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# Mortality among Chronic Kidney Failure Patients Who Have died in Last 2 years and the Correlation with Erythropoietin and /or Blood Transfusion as an Anemia Therapy in Jakarta, Indonesia's

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## Abstract

Anemia occurs in 80-90% of patients with chronic renal failure. Anemia is a complication of chronic kidney failure that often occurs in almost all patients with chronic kidney failure, it can even occur earlier than other complications of chronic kidney failure. Blood transfusion is one alternative, inexpensive, and effective treatment option for treating anemia in patients with kidney failure. In addition to blood transfusion, Erithropoietin can also be used as an alternative therapy to treat anemia in patients with chronic renal failure. The aim of this study was to determine the prevalence, survival analysis, the relationship of therapy to anemia with hemoglobin levels and the description of the cost of therapy in patients with chronic renal failure who received Erythropoietin therapy, blood transfusion, and a combination of both at the Jakarta Islamic Hospital Cempaka Putih.

This study is an analytical study, sampling was done retrospectively with the universal sampling method of medical records of patients with a primary diagnosis of chronic renal failure undergoing hospitalization and having undergone hemodialysis at Jakarta Cempaka Putih Islamic Hospital for the period of January 1, 2016 until December 31, 2017. Analysis The data in this study used data processing software SPPS 22. The results showed that Vulnerable age 46-65 (54%) and male patients (56%) contributed to giving the largest presentation for this study sample. Companion of hypertension (86%) and diabetes mellitus (66%) also contributed the largest presentation in this study sample. Anemic patients with chronic tingling failure who received combination therapy between Erythropoietin and blood transfusions had a higher survival rate compared to patients who received Erythropoietin therapy or blood transfusions. Paired Sample T-Test results showed no significant difference between the first HB level and HB died in the Eritropoietin therapy group, blood transfusion, and folic acid therapy (P value> 0.05), while in the combined therapy group between Eritropoietin and blood transfusion shows a significant relationship with a P value of 0.030. In this study the largest survival analysis was shown in hemodialysis patients using erythropoietin compared to patients who only used blood

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transfusions and the highest cost incurred by patients was the combined cost of therapy between Eritropoietin and blood transfusion, which was in the range of 1,001,121.03 - 31,120,525.54 rupiahs and with an average cost of 6,890,484.23 rupiahs.

**Keywords:** Chronic Kidney Failure; Blood Transfusion; Erythropoietin; Anemia

**Abbreviations:** ESRD: End-Stage Renal Disease; CKD: Chronic Kidney Disease; EPO: Erythropoietin; FDA: Food Drug Administration; CRF: Collection Research Form; USRDS: United State Renal Data System

## Introduction

Chronic renal failure is the loss progressive of kidney function, which occurs for months to years, characterized by gradual changes in the normal structure of the kidney accompanied by interstitial fibrosis [1]. The main causes of end-stage renal disease (ESRD) are diabetes mellitus (32%), hypertension (28%), and glumerulonephritis (45%) [2]. Acute and chronic renal failure are the main causes of morbidity and mortality. Kidney failure is the eighth cause of death in America [3]. Chronic kidney disease (CKD) is a global public health problem with increased prevalence and incidence of kidney failure, poor prognosis and high costs. The prevalence of CKD increases with the increasing number of elderly people and the incidence of diabetes mellitus and hypertension. About 1 in 10 global populations experience CKD at a certain stage. The results of a systematic review and meta-analysis conducted by Hill et al, obtained a global prevalence of CKD of 13.4%. According to the results of the Global Burden of Disease in 2010, CKD was the 27$^{th}$ leading cause of death in the world in 1990 and increased to 18th in 2010. Meanwhile in Indonesia, the treatment of kidney disease is the second largest ranking of financing from health BPJS after heart disease [4].

