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Severe Anemia and Six-Month All-Cause Mortality in Chronic Kidney Disease Patients Undergoing Hemodialysis

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Abstract

Anemia is often found in patients with Chronic Kidney Diseases (CKD). Anemia can affect poor outcomes in hemodialysis patients. However, studies examining role of severe anemia as a predictor factor in six-month all-cause mortality in hemodialysis patients in Semarang are limited. Therefore, further study was needed to answer these questions. We therefore designed this study to determine the role of severe anemia and six-month all-cause mortality in hemodialysis patients. The cohort design study was carried out from October 2019 to March 2020 at the Hemodialysis Unit of Roemani Muhammadiyah Hospital Semarang. The dependent variable was severe anemia, defined as hemoglobin levels <8.0 g/dL. The mortality rate was investigated over six months after the baseline measurements. Among 85 respondents, 35 (41.2%) respondents were categorized into severe anemia, and 50 (58.8%) respondents were categorized into non-severe anemia groups. The respondents consisted of 54 (63.5%) males and 31 (36.5%) females. The hemoglobin level in the severe and non-severe anemia groups was 7.2 ± 0.6 and 9.5 ± 1.2 (mean ± standard deviation). The Kaplan Meier survival curve showed that the non-severe anemia group had a higher survival rate than the severe anemia group (98.0% vs. 82.9%, p = 0.011). The Cox regression analysis found a significant relationship between anemia severity and 6-month all-cause mortality in hemodialysis patients (p = 0.027; Hazard ratio: 9.3). Severe anemia plays a role as a predictor factor in six-month all-cause mortality among hemodialysis patients.

Keywords

Anemia, Dialysis, End-Stage Kidney Disease, Fatality, Hemoglobin.

INTRODUCTION

Anemia is often found in patients with Chronic Kidney Disease (CKD). In CKD, Hemoglobin (Hb) levels begin to decrease in CKD stages 2 in male patients and stage 3 in female patients. However, anemia is more common in CKD Stage 4 and the End-Stage Kidney Disease (ESKD) population; anemia is present in 90% of patients (1). Anemia defined as decreasing of Hb levels <13.0 g/dL in male or <12.0 g/dL in female. Anemia is classified into non-anemia, mild anemia, moderate anemia, and severe anemia. The intervals differ between men and women. In men, anemia is classified into non-anemia if Hb levels ≥13.0 g/dL, mild anemia if Hb levels 11.0 to 12.9 g/dL, moderate anemia if Hb levels 8.0 to 10.9 g/dL, and severe anemia if Hb level <8.0 g/dL. In women, anemia is classified into non-anemia if Hb levels ≥12.0 g/dL, mild anemia if Hb levels 11.0 to 11.9 g/dL, moderate anemia if Hb levels 8.0 to 10.9 g/dL, and severe anemia if Hb levels <8.0 g/dL. Moderate and severe anemia have the same definition in men or women (2).

Guidance for the management of anemia in dialysis patients in Indonesia uses a combination of intravenous iron supplementation, erythropoietin therapy, and nutritional therapy. The targeted therapy was Hb levels ≥10.0 g/dL. Blood transfusion is the last therapeutic option for increasing Hb levels in chronic dialysis patients. Too many risks may occur during blood transfusions, such as transfusion reaction or Blood Borne Virus (BBV) transmission related to blood transfusions, such as hepatitis B, hepatitis C or Human Immunodeficiency Virus (HIV) (3). World Health Organisation (WHO) makes some recommendations about blood transfusion indication in chronic anemia is given if Hb level <7.0 g/dL in adults (4).

In Indonesia, as many as 68,153 (78%) hemodialysis patients had Hb levels <10.0 gr/dL, and 19,557 (22%) hemodialysis patients had Hb levels ≥10.0 gr/dL (5). Anemia in CKD is caused by various factors, including erythropoietin deficiency, uremic-induced erythropoiesis inhibition, decreased red blood cell survival, nutritional (folate, iron, and vitamin B12) deficiency, anorexia, and loss of dialysate (6).

Anemia can affect poor outcomes in hemodialysis patients. Anemia in hemodialysis patients decreased the quality of life, decreased the systemic hemodynamic capacity and cardiac function, increased the incidence of left ventricular enlargement of the heart, and decreased cognitive and sexual abilities of patients. Anemia also increase morbidity and hospitalization in the hemodialysis population. Meanwhile, studies investigating the association between anemia with mortality in hemodialysis patients are still limited. A long-term study is needed to determine its relationship (3).

A study published by Robinson *et al*., (7) showed that patients with Hb levels ≥11.0 g/dL have a longer survival among maintenance hemodialysis patients but show no additional survival advantages for patients with Hb levels ≥12.0 g/dL. Kuo *et al*., (8) carried out similar study and showed similar results. Patients with Hb levels <9.0 g/dL, 9.0 to 9.9 g/dL had a higher mortality than patients with Hb levels 10.0 to 10.9 g/dL. Nevertheless, patients with Hb levels 11.0 to 11.9 g/dL and ≥12.0 g/dL had lower mortality than patients with HB levels 10.0 to 10.9 g/dL. These include the studies conducted by Guinn *et al*., (9) which are showed that severe anemia is associated with increased myocardial ischemia and mortality in patients declining transfusion.

Based on the description above, no publication examined the effect of severe anemia as a predictor factor on six months – all-cause mortality in hemodialysis patients. So that further study is needed relating to this matter to answer these problems. This study aimed to determine the effects of severe anemia as a predictor factor on all-cause mortality within six months in CKD patients undergoing hemodialysis.

MATERIALS AND METHODS

Patients starting regular hemodialysis at the Roemani Muhammadiyah Hospital Semarang, Indonesia from October 2019 to March 2020 were enrolled. The inclusion criteria were patients who underwent hemodialysis ≥3 months, frequency of hemodialysis twice a week, and were willing to participate in the study. Patients with incomplete data moved to other hemodialysis units and experienced changes in the frequency of hemodialysis during the study period were excluded from this study.

Respondents included in this study had given permission and signed for informed consent. This research also has obtained authorization from Roemani Muhammadiyah Hospital. It has passed the ethical approval from the health research ethics committee of Roemani Muhammadiyah Hospital Semarang by number EA-012/KEPK-RSR/III/2021.

