013-2018.

One of the functions of the kidneys is the production of erythropoietin, a signaling molecule that stimulates the production of red blood cells, in response to reduced oxygen levels in the blood. Any disruption of this process, for example, secondary to a functional abnormality due to CKD, can potentially result in anemia, a condition in which the number of circulating red blood cells, and therefore the hemoglobin level is lower than normal. Anemia is a common complication of chronic kidney disease and a significant burden on patients and the healthcare system. According to The Kidney Disease Improvement Global Outcomes (KDIGO) clinical practice guidelines, anemia in CKD is defined as hemoglobin (Hb) <13.0 g/dl for men and <12.0 g/dl for non-pregnant women and is largely due to decreased erythropoietin (EPO) production by failing kidneys and/or altered iron homeostasis.[5,6]

The prevalence of CKD anemia also increases in patients with comorbidities and with age, from 28.0% in those aged 18-63 years to 50.1% in those aged ≥ 66 years among nondialysis-dependent (NDD) United States patients. PGK.[5,6]

Treatment with Erythropoietin stimulating agents (ESA) increases hemoglobin, reduces the need for transfusions, and improves quality of life and exercise capacity. However, treatment with an ESA to target a hemoglobin concentration of 130 g/L or more (mean concentration achieved >110 g/L or 120 g/L) has been consistently associated with high rates of cardiovascular disease, especially in ESA hyporesponsive patients.[2.6]

Hyporesponsiveness or resistance to ESA is generally defined as failure to achieve the targeted hemoglobin level despite the use of higher-than-usual doses of EPO or the continued need for higher doses of EPO to maintain the achieved hemoglobin level. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines describe ESA resistance as inappropriately low Hb for a given ESA dose, which includes patients who fail to achieve the Hb target of 11 g/dL when treated

with high ESA doses. The erythropoietic resistance index (ERI) is an important evaluation index for evaluating EPO responsiveness which is calculated by comparing the dose of EPO to the hemoglobin level.[7,8]

The mechanism of ESA hyporesponsiveness is not fully understood but is likely multifactorial, and may be related to iron deficiency, malnutrition, inflammation, and serum albumin levels (Lu et al., 2020; Yajima, and Takahashi, 2021). In a metaregression analysis, higher doses of EPO were found to be associated with increased rates of hypertension, stroke, and thrombotic events in CKD patients. Chung et al. demonstrated that in patients on regular hemodialysis, EPO resistance is associated with left ventricular mass index, left ventricular systolic function, and cardiovascular events.[9,10]

A prospective cohort study conducted by Lu et al. in Beijing showed that patients with higher ERI scores had a higher mortality rate (log-rank = 6.719; $p < 0.01$) and a higher cardiovascular mortality rate (log-rank = 7.800; $p < 0.01$). In a multivariate Cox regression analysis, the adjusted OR for all causes of death in the high ERI group was 1.781 ($p = 0.021$), even after adjusting for confounders, the OR was 1.972 ($p = 0.015$) for cardiovascular mortality.[11]

A retrospective cohort study in Japan in the geriatric population concluded that ERI is independently associated with the GNRI (Geriatric Nutritional Risk Index) and can predict cardiovascular disease, as well as all-cause mortality in patients undergoing hemodialysis. In addition, combining ERI and GNRI can not only stratify the risk of cardiovascular disease and all-cause mortality but can also increase the predictability of mortality.[8]

A prospective Japanese cohort study of 248 subjects found that patients with ERI in the highest tertile (ERI = 10.0–33.7 IU/kg/week/g/dL) had significantly higher mortality than patients with ERI in the lower two tertiles ($p = 0.0121$). The highest tertile ERI was associated with higher all-cause mortality with a hazard ratio value of 4.204 (95% CI: 1.173–15.065).[12] The purpose of the study aimed to correlate ERI and mortality rate in regular hemodialysis patients

2 Method

This study is an observational analytic study with a cross-sectional method to assess the relationship between ERI and mortality in regular hemodialysis patients. This research was conducted at Haji Adam Malik General Hospital and sampling was in May 2022. The study population was patients with chronic kidney disease undergoing regular hemodialysis. The research sample was patients with chronic kidney disease undergoing regular hemodialysis who met the inclusion and exclusion criteria. This research uses techniques of consecutive *sampling*, which is one technique of probability *sampling where* researchers take samples from all subjects who come and meet certain criteria until the required number of samples is met. This research has

passed an ethical review by the Health Research Ethics Committee of the University of North Sumatra.