Based on data in several nephrology centers in Indonesia, it is estimated that the incidence of CKD ranged from 100-150 / million people and the prevalence was 200-250 / million people in 2005 [5]. Anemia occurs in 80-90% of patients with chronic kidney disease and erythropoietin deficiency is caused that [6]. A healthy kidney produces a hormone called Erythropoietin (EPO), which stimulates the bone marrow to produce red blood cells needed to carry oxygen to vital organs. Abnormal kidneys cannot produce enough EPO. As a result the bone marrow produces only a small amount of red blood cells. Anemia in kidney failure starts in the early stages of the disease, which is when the sufferer still has 20-50% of normal kidney function [7].

Anemia is a complication of CKD that often occurs it can even occur earlier than other CKD complications and in almost all CKD patients. Anemia itself can also increase the risk of significant morbidity and mortality from CKD [5]. Anemia in CKD patients can cause various manifestations, such as decreased cognitive function and quality of life, stroke, sexual dysfunction, cardio renal syndrome and accelerated progression of kidney damage [8]. Blood transfusion is an alternative, inexpensive, and effective choice for treating anemia in patients with kidney failure. Therapy for giving blood transfusions must be careful because it can cause sudden death [9].

In addition to blood transfusion EPO administration can also be done as an alternative therapy to overcome anemia in patients with kidney failure. EPO is a drug that has been approved by the drug & food administration body (FDA) which can be used to treat low red blood cell counts (anemia). EPO is needed to treat anemia in kidney chronic diseases [7]. Very effective and promising therapy is available using recombinant human Eritropoetin which has been produced for therapeutic applications. As demonstrated by erythropoietin-rich uremia goat plasma, human recombinant erythropoietin was administered intravenously to hemodialysis patients, has been shown to cause a drastic increase in erythropoietin [10].

## Materials and Method

### Study location

The research was carried out in the medical record section of Cempaka Putih Islamic Hospital, Jakarta, Indonesia.

### Study participants

All patients who died from January to December 2017 at Cempaka Putih Islamic Hospital Jakarta and diagnosed with chronic kidney diseases or renal failure were included in this study. The population in this study was 336 patients

### Study design

This was a cohort retrospective study

**Inclusion criteria:** Patients who were diagnosed with chronic renal failure male and female and aged over 18 years and had undergone hemodialysis

**Exclusion criteria:**

a. Patients <18 years
b. Cancer patients
c. Pregnancy patients
d. HIV/AIDS patients
e. Systemic lupus erythema patients

## Ethical Clearance

Ethical clearance was sourced from the Ethical Medical Committee of the Faculty of Medicine in Indonesia.

## Data Collection and Handling

1. Listed Patients according To Inclusion Criteria
2. Looked to the medical record
3. Transferred data to the collection research form (CRF)
4. Analyzed Data

Data were analyzed descriptively by using SPSS 22 version software. Significance correlation was showed by P-value < 0.05

## Results

The research subjects who met the inclusion criteria in this study were 70 patients. In this study a group of patients using Ertitropoietin obtained 6 patients, a group of patients using blood transfusions 30 patients, groups of patients using erythropoietin and blood transfusions 23 patients and 11 patients did not get erythropoietin therapy or blood transfusions but received folic acid therapy. Based on the results of research conducted at the Jakarta Islamic Hospital Cempaka Putih to 70 samples of patients died with a diagnosis of chronic kidney failure and had undergone hemodialysis. The following results are obtained:

| | EPO (n=6) | Blood transfusion (n=30) | EPO and Blood transfusion (n=23) | Folic acid therapy (n=11) | Total | % |
|---|---|---|---|---|---|---|
| Gender | | | | | | |
| Male | 4 | 13 | 13 | 9 | 39 | 56% |
| Female | 2 | 17 | 10 | 2 | 31 | 44% |
| Age (year) | | | | | | |
| 26-45 | 0 | 2 | 2 | 2 | 6 | 9% |
| 46-65 | 1 | 20 | 15 | 2 | 38 | 54% |
| >66 | 5 | 8 | 6 | 7 | 26 | 37% |
| Hypertension | | | | | | |
| Yes | 4 | 26 | 22 | 8 | 60 | 86% |
| No | 2 | 4 | 1 | 3 | 10 | 14% |
| Diabetes mellitus | | | | | | |
| Yes | 6 | 21 | 13 | 6 | 46 | 66% |
| No | 0 | 9 | 10 | 5 | 24 | 34% |
| Smoking | | | | | | |
| Yes | 1 | 6 | 1 | 2 | 10 | 14% |
| No | 5 | 24 | 22 | 9 | 60 | 86% |
| Total | | | | | 70 | 100% |

Table 1: Patients with chronic renal failure.

Table 1 show patients with chronic renal failure with anemia who underwent hemodialysis in this study with ages 26-45 years old (9%), aged 46-65 (54%) and aged> 66 years (37%). In this study, the number of patients with male sex is greater; this is indicated by the percentage of male patients by 56% and female patients by 44%. The accompanying disease in patients with chronic renal failure with anemia who underwent hemodialysis in this study was hypertension by 86% and diabetes mellitus by 66%. Patients with smoking history in this study were 14% and 86% did not smoke.

| Characteristics | Test | P value |
|---|---|---|
| Total hemodialysis vs age | Kruskall-Wallis Test | 0,618 |
| Total hemodialysis vs gender | Mann-Whitney Test | 0,868 |
| Total hemodialysis vs comorbidities | Kruskall-Wallis Test | 0,457 |
| Total hemodialysis vs smoke history | Mann-Whitney Test | 0,638 |

Table 2: Non parametric test between total hemodialysis and characteristics patient.

Table 2 Non-parametric test with Kruskas-Wallis shows that the P value is 0.618 which means there is no significant difference between the age and total hemodialysis performed. The non-parametric test using Mann-Whitney showed a P value of 0.868, meaning that there was no significant difference between sexes and total hemodialysis. The Kruskas-Wallis test showed a P value of 0.457, meaning that there was no significant difference between comorbidities and total hemodialysis. The Mann-Whitney test showed a P value of 0.638, meaning that there was no significant difference between total hemodialysis and a history of smoking.

| Characteristics | Test | P value |
|---|---|---|
| average hemoglobin vs age | One Way Annova | 0,051 |
| average hemoglobin vs gender | Independent T Test | 0,009 |
| average hemoglobin vs comorbidities | One Way Annova | 0,263 |
| average hemoglobin vs smoke history | Independent T Test | 0,042 |

Table 3: Non parametric test between total hemodialysis and characteristics patient.

Table 3 One Way Annova test shows no significant difference between HB levels with average age, which is indicated by the P value of 0.051. The Independent T Test shows that there is a significant difference between HB levels with sex, which is indicated by the P value of 0.009. The One Way Annova test shows that there is no significant difference between the average HB level and comorbidities, which is indicated by the P value of 0.263. The Independent T Test shows that there is a significant difference between the average HB level and the smoking history, which is indicated by the P value of 0.042.

| Duration of hemodialysis | Total | % |
|---|---|---|
| <1 year | 40 | 57% |
| 1-2 year | 17 | 24% |
| 3-4 year | 7 | 10% |
| >4 year | 6 | 9% |
| Total | 70 | 100% |

Table 4: Duration of hemodialysis.

Table 4 showing the length of time patients undergo hemodialysis. Based on duration of hemodialysis, patients who underwent hemodialysis less than one year has the biggest number of patients; 40 patients (57%) and duration of hemodialysis more than 4 years has the smallest number of patients; 6 patients (9%).