The independent variable was Severe Anemia, categorized into severe anemia and non-severe anemia. Severe anemia defined as Hb level <8.0 g/dL and non-severe anemia group if defined as Hb level ≥8.0 g/dL. Three milliliters (mL) pre-dialytic blood sample was taken and checked for Hb levels using the spectophotometry method in the laboratory unit of Roemani Muhammadiyah Hospital in October 2019. All-cause mortality was observed from October 2019 until March 2020. The collected data was then analyzed using Kaplan Meier and Cox Regression analysis using SPSS 18.0 program. The Kaplan Meier was used to approximates the survival function using at most one predictor.

For purpose of this research, approximately 115 respondents underwent hemodialysis in Roemani Muhammadiyah Hospital Semarang. Seven-teen respondents were excluded from the study because did not meet inclusion criteria. It was considered since six respondents underwent hemodialysis less than twice a week, and 11 respondents underwent hemodialysis <3 months.

Ninety eight respondents were met inclusion criteria, threeten respondents were excluded from the study because seven respondents found incomplete data. As much as two respondents moved to another hemodialysis unit during the study period, and four respondents experienced changes in the frequency of hemodialysis during the study period. After going through inclusion and exclusion, there were 85 respondents whose data had been proceed and analyzed.

As shown in Figure 1, details the numbers excluded and reasons for their exclusion in this study.

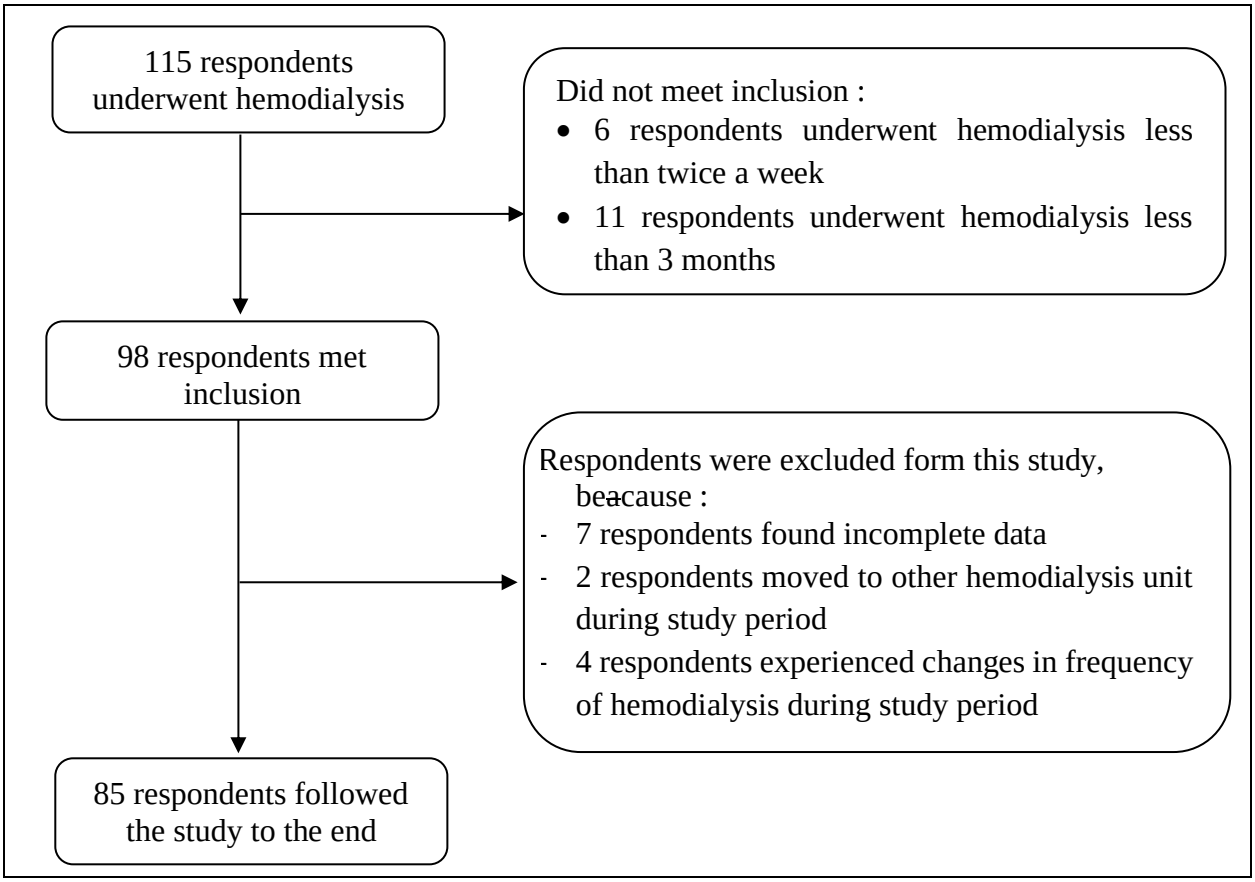

Figure 1. Sample selection flow chart

RESULTS

A fotal of 85 patients were enrolled in the study. As much as 33 (38.8%) respondents were diabetic, and 52 (61.2%) respondents were non-diabetic. Of them, 54 (63.5%) respondents were male and 31 (36.5%) respondents were female. The mean age of respondents is 50.9 ± 10.6 years. The

duration of hemodialysis was 24 ± 19.5 months. From the clinical examination, we got the mean Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and Mean Arterial Pressure (MAP) was 161.2 ± 21 mmHg, 86.1 ± 15.7 mmHg, and 111.1 ± 15.2 mmHg, respectively. The mean Hb level of all in these studies was 8.5 ± 1.5 g/dL. Result from chemical laboratory parameters test were the mean ureum and creatinin levels were 133.1 ± 38 mg/dL and 13.1 ± 4.5 mg/dL. Based on the calculation, we found that the mean estimated Glomerulus Filtration Rate (eGFR) was 5.9 ± 2 mL/min/1.73m^2. In addition, dialysis-related factor parameters were showed that the mean Adequacy of dialysis (Kt/V) was 1.1 ± 0.2. The mean ultrafiltration (UF) rate and Quick of blood (Qb) were 2,610 ± 969 mL and 195.5 ± 21.1 mL/min. Table 1 shows sociodemographic data and clinical examination of the respondents.