The inclusion criteria in this study were aged over 18 years with a duration of hemodialysis treatment of more than 3 months with stable conditions and the use of arteriovenous *fistula.* Exclusion criteria in this study were a severe cardiovascular or cerebrovascular disease, infectious disease within one month, active liver disease or cancer, recent blood transfusion or surgical procedure, active bleeding or aplastic anemia, no treatment with rHuEPO and deficiency extremity.

Measurement of ERI, which is an index to evaluate EPO responsiveness, which is calculated by comparing the dose of EPO to the hemoglobin level with a low measurement result if it is below the median and a high if it is above the median. Ferritin was measured by laboratory tests with results measuring ng/mL and mortality, namely all causes of death in the study period with measuring results of life and death. In addition, Hb, serum iron, TIBC, TSAT, and albumin were also measured.

The data that has been collected is checked for completeness, then the data is coded, tabulated, and entered into the SPSS 22.00 computer program. Descriptive statistical analysis using the Kolmogorov-Smirnov test was used for demographic data. Chi-Square analytic statistical analysis was used to examine differences in research variables. Research data were analyzed statistically and differences were considered statistically significant if $p < 0.05$.

3 Results

Based on table 1, shows that most of the respondents were male, 32 people (64%) with a median age of 54.7 years. The average respondent had a Hb level of 8.21 ± 1.76 g/dL, serum iron level of 63.22 ± 37.04 µg/dL, TIBC level of 190.78 ± 61.7 µg/dL, ferritin level of 195.59 ± 129.2 ng/mL, TSAT level 19.2 ± 12.1 µg/dL, and albumin level 2.94 ± 0.57 g/dL.

Table 1 Sample distribution

Characteristics	**Mean ± SD (Min-Max)**	**n**	**(%)**
Gender (n)			
Man		32	64.0
Woman		18	36.0
Age (yr)	54.7 (28-77)		
Hb (g/dL)	8.21 ± 1.76		
Iron Serum (µg/dL)	63.22 ± 37.04		
TIBC (µg/dL)	190.78 ± 61.7		
Ferritin (ng/mL)	195.59 ± 129.2		
TSAT (µg/dL)	19.2 ± 12.1		
Albumin (g/dL)	2.94 ± 0.57		

TSAT: Transferrin Saturation Value, TIBC: total iron binding capacity

Based in Table 2. shows that mostly for the low category of ERI, there were low index ERI 17 (34%) people, and for the High category were 33 (66%) peoples

Table 2 Distribution of respondents based on the value of ERI

ERI	Frequency	Percentage (%)
Low	17	34
High	33	66
Total	50	100

Based in Table 3, shows that mostly for the category of mortality rates 27 (54%) people and survived 23 (46%) people

Table 3 Distribution of respondents based on mortality rates

Mortality Rate	Frequency	Percentage (%)
Life	23	46
Die	27	54
Total	50	100

Based on Table 4, shows that most of the patients had low albumin values, who died 24 (63.2%) and 14 (36.8%) survived. Patients had normal albumin values who survive 9 (75%) people and died 3 (25%). There is a relationship between low albumin levels and high mortality rates in this study (p=0.021).

Table 4 The Relationship Between Albumin Value and Mortality in regular hemodialysis patients

Albumin Level Value	Patient Mortality				Amount		p-value
	Life		Die				
	n	%	n	%	n	%	
Normal	9	75	3	25	12	100	0.021
Low	14	36,8	24	63,2	38	100	
Amount	23	46.0	27	54.0	50	100	

Based in Table 5, shows that patients had high ERI values, died 22 (66.7%), and survived 11 (33.3%). Patients who had low ERI values survived 12 (70.6%) and died 5 (29.4%). There is a relationship significantly between ERI and the patient's mortality rate, (p=0.012).