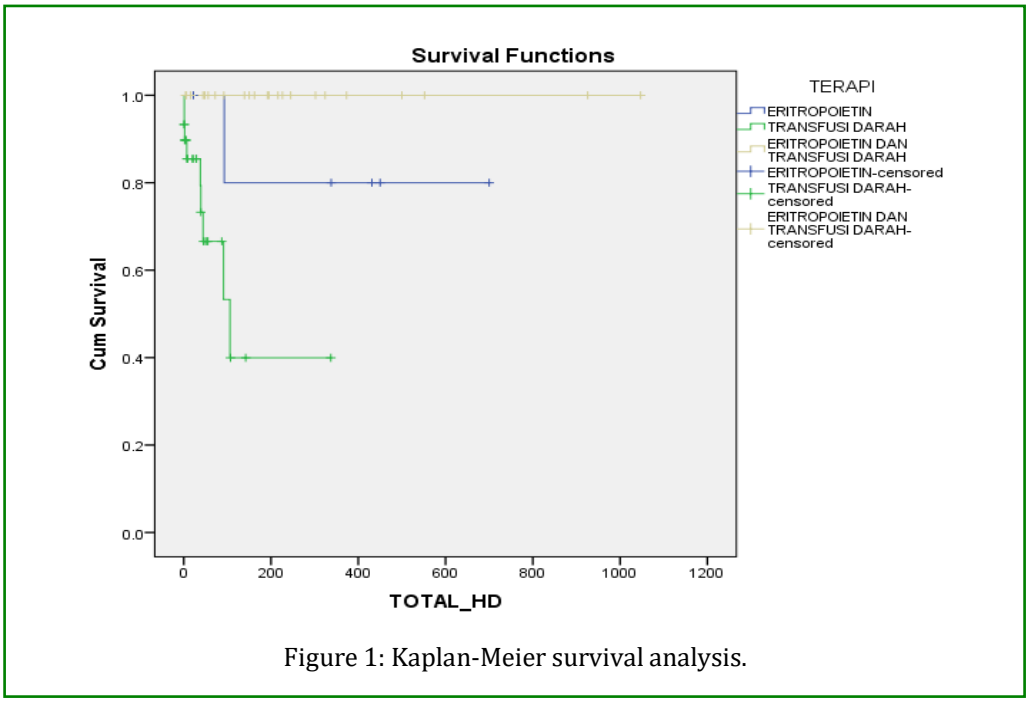


Figure 1: Kaplan-Meier survival analysis.

Figure 1. Explains that hemodialysis patients who receive blood transfusions have a survival presentation of 40% which starts when patients undergo about 110 times hemodialysis. Patients who received Erythropoietin had an 80% survival presentation which began when patients underwent about 100 times hemodialysis and patients

who received combined Erythropoietin therapy and blood transfusions had a 100% survival presentation which began when the patient underwent about 20 times hemodialysis.

| Paired Sample Correlation | First HB | Died HB | P-value* |
|---|---|---|---|
| Erythropoietin | N= 6 | N=6 | 0.718 |
| (Mean±SD) | (8,667 ± 0,6593) | (8,933±1,8662) | |
| Blood transfusion | N= 30 | N=30 | 0.113 |
| (Mean±SD) | (7,930±1,9072) | (8,663±2,0810) | |
| Eritropoietin and Blood transfusion | N= 23 | N=23 | 0.03 |
| (Mean±SD) | (7,896±1,1487) | (9,052±1,7018) | |
| Folic acid therapy | N= 11 | N=11 | 0.345 |
| (Mean±SD) | (11,118±1,1737) | (10,464±2,3291) | |

Table 5: Relationship between HB and anemia therapy.