Table 1. Sociodemographic data and clinical examination of the respondents

Variables			**N (%)**
Diabetes Mellitus (DM)			
• Yes			33 (38.8)
• No			52 (61.2)
Gender			
• Male			54 (63.5)
• Female			31 (36.5)
Anemia Levels			
• Severe Anemia (Hb <8 mg/dl)			35 (41.2)
• Non Severe Anemia (Hb ≥8 mg/dl)			50 (58.8)
Variables	**Min**	**Max**	**Mean ± SD**
Ages (years)	27	79	50.9 ± 10.6
Duration of HD (months)	3	109	24 ± 19.5
eGFR (mL/min/1.73m^2)	3.2	13.1	5.9 ± 2
Pre dialysis SBP (mmHg)	108	224	161.2 ± 21
Pre dialysis DBP (mmHg)	52	147	86.1 ± 15.7
Pre dialysis MAP (mmHg)	79	167	111.1 ± 15.2
Hb (g/dL)	6	12.9	8.5 ± 1.5
Ureum (mg/dL)	53	219	133.1 ± 38
Creatinin (mg/dL)	5.2	24.8	13.1 ± 4.5
Kt/V	0.7	1.8	1.1 ± 0.2
UF Rate (mL)	500	4,500	2,610 ± 969
Qb (mL/min)	180	300	195.5 ± 21.1

N: Number of cases

In the severe anemia group, 20 (57.1%) respondents were male, and 15 (42.9%) respondents were females. While in the Non-severe anemia group, 34 (68%) respondents were male, and 16 (32%) respondents were female. In the severe anemia group, 15

(42.9%) respondents had diabetes, and 20 (57.1%) respondents were non-diabetic. While in the non-severe anemia group, 18 (36%) respondents had diabetes, and 32 (64%) respondents were non-diabetic.

The mean Hb level in the severe and Non-severe anemia groups was (mean ± standard error; 7.2 ± 0.6 VS 9.5 ± 1.2 g/dL). The mean age of respondents in the severe anemia and non-severe anemia group was 50.4 ± 8.8 VS 51.2 ± 11.7 years, and the mean duration of hemodialysis in the severe anemia and non-severe anemia group was 23.5 ± 16.9 VS 24.3 ± 21.4 months.

In Table 2, we measured and compare SBP, DBP, and MAP in severe anemia and non-severe anemia group were 164.2 ± 20.1 VS 159.2 ± 21.5 mmHg; 83.8 ± 14.6 VS 87.6 ± 16.4 mmHg; and 110.6 ± 14.5 VS 111.5 ± 15.8 mmHg). The mean eGFR in the severe anemia group was 5.8 ± 1.7 mL/min/1.73m^2, and in the Non-severe anemia group was 6.0 ± 2.2 mL/min/1.73m^2.

Other parameters such as mean of ureum and creatinin levels in severe anemia and non severe anemia group were 138.6 ± 37.5 VS 129.2 ± 38.2 mg/dL; and 13.0 ± 4.1 VS 13.2 ± 4.9 mg/dL. Dialysis parameters were mean of Kt/V, UF Rate, and Qb namely 1.1 ± 0.2 VS 1.1 ± 0.2; 2,900 ± 900 mL VS 2,400 ± 100 mL; 195.7 ± 20.4 VS 195.3 ± 21.7 mL/min.

The overall survival in Kaplan-Meier analysis for respondents in the Non-Severe Anemia group was higher than respondents in the Severe Anemia group (Figure 2). However, the overall survival rates in the two groups were significantly different (98.0% VS 82.9%; p-value = 0.011).

Table 2. Characteristic data on each group

Variables	**Severe Anemia Group**		**Non-Severe Anemia Group**	
	Male N (%)	**Female N (%)**	**Male N (%)**	**Female N (%)**
Gender	20 (57.1)	15 (42.9)	34 (68)	16 (32)
	Yes N (%)	**No N (%)**	**Yes N (%)**	**No N (%)**
Diabetes Melitus	15 (42.9)	20 (57.1)	18 (36)	32 (64)
Variables	**SA Group (Mean ± SD)**	**Non SA Group (Mean ± SD)**	**P Value**	**95% CI**
Ages (years)	50.4 ± 8.8	51.2 ± 11.7	0.101	- 5.408 – 3.905
Duration of HD (months)	23.5 ± 16.9	24.3 ± 21.4	0.157	- 7.897 – 9.601
eGFR (mL/min/1,73m^2)	5.8 ± 1.7	6 ± 2.2	0.437	- 1.060 – 0.683
Pre dialysis SBP (mmHg)	164.2 ± 20.1	159.2 ± 21.5	0.751	- 4.156 – 14.196
Pre dialysis DBP (mmHg)	83.8 ± 14.6	87.6 ± 16.4	0.845	- 10.681 – 3.058
Pre dialysis MAP (mmHg)	110.6 ± 14.5	111.5 ± 15.8	0.830	- 7.569 – 5.826
Hb (g/dl)	7.2 ± 0.6	9.5 ± 1.2	0.000	- 2.760 – - 1.877
Ureum (mg/dl)	138.6 ± 37.5	129.2 ± 38.2	0.750	- 7.179 – 26.059
Creatinin (mg/dl)	13 ± 4.1	13.2 ± 4.9	0.355	- 2.153 – 1.855
Kt/V	1.1 ± 0.2	1.1 ± 0.2	0.594	- 0.075 – 0.099
UF Rate (liters)	2,900 ± 900	2,400 ± 100	0.279	0.045 – 0.876
Qb (mL/min)	195.7 ± 20.4	195.3 ± 21.7	0.390	- 8.869 – 9.698