Table 5 Data distribution based on the relationship between albumin levels and mortality in regular hemodialysis patients

ERI	Patient Mortality				Amount		p-value
	Life		Die				
	n	%	n	%	n	%	
Low	12	70,6	5	29,4	17	100	0.012
High	11	33,3	22	66,7	33	100	
Amount	23	46.0	27	54.0	50	100	

Based Table 6, shows that patients had transferrin saturation <20%, died 23 (65.7%), and survived 12 (34.3%). Patients had transferrin saturation value of ≥ 20%, survived 11 (73.3%), and died 4

(26.7%) people. There is a relationship between transferrin saturation and the mortality rate of patients undergoing regular hemodialysis (p=0.011).

Table 6 Data distribution based on the relationship between Transferrin Saturation and Mortality in Regular Hemodialysis Patients

TSAT	Patient Mortality				Amount		p-value
	Life		Die				
	n	%	n	%	n	%	
≥ 20%	11	73,3	4	26,7	15	100	0.011
< 20%	12	34,3	23	65,7	35	100	
Amount	23	46.0	27	54.0	50	100	

Transferrin Saturation Value (TSAT)

4 Discussion

This study consisted of 50 respondents, some of the respondents were male in the old adult age category. Older age and male gender are associated with higher resistance to EPO in patients on dialysis. This result is in line with a previous study conducted in China.[11] The average patient had a low Hb level. Anemia is a common complication of chronic kidney disease (CKD). The incidence and severity of anemia increase as kidney function declines, and more than 90% of patients with end-stage renal disease have been diagnosed with anemia. In addition to the hematimetric indices, laboratory tests include complete blood cell count, reticulocyte count, serum iron, determination of serum transferrin and ferritin saturation, as well as occult blood in the stool, and levels of folic acid and vitamin B12. The main cause of anemia in regular hemodialysis patients is the deficiency of erythropoietin and iron.[13]

The pathogenesis of anemia in renal disease is complex, and endogenous or relative EPO deficiency is the main cause of renal anemia. Renal anemia not only causes fatigue, palpitation, and dyspnea and affects the quality of life among hemodialysis patients, but is also an important sign of poor prognosis in hemodialysis patients. Patients with chronic kidney disease (CKD) have relatively low production of erythropoietin (EPO), and this is the main cause of anemia in this group. In severe conditions, anemia can reduce the quality of life and increase the risk of cardiovascular disease and mortality in dialysis patients, therefore, the implementation of prevention and control measures is highly recommended.[14]

KDIGO (2012) describes the target level of hemoglobin in anemic patients with CKD, which is less than or equal to 11.5 g/dL. Transferrin saturation and serum ferritin levels can help differentiate between conditions associated with iron deficiency or impaired availability.[13]

In CKD patients, EPO levels are not sufficiently low concerning the degree of anemia. EPO deficiency begins early in the course of CKD, but it appears that when eGFR falls below 30 ml/min per 1.73 m2 this deficiency becomes more severe. This results in the adaptation of the renal tissue to consume less oxygen and thus maintain a normal tissue oxygen gradient. As a

result, the PHD enzyme remains active, the HIF heterodimer is not formed and the EPO gene is not activated.[15]

In this study, the average patient transferrin saturation value was 19.2% and the serum ferritin level was 195.5 ng/mL. The laboratory criteria used to define iron deficiency and provide indications for treatment differ in CKD compared to normal kidney function. In CKD, very severe iron deficiency is most likely to occur when the TSAT is ≤20% and the serum ferritin concentration is ≤100 ng/mL in patients undergoing predialysis and peritoneal dialysis (PD), or ≤200 ng/mL in patients undergoing dialysis hemodialysis. In comparison, with normal renal function, iron deficiency anemia is usually defined as a serum ferritin concentration <30 ng/mL. Functional iron deficiency, both ESA-induced functional deficiency and chronic disease anemia are usually characterized by TSAT ≤20% and elevated ferritin levels (as high as 800 ng/mL).[16]