Table 5 using the Paired Sample T-Test showed no significant difference between the first HB level and HB died in the Eritropoietin therapy group, blood transfusion, and folic acid therapy because the P value was> 0.05, whereas in the combined therapy group between Eritropoietin with blood transfusion showed a significant relationship with a P value of 0.030 where P <0.05.

| Therapy | Cost | Average costs |
|---|---|---|
| Erythropoietin | Rp. 358.142,40 - Rp 9.666.561,18 | Rp. 3.403.192,87 |
| Blood transfusion | Rp. 621.000,00 – Rp. 8.694.000,00 | Rp. 2.587.500,00 |
| Eritropoietin and Blood transfusion | Rp. 1.001.121,03 – Rp. 31.120.525,54 | Rp. 6.890.484,23 |

Table 6: An overview of the amount of anemia therapy costs.

| Therapy | Cost | Average costs | Average HB | P-value* |
|---|---|---|---|---|
| Erythropoietin | Rp. 358.142,40- Rp 9.666.561,18 | Rp. 3.403.192,87 | 8.9 | 0.599 |
| Blood transfusion | Rp. 621.000,00 – Rp. 8.694.000,00 | Rp. 2.587.500,00 | 8.6 | 0.034 |
| Eritropoietin and Blood transfusion | Rp. 1.001.121,03–Rp.31.120.525,54 | Rp. 6.890.484,23 | 8.3 | 0.442 |

Table 7: Relationship costs with average Hemoglobin.

## One Way Annova Test

Table 7 Shows that based on the statistical analysis carried out with one way annova test, there was no significant difference between the total costs incurred by patients to get Erythropoietin therapy for the average Hb level of patients. This is indicated by the P value of 0.599 where P is 0.599> 0.05 and there is a significant difference between the total costs incurred by patients to perform blood transfusions on Hb levels on average patients. This is indicated by the P value of 0.034 where P 0.034 <0.05. Statistical analysis that has been done shows that there is no significant difference between the costs incurred by patients for a combination of Erythropoietin therapy and blood transfusions on hb levels on average patients. This is indicated by the P value of 0.442 where P is 0.442> 0.05.

| Therapy | Cost | Average costs | Total HD | P-value* |
|---|---|---|---|---|
| Erythropoietin | Rp. 358.142,40- Rp 9.666.561,18 | Rp. 3.403.192,87 | 2034 | 0.675 |
| Blood transfusion | Rp. 621.000,00 – Rp. 8.694.000,00 | Rp. 2.587.500,00 | 1375 | 0.378 |
| Eritropoietin and Blood transfusion | Rp. 1.001.121,03–Rp.31.120.525,54 | Rp. 6.890.484,23 | 5887 | 0.016 |

Table 8: Relationship costs with total hemodialysis.

## Kruskall-Wallis Test

Based on the statistical analysis that has been carried out, there is no significant difference between the total costs incurred by patients to carry out blood transfusions on the total overall hemodialysis performed. This is indicated by the P value of 0.675 where P is 0.675> 0.05. There was no significant difference between the total costs incurred

by patients to get Erythropoietin therapy for the total hemodialysis performed. This is indicated by the P value of 0.378 where P is 0.378> 0.05 and there is a significant difference between the total costs incurred by patients to get Erythropoietin therapy and blood transfusions on the total overall hemodialysis performed. This is indicated by the P value of 0.016 where P 0.016 <0.05.

## Discussion

Anemia is found in patients with renal failure (80% -95%) with many factors that play a role in pathogenesis. Anemia is a complication of ESRD. Anemia can increase morbidity and mortality among ESRD patients [11]. Based on research conducted at the Jakarta Islamic Hospital Cempaka Putih, showing the most vulnerable age of chronic kidney failure patients with anemia is 46-65 years old with a 54% percentage of the National Kidney Foundation stating the prevalence of GGK increases with age due to a decrease in GFR (Glomerular Filtrate Rate) [12]. According to Tonelli and Riella [13] the prevalence of CRF is higher with age.