N: Number of cases

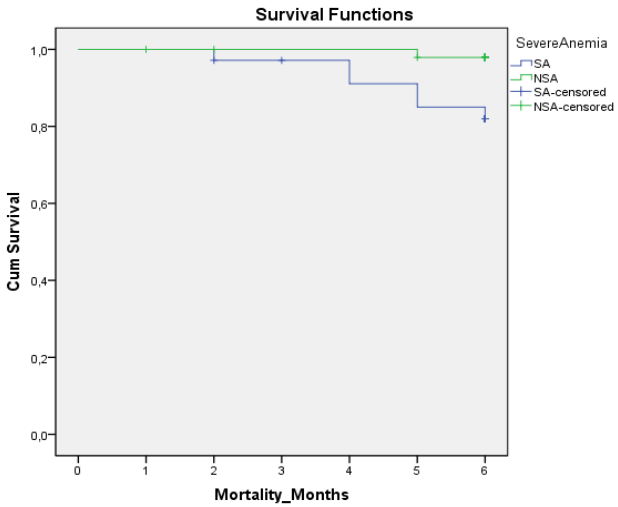

Figure 2. Kaplan Meier Overall Survival Curve**.** The survival in NSA (Non-Severe Anemia) group was higher than in SA (Severe Anemia) group (98.0% VS 82.9%; p-value = 0.011).

Table 3 shows he output of this multiple Cox regression analysis. The results show that severe anemia is a predictive factor of six months of all-cause mortality among hemodialysis patients (p = 0.027, Hazard ratio: 9.3). We find that the patient with Severe Anemia (Hb level less than 8 mg/dL) had a 9.3 times higher mortality rate than patients without Severe Anemia (Hb level more than equal to 8 mg/dL). On the other hand, other variables like gender, ages, duration of hemodialysis, ureum levels, creatinin levels, eGFR, dialysis adequacy, and diabetes mellitus did not play a role in predicting six months of all-cause mortality in hemodialysis patients (p-value ≥ 0.05).

Table 3. Cox Regression Analysis for Mortality

Parameters	p-Value	Hazard Ratio (95% CI)
Gender	0.663	1.4 (0.312 – 6.236)
Age	0.614	1.0 (0.950 – 1.090)
Duration of HD	0.608	1.0 (0.944 – 1.035)
Severe Anemia	0.027	9.3 (1.118 – 77.194)
Ureum	0.356	1.0 (0.990 – 1.290)
Creatinine	0.570	1.1 (0.788 – 1.541)
eGFR	0.441	0.9 (0.021 – 39.9)
Kt/V	0.926	0.9 (0.021 – 39.9)
Diabetes Mellitus	0.809	0.8 (0.186 – 3.714)

CI, confidence interval

The mortality rate in this study was 8.2%. During six months, seven respondents died, including six respondents (three males and three females) in severe anemia groups and one respondent (a male) in non-severe anemia groups. The limitation of this study is that there is no data related to the cause of death. In comparison, based on Indonesian

Renal Registry (IRR) data in 2018, the most common cause of death among hemodialysis patients in Indonesia was Cardiovascular events that around 42%, then followed by sepsis around 10%, cerebrovascular events 8%, gastrointestinal bleeding 3%, other cause 6% and no data 31% (5).

The overall mortality in Cox Regression analysis for respondents in the non-severe anemia group was lower than respondents in the severe anemia group as shows in Figure 3. However, the overall mortality rates in the two groups were significantly different (2.0% VS 17.1%; p-value = 0.027).

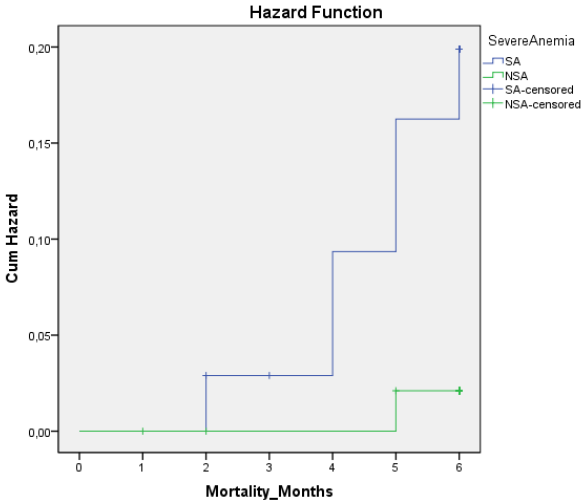

Figure 3. Cox regression overall mortality curve

DISCUSSION

Anemia in CKD and Its Management

The prevalence of severe anemia in this study was 41.2%. If we compare with the general population in the United States (US), the prevalence of severe anemia was 1.5% (10). Compare with previous studies, severe anemia prevalence among hospitalized patients was 14.7% (11). No other reference describes the prevalence of severe anemia among hemodialysis populations. This difference is due to differences in the people in this study were only hemodialysis patients. Anemia in CKD is caused by various factors, including erythropoietin deficiency, circulating uremic-induced inhibitors of erythropoiesis, shortened red blood cell survival, nutritional deficiencies such as folate, iron, and vitamin B12, anorexia, and dialysate losses (6).

Renal anemia is anemia in CKD mainly due to decreased erythropoietin production capacity. Other factors contributing to renal anemia are iron deficiency, the short lifespan of erythrocytes, secondary hyperparathyroidism, infection - inflammation, hemoglobinopathy, hypothyroidism, and folic acid deficiency.