Deficiency or lack of total iron stores can occur due to increased nutritional requirements during the production of red blood cells in the bone marrow. Absolute iron deficiency is also not always related to dialysis procedures, which lead to early destruction of red blood cells, but also to gastrointestinal bleeding, frequent laboratory tests, and surgery. Although the development of the erythroid lineage from multipotential myeloid stem cells is regulated by EPO, differentiation from erythroblasts to reticulocytes is an iron-dependent process. Therefore, iron deficiency will limit responsiveness to EPO. Iron is absorbed in the gastrointestinal tract and bound to serum transferrin.[17]

Iron is transported to the liver and spleen, where it is bound to ferritin for storage, or to the bone marrow where it is used for erythropoiesis. Although dietary intake is usually sufficient to replace most of the daily iron loss, most iron stores are replenished by macrophage phagocytosis of destroyed RBCs and iron recycling is an EPO-influenced process. Iron metabolism is further regulated by hepcidin, a peptide hormone synthesized mainly in the liver.[18] Hepcidin regulates iron absorption from the gut and the release of iron from iron stores. Hepcidin binds to ferroportin, an iron transporter present in intestinal duodenal cells, macrophages, and placental cells, and regulates the release of iron into the plasma. When hepcidin concentrations are low, Ferroportin molecules are exposed to the plasma membrane and release iron. When hepcidin levels increase, hepcidin binds to ferroportin which induces its internalization and degradation, causing a decrease in iron release. [19]

Low serum albumin level is a risk factor for erythropoietin hyporesponsiveness. The research conducted found that the patient's mean albumin was low, namely 2.94. This is in line with a study conducted in Spain which explained that there is a relationship between albumin levels and the ERI. Of the 297 patients with serum albumin below 35 g/l had an average ERI of 12.0±8.1U/kg/week/g per 100 ml. A decrease in serum albumin levels was followed by an increase in the ERI. This finding may indicate poorer nutritional status among hyporesponsive patients.[20]

It is known that CKD itself causes increased inflammation and immune activation molecules, which inhibit hypoxia-induced EPO production. However, this mechanism of EPO production appears to be decreased and cannot be separated in some CKD patients, because CKD patients may produce additional endogenous EPO in the kidney and liver under certain circumstances. No prospective studies are showing that improvement in anemia after treatment with ESA is accompanied by an increase in survival. In addition, studies of large numbers of patients have shown that those with more severe anemia received higher doses of EPO.[21]

Treatment of anemia in CKD patients usually involves the use of recombinant human erythropoietin (rHuEPO). Anemia and resistance to erythropoietin therapy contribute to the mortality and morbidity of patients with CKD (Chronic Kidney Disease). Treatment with rHuEPO therapy has a major impact on the clinical outcome and quality of life of patients. The main cause of failure of rHuEPO treatment is loss or low availability of iron. The prevalence of iron deficiency is very common in CKD, affecting as many as 50% of patients. However, despite the presence of EPO and intravenous iron in the majority of patients, the prevalence of anemia is as high as 34% in Brazil. This indicates that there are other important factors associated with EPO resistance.[13]

The parameter used to assess anemia and its response to EPO therapy is the ERI (Erythropoietin Resistance Index) as observed in several studies. In this study, 66% of the samples had a high level of erythropoietin resistance, and 34% had a low level of erythropoietin resistance. A study in Iraq showed that there CKD patients who responded well to EPO therapy were significantly lower ($p<0.001$) compared to that observed in patients who did not respond to EPO therapy. This shows that most of the samples did not respond to EPO therapy.[22]

ESAs are commonly used to control anemia and reduce the need for blood transfusions in patients with CKD. Several ESAs are currently available, including epoetin alpha or beta, biosimilar epoetin alpha, and longer-acting agents such as darbepoetin alpha and methoxy polyethylene glycol-epoetin beta. Clinical practice guidelines on the use of ESAs were developed and refined with a focus on evidence-based medicine.[21]

The development of erythropoietin resistance may indicate a significant decrease in blood hemoglobin concentration in addition to a constant dose of erythropoietin, a significant increase in the dose of erythropoietin to maintain target hemoglobin concentration, or an inability to increase hemoglobin concentration at a level above 110 g/l despite administering erythropoietin at a dose ≥ 500 IU/kg/week.[23]