Patients with chronic kidney failure with anemia in this study more patients with male sex; this is indicated by the percentage of male patients by 56% and female patients by 44%. Based on an evaluation conducted by the United State Renal Data System (USRDS), the number of patients with chronic renal failure in men was more than women [14]. The most common comorbidities in this study were hypertension with a percentage of 86%. According to Fraser et al. [15], hypertension is the highest concomitant disease in patients with chronic renal failure. Decreasing kidney function is a risk factor for hypertension and diabetes mellitus so that it will worsen the condition of patients with CRF [16]. Based on the Indonesian Society of Nephrology (InaSN) in 2000, diabetes and hypertension are the second and third causes of chronic renal failure in Indonesia after glomerulonephritis. From these data it can be seen that the main cause of chronic kidney disease in Indonesia is not only infectious diseases. Non-infectious diseases such as diabetes mellitus and hypertension have also become major risk factors. This is due to changes in lifestyle and diet in Indonesia which have adopted many western habits [17].

The history of smoking in patients with chronic kidney failure with anemia who underwent hemodialysis in this study was 14% smoking and 86% did not smoke. From the results of the percentage of this study showed patients who did not smoke had a higher percentage than patients who smoked. However, according to a study conducted by Pranandari and Supadmi patients with chronic renal failure with hemodialysis who have a history of smoking have a risk twice the incidence of chronic renal failure compared to patients without a history of smoking. The acute phase effect of smoking is to increase sympathetic race which will result in increased blood pressure, tachycardia and accumulation of catecholamines in the circulation. In the acute phase, some blood vessels also often experience vasoconstriction, for example in coronary arteries, so that acute smokers are often followed by increased renal vascular resistance resulting in a decrease in glomerular filtration rate and filter fraction [18].

Non-parametric test with Kruskall-Wallis and Mann-Whitney performed between total hemodialysis and patient characteristics such as age, sex, comorbidities, and smoking history resulted in P value> 0.05. This means there is no significant difference between the total or duration of the patient undergoing hemodialysis with characteristics such as age, gender, comorbidities and smoking history. One Way Annova parametric test between HB on average with age and patient disease resulted in a P value of 0.051 and 0.263, where the value of P> 0.05. This means that there is no significant difference between age and comorbidities with HB levels on average patients. The Indipendent T Test parametric test between HB and sex and the patient's smoking history resulted in a P value of 0.009 and 0.042, where the P value was <0.05. This means that there is a significant difference between sex and smoking history with HB levels on average patients. Research conducted by Zukefeli [19], states that smoking causes an increase in blood hemoglobin levels. According to WHO, anemia is defined as a condition where the number of red blood cells or oxygen binding capacity is lower than a person's physiological needs, which vary according to age, sex, smoking habits and pregnancy status [20].

Based on the duration of the patient undergoing hemodialysis, the old group of hemodialysis less than 1 year amounted to 40 patients (57%), patients undergoing one to two years hemodialysis amounted to 17 patients (24%), patients undergoing three to four years hemodialysis totaling 7 patients (10 %) and patients undergoing hemodialysis more than four years amounted to 6 patients (9%). The highest frequency in this study was a group of patients who underwent less than one year of hemodialysis as many as 40 patients (57%). Nurchayati's study revealed that hemodialysis is a kidney replacement therapy used in patients with acute illness and patients with terminal stage kidney disease. Someone who has been convicted of kidney failure must undergo kidney replacement therapy for life, and one option is hemodialysis. Kaplan-Meier survival analysis in this study showed a significant relationship between the overall

comparison between survival analysis with duration or total hemodialysis among patients with anemia in chronic renal failure who received Erythropoietin therapy, blood transfusion, and a combination of both therapies. When viewed from a group of patients whowere treated with anemia, anemia patients on chronic tread failure who received combination therapy between Erythropoietin and blood transfusions had a higher survival rate compared to patients who received Erythropoietin therapy or blood transfusions.

This is because there is an increase in HB levels in patients receiving Erythropoietin therapy and blood transfusions in accordance with research conducted by Rahmawati [21], which states that HB levels increase after receiving combined blood transfusion and erythropoietin therapy in patients with chronic kidney failure who suffer from anemia in PKU Muhammadiyah Yogyakarta hospital where the increase was 73.33% after receiving a blood transfusion and 60% after receiving Erythropoietin. Then the research conducted by Astrini [22] states that there is a relationship between Hb levels and the quality of life of CRF patients undergoing hemodialysis with a value of p = 0,000.