Based on the Indonesian Society of Nephrology (InaSN) recommendation, iron status should be checked first before giving Erythropoietin Stimulating Agents (ESA). For the optimal erythropoiesis response, iron status must be sufficient. The iron status that should be checked includes Serum Iron, Total Iron Binding Capacity (TIBC), transferrin saturation, and ferritin serum. If we find a condition of iron deficiency anemia, it should be corrected first. Iron therapy indicated in absolute iron deficiency anemia, functional iron deficiency anemia, and the maintenance stage of iron status. Among hemodialysis patients, it is categorized to be absolute iron deficiency anemia if transferrin saturation <20%, and ferritin serum <200 ng/mL, functional iron deficiency anemia if transferrin saturation <20% and ferritin serum ≥200 ng/mL, and enough iron if transferrin saturation ≥20% and ferritin serum ≥200 ng/mL. Parenteral iron therapy is divided into the correction phase and maintenance phase. In absolute and functional iron deficiency anemia, the correction phase is done by giving 100 mg iron sucrose or iron dextran twice a week for five weeks. The targeted therapy reached if transferrin saturation >20% and ferritin serum >200 ng/mL. On the other hand, the maintenance phase ensures that erythropoiesis has sufficient iron during ESA therapy. The targeted therapy reached if transferrin saturation ranged between 20 – 50% and ferritin serum ranged between 200 – 500 ng/mL (3). The use of parenteral iron supplementation among hemodialysis patients has increased from year to year. In 2017, there were 27.2% increases in the use of parenteral iron supplementation to 34,430 ampoules per year. Data from IRR, only 6% of patients with serum Fe levels ≥150 mg/dl and 52% patients with transferrin saturation ≥20 (5). The limitation of this study is that the respondents did not check for serum iron, TiBC, transferrin saturation, and ferritin serum. Furthermore, it is unknown whether the patient's iron status is sufficient, absolute iron deficiency anemia, or functional iron deficiency anemia.

The use of ESA therapy is determined based on some factors, such as clinical evidence of the benefit of ESA therapy, cost-effectiveness, and the negative impact that may be found in the administration of ESA therapy. ESA therapy can be given in patients with Hb levels <10 g/dL, and other causes of anemia have been ruled out. ESA therapy can improve Hb levels in renal anemia patients with no absolute iron deficiency anemia and no severe infection. The targeted therapy of Hb in ESA therapy is 10 - 12 g/dL. ESA therapy is divided into correction and maintenance phases based on the InaSN recommendation of anemia therapy in CKD. The correction phase has been done if target therapy of Hb has not been reached by giving ESA 2,000 – 5,000 IU twice a week or 80 -

120 unit/kg/weeks. In contrast, the maintenance phase is done if target therapy of Hb has been reached by giving ESA 2,000 – 5,000 IU per week. If the patient's Hb level is >13 g/dL or ESA hypersensitivity reaction occurs, ESA therapy should not be given. Some side effects that may be occurred in ESA therapy are hypertension and thrombosis. However, these recommendations in Indonesia have not been implemented optimally. It can be caused by many factors, including differences in regulations in each hemodialysis unit or hospital differences in hemodialysis financing claims between hospitals depending on the level of the hospital (3). ESA therapy use among hemodialysis patients also increased from year to year. In 2017, there were 36.6% increases in the use of ESA therapy to 652,708 injections per year (5).

Nutritional therapy plays an important role in increasing Hb levels in renal anemia patients. There are various benefits of nutritional therapy in hemodialysis patients, including fixing and maintaining optimal nutritional status, preventing excess metabolic waste, regulating water and electrolyte balance, and controlling CKD-related conditions such as anemia, hypertension, bone disorder, and cardiovascular disease. Energy intake in CKD patient is recommended at 35 calories/kg/day in non geriatric (age <60 years) patients, and 30 – 35 calories/kg/day in geriatric (age ≥60 years) patient. Protein intake is also important. The recommendation is 1.2 g/kg/day in hemodialysis patients. The protein given contains at least 50% with high biological content (animal protein). The recommendation of lipid intake in hemodialysis patients ranged around 25 - 30% total daily calories with restriction of saturated fat 10% (12).

Blood transfusion becomes the last choice for Hb correction in renal anemia. Blood transfusion can be given in under the conditions: patient with Hb level <7 g/dL with or without anemia symptoms, Hb level <8 g/dL with cardiovascular disorder, acute bleeding with hemodynamic disturbance symptoms, and pre-surgical procedure. Target Hb in transfusion is different than in ESA therapy. The target is ranged between 7 – 9 g/dL. Blood transfusion is a relatively safe procedure, but it does not mean that there are no side effects. Some side effects that may be occurred during blood transfusion are circulation overload, allergic or anaphylactic reaction, iron overload, hemolytic reaction, febrile non-hemolytic reaction, blood-borne infection such as hepatitis B, hepatitis C, and HIV (3). The use of blood transfusion among hemodialysis patients has increased from year to year. In 2017, there were 22.6% increases in the use of blood transfusion to 46,362 bags per year (5).

Factors Related to Mortality Prediction

The patient's age does not play a role as a prediction factor in six months of all-cause mortality in hemodialysis patients (p-value = 0.614). It is the opposite of Msaad *et al*. (13) study, that described the surviving patients were younger than the deceased (43.07 ± 13.52 years VS 53.09 ± 13.56 years). The survival of non-geriatric patients is 82% and 53% in non-geriatric patients after four years of follow-up (13).

Gender does not play a role as a predictive factor of all-cause mortality in the next six months in hemodialysis patients (p-value = 0.663). It is similar to Vongsanim *et al.*, (14) study that described gender does not play a role as prediction mortality in hemodialysis patients. Women have a higher survival rate than men in the general population, but it is not similar in hemodialysis populations (14).

Urea blood level does not play as a predictive factor of all-cause mortality in the next six months in hemodialysis populations (p-value = 0.356). It is similar to Stosovic *et al.*, (15) study that described the lowest mortality observed in urea levels 28 – 31 mmol/L at the baseline data and 25 – 27 mmol/L in the whole observation period. In conclusion, urea level was not a predictor of mortality in the whole cohort. However, low urea and high urea were independent predictors of mortality in the corresponding models using Cox regression (15).

In this study, creatinine level does not play as a predictive factor of all-cause mortality in hemodialysis patients within the next six months (p-value = 0.570). It contradicts with Ajiro *et al.*, (16) studies that explained a significant relationship between serum level creatinine with mortality after ten years undergoing hemodialysis. In the population who had undergone hemodialysis >10 years, pre-dialysis serum creatinines plays a role as a predictor of mortality risk than in the population who had undergone hemodialysis ≤ 10 years. We found that low serum creatinine (<11.0 mg/dL) was associated with a high death risk. Patients with high serum creatinine may be better nourished with a greater somatic protein mass (16).