According to European recommendations, resistance to erythropoietin activity is defined as the inability to achieve the target blood hemoglobin concentration (Hb = 11.0-12.0 g/l) using erythropoietin at a dose of ≥ 300 IU/kg/week (≥ 20,000IU/week) or darbepoetin-a at doses ≥ 1.5 μg/kg/wk (≥ 100 μg/wk) or as the constant need for high-dose erythropoietin to maintain target

hemoglobin concentrations. An alternative method for measuring the severity of resistance to erythropoietin activity is the ERI, which shows the ratio of weekly doses of erythropoietin to body weight and blood hemoglobin (EPO/kg/week/Hb). The parameter to determine the occurrence of erythropoietin resistance is >0.02 μg/kg/week/g Hb.[23]

The pathophysiological mechanisms underlying this condition have not been fully elucidated; however, processes leading to anemia in chronic disease play a role.[24] This fact is clinically important because resistance to EPO increases the risk of death in patients with CKD because of its association with increased blood pressure (increased cardiovascular risk), increased blood viscosity (endothelial stress), and increased platelet function (prothrombotic effect). Therefore, the identification of factors that modify the response to the use of this class of drugs and the development of strategies to optimize the benefits of anemia treatment is essential.[25]

The results of the research conducted showed that there was a relationship between the Erythropoietin Resistance Index and the mortality rate in patients undergoing regular hemodialysis (p=0.012). This is in line with a study conducted in China which found a relationship between comorbid factors and erythropoietin resistance in regular hemodialysis patients and its negative effect on survival. When patients were divided into 2 groups based on median ERI (below or above median 11.04), the Kaplan-Meier curve showed that patients with higher ERI scores had higher all-cause mortality (log-rank = 6.719; $p < 0.01$) and higher cardiovascular mortality (log-rank = 7.800; $p < 0.01$). This study also showed that the risk of all-cause mortality and cardiovascular mortality differed significantly between groups.[11]

The process of red blood cell formation (erythropoiesis) occurs in the spinal cord, where endogenous and exogenous erythropoietin acting on erythroid precursors is then converted from reticulocytes to mature erythrocytes. This process involves several cytokines IL-3, IL-I2, IGF-1, and granulocyte-monocyte colony-stimulating factors that can stimulate cell proliferation, while several factors such as IL-1, IL-6, TNF- and INF- can inhibit this process. The latter cytokines may also be involved in inflammation, acute and chronic infections, and neoplasia. Either of these conditions can increase the resistance of erythropoiesis.[20]

Erythropoietin receptors have been found not only in human endothelial cells but also in tumor cells. Higher ESA concentrations can increase the risk of death. It is important to determine the appropriate method for estimating ESA responsiveness for the management of renal anemia. Given that the ERI was calculated based on preliminary data, it may be influenced by the long-term follow-up period and inflammation and nutritional status.[27]

When the ERI is elevated simultaneously in several patients on the dialysis unit, this occurrence should be considered evidence of a common cause, most likely related to the type of water used in the dialysis fluid.[20]

Heart failure is a frequent cause of death among patients undergoing hemodialysis and is an independent risk factor for mortality. Anemia is known as an independent risk factor for the development of heart failure. In a Swedish study, it was found that patients with a history of heart failure had a higher ERI than patients without this history. 28 Anemia and heart failure appear to be related and influence each other in a vicious circle of comorbidities that increase the risk of death.[8]

There are limitations in this study, namely the number of samples studied in the study was still lacking, so the researchers suggested further research with a larger sample size and assessing comorbid factors in patients so that more accurate results could be obtained

5 Conclusion

The majority of research subjects were male with an average age of 54.7 years. The average study subjects suffered from anemia, increased TIBC levels, low ferritin and TSAT, and low albumin levels. The majority of research subjects had hyporesponsiveness to EPO therapy with a high level of ERI, There is a relationship significantly between albumin levels, transferrin saturation values, and the index of erythropoietin resistance.

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