Based on statistical analysis carried out there was no significant difference between the use of Erythropoietin and HB levels, this was indicated by the P value of 0.718. According to Notopoero Erythropoietin therapy takes longer to increase HB because it must go through the erythropoiesis process needed for 2-4 weeks, while PERNEFRI explains that HB increase occurs up to 4 weeks of Erythropoietin administration in patients with Chronic Kidney Failure with anemia [23,24].

Table 5. also shows that there is no significant difference between the use of blood transfusions and HB levels, this is indicated by the P value of 0.113. Giving human recombinant erythropoietin (rhu-EPO) better than red blood transfusion because transfusion can increase the risk of infection and can cause risk of hemolytic, nonhemolytic, iron accumulation, immunosuppression, and also suppress endogenous erythropoietin rhu-EPO consisting of 166 glycoprotein amino acids and can increase erythrocyte cells and also increase oxygen in cells [11].

The relationship between the use of folic acid and the patient's HB level did not show a significant difference, this is indicated by a P value of 0.345, this is because iron alone is not strong enough to increase Hemoglobin levels in patients with Chronic Kidney Failure who undergo hemodialysis. This is different from the research conducted by Ramatillah in Jakarta Islamic Hospital Cempaka Putih shows that the use of iron such as Folic Acid can increase hemoglobin levels in patients with Chronic Kidney Failure, although it is no more effective than using Erythropoietin.

The relationship of HB with anemia therapy showed a significant difference in patients who received a combination of Erythropoietin therapy with blood transfusion, this was indicated by the P value of 0.030 where P <0.05. This is consistent with research conducted by Rahmawati, which states that an increase in HB levels after receiving a combination of blood transfusion therapy and Erythropoietin in Chronic Kidney Failure sufferers who suffer from anemia in PKU Muhammadiyah Yogyakarta hospital where the increase was 73.33% after got a blood transfusion and 60% after receiving erythropoietin [11].

Cost analysis in this study is based on the hospital perspective as a provider of health services. The analysis was carried out by calculating the number of anemia therapies such as Erythropoietin, blood transfusion, and the combination of both therapies obtained by patients during the patient's treatment at the Jakarta Islamic Hospital Cempaka Putih. The amount is then multiplied by the rate of blood transfusion and Erythropoietin rates that have been determined by the hospital. In this study the greatest cost incurred by patients is the combined cost of therapy between Eritropoietin and blood transfusions, which is a cost range of 1,001,121.03 - 31,120,525.54 rupiah and with an average cost of 6,890,484.23 rupiah.

Based on statistical analysis that has been done with the One Way Annova method there is a significant relationship between HB patients with the cost of blood transfusion therapy, this is indicated by the P value of 0.034 and a significant relationship between total hemodialysis and the combined cost of Erythropoietin therapy and blood transfusions. Indicated by the P value of 0.016. The research conducted by Dwianti in states that the age of the patient, the frequency of hemodialysis, the class of care, and the type of financing affect the total cost of therapy (P <0.05) [25].

## Conclusion

The most age patients chronic kidney failure with anemia are 46-65 years old (54%), male patients (56%) and female patients (44%). Hypertensive comorbidities (86%) and diabetes mellitus were (66%). Patients smoke (14%) and do not smoke (86%). Anemic patients with chronic treadmill failure who receive combination therapy between Erythropoietin and blood transfusions have a greater survival rate. There was a significant difference

between the first HB level and HB died in the combined therapy group between Eritropoietin and blood transfusion, P value 0.030 where P <0.05. The greatest cost incurred by patients is the combined cost of providing therapy between Erythropoietin and blood transfusion. In this study patients underwent less than one year of hemodialysis, namely 40 patients (57%), one to two years 17 patients (24%), three to four years 7 patients (10%), and more than four years 6 patients (9 %).

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