In this study, eGFR does not play a role as a predictive factor of mortality in the next six months among hemodialysis populations (p-value = 0.444). No study correlated eGFR and mortality among hemodialysis patients. Haas *et al.*, (17) showed reduced eGFR at the time of admission is a strong and dependent predictor for 30 days mortality among populations of patients admitted to medical emergency departments. The 30 days mortality risk was 1.8%, 3.5%, 6.9%, 11.1%, 13.6%, and 14.2% in patients with eGFR of ≥90, 60 - 89, 45 - 59, 30 - 44, 15 - 29, and <15 mL/min/1.73m^2. The eGFR was also significantly associated with in-hospital mortality, the percentage of ICU admission,

and a longer hospital stay. Lin *et al*., (18) showed that early dialysis initiation for ESKD patients is associated with increased mortality risk among East Asian populations. However, cardiocerebrovascular mortality between the early and late dialysis showed no survival differences. The limitation of this study is that there are no data about eGFR at dialysis initiation among respondents.

In this study, adequacy dialysis does not play as a predictor factor for six months of all-cause mortality among hemodialysis patients (p-value = 0.926). The mean Kt/V in this study is 1.1 ± 0.2. This value is considerably lower than the Kt/V target for the population undergoing hemodialysis twice a week (Kt/V target = 1.8). It contradicts with Hong *et al.*, study (19) that showed an association between Kt/V and mortality in hemodialysis patients might be modified by Body Mass Index (BMI). A higher Kt/V and BMI were independently associated with lower mortality risk for all-cause mortality in hemodialysis patients. Among patients with low BMI (<20 kg/m^2) and normal BMI (20 to <23 kg/m^2), higher Kt/V was associated with lower all-cause mortality compared to the reference group (Kt/V 1.2 to 1.4). On the other hand, among patients with high BMI (>23 kg/m^2), the association between higher Kt/V and lower all-cause mortality was attenuated. On the other hand, compared to patients with normal BMI and Kt/V within the target range, those with low BMI had a higher risk for all-cause mortality. However, increasing Kt/V values was associated with narrowing the mortality risk gap. Compared to patients with normal BMI and Kt/V within the target range, those with high BMI and Kt/V <1.2 did not have an increased risk for all-cause mortality despite low dialysis adequacy. Moreover, high BMI patients with Kt/V >1.2 were at lower risk for all-cause mortality than those with normal BMI and Kt/V within the target range. The differences between the low and high BMI groups may be explained in several ways: Malnutrition Inflammation Complex Syndrome (MICS) and Protein Energy Wasting (PEW) likely account for the more significant mortality among hemodialysis patients. Then, the improvement of dialysis adequacy has been associated with better nutritional status as assessed by serum albumin, which is linked to more remarkable survival in hemodialysis patients. On the other hand, high BMI also indicates good nutritional conditions. Al Sahow *et al*. study (20) showed that low Kt/V was strongly associated with higher mortality in women but not in men. Women hemodialysis patients with lower Kt/V had a 1.91 higher mortality risk than in higher Kt/V women hemodialysis patients. Since we know that dialysis dose as measured by Kt/V can be influenced by so many factors, such as Time of dialysis, Qb, dialysate flow, interruption session (hypotension or clotting), access

functionality (stenosis and recirculation), needle size, and placement, dialyzer characteristics, and proper blood sampling. In order to achieve higher survival among the hemodialysis population, Qb must be increased to >350 mL/min. The dialysis time must be increased to ≥4 hours thrice weekly, which will reduce low Kt/V prevalence and improve survival in hemodialysis patients.

In this study, diabetes does not correlate with a predictor factor in all-cause mortality among hemodialysis patients (p-value = 0.809). It is similar to Ajiro *et al.,* (16) study that explained that patients with diabetes had a higher mortality rate than patients without diabetes in the group with ≤10 years of hemodialysis. However, they were not at a greater risk for death in the group with >10 years of hemodialysis (16). Racki *et al.*, (21) reported a similar result that diabetic patients had significantly lower survival than non-diabetic patients, and cardiovascular disease remained the primary cause of death in both groups.

This study found that severe anemia plays a role as a prediction factor in six months of all-cause mortality in hemodialysis patients (p-value = 0.027, Hazard ratio: 9.3). Hemodialysis patients with severe anemia have a 9.3 times higher mortality risk in the next six months than in hemodialysis patients without severe anemia. No previous study examined the effect of severe anemia and six months of all-cause mortality in hemodialysis patients. Robinson *et al*., (7) and Kuo *et al*., (8) were showed that hemodialysis patients with Hb level ≥11 g/dL had high survival. The difference between these studies and Robinson *et al*., with Kuo *et al*., (8) are the respondents grouped into severe anemia with Hb level <8 g/dL and non-severe anemia, which Hb level ≥ 8 g/dL. While in Robinson *et al*., (7) and Kuo *et al*., (8) have found that the respondents were grouped into patients with Hb level ≥11 g/dL and patients with Hb <11 g/dL.

Anemia as Predictor Factor for Mortality

There are so many different definitions of terms for malnutrition in the dialysis populations, such as Protein Energy Wasting (PEW), Protein Energy Malnutrition (PEM), MICS, Malnutrition Inflammation Atherosclerosis (MIA), and Uremic Wasting Syndrome depending on the involvement of inflammation, hypercatabolism, and increased in uremia levels. However, there are no uniform diagnostic criteria for malnutrition. Comorbidities such as heart failure and CKD-mineral bone disorder have a bidirectional correlation with nutritional status. The pathomechanism relates to malabsorption due to gut edema, poor appetite due to cytokine production, and difficulty in oral intake and food preparation arising from fatigue and breathing difficulty.

Contributing factors related to the development of malnutrition are categorized as iatrogenic and non-iatrogenic origin.

Iatrogenic or physician-induced malnutrition develops from a medical procedure, pharmacological treatment, prolonged hospitalization, nosocomial infection, or delayed wound healing. On the other hand, iatrogenic malnutrition is an adverse dialysis event in ESKD patients. The factors related include dialysis-induced nutrient losses, multiple dialyzers use dialysis-induced inflammation, the efficacy of uremia corrections, dialysis adequacy, dialysis frequency, dialysis duration, and efficacy of metabolic acidosis correction (22).

A major goal of dialysis therapy is to remove uremic waste products through partial removal of uremic solutes. In uremia conditions, transamination activities inhibited and impacted protein and amino acid metabolism. The removal of uremic solutes by the hemodialysis process depends on many factors, such as duration of the dialysis session, dialysis adequacy, dialyzer membrane permeability, and dialysis frequency (22).

The dialysis process impacts chronic nutrient losses. Around 6 – 12 g of amino acids and 7 – 8 g protein losses during each dialysis session. It contributes to hypoalbumin conditions that play a strong predictor of malnutrition and mortality among hemodialysis patients. Nutrient losses depend on the dialyzer / Hollow Fiber (HF) membrane and the mechanism of solute removal. Increasing the pore size of the HF membrane allows the release of a larger intermediate molecule and increases the involuntary loss of albumin by about 2–14 g. It depends on the degree of membrane permeability condition such as membrane bio-incompatibility, high flux membrane, hemofiltration technique, hemodiafiltration technique (HDF), and the practice of multiple dialyzers that induce greater membrane permeability and facilitate the greater loss of amino acids into the dialysate (22).

In some countries, including Indonesia, dialyzer reuse is common. InaSN recommends that the hemodialysis unit reuse the dialyzer seven times during the hemodialysis process (23). However, dialyzer reuse may contribute to adverse effects such as infection risk, biochemical and immunologic reactions, improper sterilization, increased membrane permeability, and performance loss, leading to inadequate dialysis (22).

Many factors lead to inflammation in hemodialysis patients, such as biocompatibility of the dialyzer membrane, infection related to dialysis access, and impure dialysate containing endotoxins. Generally, the high flux dialyzer membrane and HDF technique are associated with lower inflammation grades in hemodialysis patients when compared to the low flux dialyzer membrane. The differences are attributed to processing technology for structuring and composing the membrane, dialyzer

bioincompatibility, water permeability, clearance, and appropriate sieving coefficients. In some studies, hemodialysis patients with catheter access had a significantly higher malnutrition inflammation score and lower serum albumin. Inflammation also occurs with dialysate contamination by a microorganism that produces endotoxin that passes through the dialyzer membrane and enters into blood circulation, affecting the production of proinflammatory cytokines such as Interleukin (IL)-1, IL-6, and Tumor Necrosis Factor (TNF-a) that are not effectively removed by dialysis treatment using low flux dialyzer. Overall, dialysis patients are vulnerable to oxidative stress with increased Reactive Oxygen Species (ROS) production and antioxidant depletion. ROS induced activation of nuclear factor kappa B (NF-KB), which translocated the cell nucleus stimulating cytokine production that causes inflammation.

Another impact of hemodialysis treatment is the activation of polymorphonuclear leucocytes that trigger ROS production. On the other hand, low antioxidant levels in hemodialysis patients may also occur from limited consumption of vegetables and fruits to prevent hyperkalemia. When malnutrition coexists with inflammation, the combination is MICS, reduces albumin production, and fosters poor appetite (22).

Metabolic acidosis develops in the early stages of CKD from the kidney's inabilities to excrete non-volatile acids and synthesize bicarbonate to maintain acid-base imbalance. Metabolic acidosis contributes to malnutrition by reducing protein synthesis and increasing muscle degradation. The malnutrition pathway in hemodialysis patients involves protein catabolism, secondary insulin resistance, inflammation, and increased serum leptin level. In metabolic acidosis, muscle degradation occurs due to two mechanisms. This mechanism increased Branched Chain Keto Acid Dehydrogenase (BCKAD) and the ATP-dependent Ubiquitin Proteosome System (UPS) pathway. In acidosis conditions, there is an increase in gene transcription and activity of BCKAD enzyme to degrade the Branched Chain Amino Acid (BCAA) that play a role as precursors for protein synthesis and is mainly metabolized in the muscle. Differently, metabolic acidosis activates UPS by increasing gene transcription of the proteasome and ATP-dependent ubiquitin, leading to increased caspase three activity, which promotes cleaving of muscle fibers, resulting in poor muscle mass. Additionally, the acidic environment affects insulin binding to receptors, reducing tissue sensitivity to insulin and affecting glucose uptake, and inhibiting insulin's anabolic effect, causing muscle depletion (22).

While non-iatrogenic factors develop spontaneously from contributive factors accompanying CKD progression, they are not related to the primary treatment. Non-iatrogenic factors may contribute to malnutrition conditions in hemodialysis patients. The factors related include suboptimal dietary intake, taste alteration, poor appetite, insulin resistance, and psychosocial factors, such as depression, lack of social support, financial constraints, and decreased physical functioning (22).

Suboptimal dietary intake is a primary contributing factor to malnutrition and mortality among hemodialysis patients. Adult recommendation for Dietary Energy Intake (DEI) and Dietary Protein Intake (DPI) to achieve nutrient adequacy within 25 – 35 kcal/kg ideal body weight (IBW)/day and 1.0 – 1.2 g protein/kg IBW/day. However, achieving DEI and DPI goals is still challenging among hemodialysis patients.

The inadequate diet may be attributed to monotonous dietary patterns, poor diet quality, anorexia, alterations in taste, and poor appetite. Taste alterations develop food aversion learning, which impacts appetite and reduces overall dietary quality, contributing to malnutrition. The reduction in taste perception itself may be related to zinc deficiency. On the other hand, the pathomechanism of poor appetite is explained by changes in appetite hormones. Ghrelin, an orexigenic hormone mainly secreted by the stomach, regulates appetite by stimulating spontaneous food intake (22).

Insulin at physiological levels bears catabolic and anabolic effects on skeletal muscle by promoting BCAA transport, regulating protein synthesis in the muscle, and facilitating glucose transport and uptake by muscle tissues. Insulin resistance is associated with peripheral resistance of glucose uptake at the skeletal muscle site and manifests as impaired insulin signaling through the phosphorylation of insulin receptor substrate-1. In another pathway, high Retinol Binding Protein 4 (RBP4) plays a role in glucose metabolism by inducing gluconeogenesis and inhibiting glucose uptake in the muscle. Educes insulin activity affects BCAA transport and blunts insulin's anabolic effects for decreasing skeletal muscle breakdown (22).

Psychological factors such as depression, lack of social support, financial constraints, and decreased physical functioning may negatively impact nutritional status in hemodialysis patients. Hemodialysis patients lacking social support have a higher prevalence of diminished appetite, depression, reduced physical functioning, and poor adherence to hemodialysis treatment that may be associated with malnutrition conditions. Lack of income is common among hemodialysis patients, and it is linked to poor dietary adherence because

patients' access to healthy food options is limited by cost (22).

In Guinn *et al.,* study (9), it was shown that severe anemia is associated with increased myocardial ischemia and mortality in patients declining transfusion. The all-cause mortality rate within 30 days was 19.8%, and the risk of death increases 55% per 1g/dL decrease in nadir Hb. The result is similar to this study: severe anemia is associated with six-month all-cause mortality in hemodialysis patients. The difference between Guinn *et al.,* (9) study and this study is in its population. The population in this study is only CKD patients who are undergoing hemodialysis. So, the population sample is more homogenous than in Guinn *et al.,* (9) study. The population of Guinn *et al.,* (9) study is all patients with blood transfusion refusal, which has many different underlying causes of anemia. On the other hand, the duration of observation on mortality patients is also different. Guinn *et al.,* (19) study observed all-cause mortality within 30 days, but in this study, we observed the all-cause mortality within six months.

In Park *et al.,* study (24), it was shown that a significant correlation between low Hb and the risk of Left Ventricular Hypertrophy (LVH). Adaptive changes in cardiac geometry are common in chronic anemia patients, including those with CKD. Low Hb patients' echocardiograms reveal an abnormal pattern of cardiac remodeling. Hemodynamic compensation for anemia includes reducing afterload due to decreased systemic vascular resistance, increased preload due to increased venous return, and increased sympathetic activity and inotropic factors. These adaptive physiological changes may lead to cardiac volume overload, resulting in eccentric LVH. In ESKD, these geometric changes are accompanied by arterial stiffening that can worsen LVH and abnormal coronary perfusion, increasing mortality due to cardiac events. Unfortunately, there were no data regarding the result of the patient's echocardiography in this study.

Perdhana *et al.,* (25) studies have found that a significant correlation between anemia and Intradialytic Hypertension (IDH). Patients with Hb level <10 g/dL had 5.9 more significant risks of experiencing IDH than patients with Hb level ≥10 g/dL. IDH is one of several complications that may be occurred during hemodialysis. IDH increases blood pressure from the beginning to the end of the hemodialysis process. The patient's blood pressure may be normal when hemodialysis started but then increased to hypertensive during and at the end of hemodialysis (26).

There are several definitions of IDH. In some studies, IDH was defined as increasing Mean Arterial Pressure (MAP) >15 mmHg within or immediately post-dialysis. In others defined as increasing >10 mmHg in systolic

blood pressure (SBP), and in some others defined as blood pressure rising to any degree during the second or third intradialytic hours. However, there are no accurate definitions considered as criteria for adjusting the diagnosis of intradialytic hypertension (27).

In several studies, IDH has been associated with poor outcomes in hemodialysis patients, including increased hospitalizations, higher blood pressure, cardiovascular morbidity, and all-cause mortality (28). In addition, previous studies have found that IDH had a significant relationship as a predictor factor of six-month all-cause mortality among hemodialysis patients (29). Hemodialysis patients with IDH complications had 7.6 times higher risk of all-cause mortality within six months than hemodialysis patients without IDH. Shamir *et al.,* (28) study showed an association of IDH with an increase in the Left Ventricular Mass Index (LVMI). LVMI is a strong and independent predictor of survival and cardiovascular events in hemodialysis patients. IDH and Left Ventricular Hypertrophy (LVH) may share common underlying pathomechanisms like extracellular volume overload and increased peripheral vascular resistance due to endothelial dysfunction. On the other hand, IDH has also been associated with increased ambulatory blood pressure in hemodialysis patients, increasing cardiovascular events and mortality (28).

Iron deficiency is one of the causes of anemia in CKD patients (6). In CKD, imbalance in iron homeostasis results from increased iron losses, reduced iron absorption, and iron storage and mobilization disruption. So, intravenous iron supplementation plays a vital role in treating anemia in ESKD (30). On the other hand, a high iron level could increase the risk of infection through impairment of neutrophil and T cell function and promotion of microbial growth (31). Even though hemodialysis patients also have a high risk of infection due to immunity dysfunction (32). Any such increase in risk may be substantial because the infection is a significant cause of mortality in dialysis patients (33). Unfortunately, there were no data regarding the results of the patient's iron levels in this study.

The hemopoietic tissue has a high nutritional requirement. Malnourished people are more likely to develop anemia and leucopenia. The lack of protein reserves and other nutrients to support the hemopoiesis process is the cause of this condition. [34] It means that lower hemoglobin is a marker of low protein intake and malnutrition. Malnutrition and anemia are reported as specific cardiovascular risk factors for dialysis patients, and each of the MIA syndrome components worsens the survival of these patients. Malnutrition is related to metabolic acidosis due to increased protein

catabolism, decreased protein synthesis, endocrine abnormalities, and inflammation among dialysis patients. Metabolic acidosis resulting in inflammatory stimulation, lipids oxidation, and oxidative stress can increase the risk of atherosclerosis and cardiovascular events (35).

Any other limitation of this study was that it did not perform regular evaluations of clinical and laboratory parameters during this study period. On the other hand, there is no clear information about the cause of death in the recruited respondents.

CONCLUSIONS

We showed that severe anemia is a predictor factor in all-cause mortality among hemodialysis patients in the next six months. Anemia affects the incidence of cardiomegaly, which increases the risk of cardiovascular death. In addition, anemia decreases immunity in patients and increases the risk of infection. Many factors cause anemia among hemodialysis patients, such as malnutrition, inadequate hemodialysis, iron deficiency, and erythropoietin deficiency. If anemia can be appropriately treated, the survival of hemodialysis patients will also improve.

AUTHOR CONTRIBUTIONS

Langgeng Perdhana: conceived and designed the analysis, collected the data, wrote the paper; Shofa Chasani: contributed data or analysis tools, wrote the paper.

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CONFLICT OF INTEREST

There are no conflict of interest declared in this study.

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