The Effect of Anemia and Hypoalbuminemia on Six-Months Hospitalization Risk in End Stage Chronic Kidney Disease Patients Undergoing Hemodialysis: A Retrospective Cohort Study

Octavianus Umboh, Emma Syarifih Moies, Stella Palar*

Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University - Prof. Dr. R. D. Kandou Hospital, Manado, Indonesia.

Corresponding Author:
Octavianus Umboh, MD. Department of Internal Medicine, Faculty of Medicine, Sam Ratulangi University, Prof. Dr. R. D. Kandou Hospital. Jalan Raya Tanawangko, Manado, Indonesia. Email: octavianus.umboh@gmail.com.

ABSTRACT

Background: *Chronic kidney disease (CKD) patients, particularly those who require renal replacement therapy, have a higher risk of hospitalization and mortality compared than the general population. The patients can suffer hypoalbuminemia and anemia due to chronic inflammations, that might affect the risk of hospitalization risk. The aim of this study is to investigate the effect of albumin dan hemoglobin levels on the hospitalization incidence of patients with stage 5 chronic kidney disease who undergo chronic hemodialysis.* ***Methods:*** *This retrospective cohort study enrolled patients aged 18 years and older with end stage kidney disease who underwent regular hemodialysis at the Prof. dr. R. D Kandou Hospital, Manado, Indonesia. Patients with malignancy were excluded. We measured the hemoglobin and albumin baseline level and observed the hospitalization incidence over the next 6 months. We used the Chi Square test with significance level of p-value 0.05, to analyze the association between both anemia and hypoalbuminemia with risk of hospitalization over 6 months of follow up period.* ***Results:*** *We enrolled 202 patients as our participants, most of whom were men (61.8%), with a mean age of 60.21±9.32 years. There were 120 participants (59.4%) being hospitalized during 6-months-follow-up period. The mean level of albumin was 3.29±0.63 g/dl, while the mean hemoglobin level was 9.43±1.75 g/dl. This study found that most of the participants had hypoalbuminemia (62.9%) while 45% had anemia. We found significant associations between hypoalbuminemia and anemia with the risk of hospitalization within 6 months, with p values 0.001 and 0.007, respectively. The relative risk for being hospitalized over 6 months follow up period in patients having anemia was 2.32 (95% CI 1.29-4.17), and for hypoalbuminemia was 2.77 (95% CI 1.54-4.99).* ***Conclusion:*** *Hypoalbuminemia and anemia are associated with increased risk of all causes hospitalization within 6 months in stage 5 chronic kidney disease patients undergoing hemodialysis.*

Keywords**:** *anemia, hypoalbuminemia, chronic kidney disease, hemodialysis, hospitalization.*

INTRODUCTION

Chronic kidney disease (CKD) is defined as an abnormality in the structure or function of the kidneys that occurs over a three-month period. Chronic kidney disease is a progressive disease that affects more than 10% of the world's population.[2] According to the Basic Health Research of the Republic of Indonesia in 2018, the prevalence of CKD among the Indonesian population was 0.38%. This number was higher than the prevalence of CKD in 2013, which was 0.2% nationwide. Chronic kidney disease mostly found in a population between the ages of 65 and 74 years old, and it is more common in

men.[3] Obesity, hypertension, and type 2 diabetes mellitus, are akso risk factors of CKD.[4] The failure of the excretion function of the kidneys leads to an accumulation of uremic particles, which act as oxidants and causes a chronic inflammatory condition.[5]

The classification of CKD can be assessed based on the glomerular filtration rates (GFR) which classify it into five stages. The patients with end stage CKD (stage 5) requires renal replacement therapy (hemodialysis).[1] Hemodialysis is one of the renal replacement therapies methods. It uses a special device to eliminate uremic toxins and regulate the body's electrolyte fluids.[6] According to the data published by the Indonesian Ministry of Health in 2018, only 19.3% of patients with end stage CKD underwent hemodialysis therapy [3]. In fact, if the treatment is not carried out properly, it can increase the risk of complications, for example, anemia. Anemia is caused by a decreased in the level of erythropoietin produced by the kidneys, with is followed by decreased GFR.[7] Some laboratory parameters, including albumin and hemoglobin levels, can be used to evaluate the progression of of CKD, predicting its clinical outcomes, evaluating response to treatment, as well as predicting of the prognosis.[8]

To date, most of the published studies on this topic were conducted in Japanese ,Taiwanese, and Singaporean populations, which may have different profile compared with Indonesian patients in terms of ethnicity, lifestyle, socioeconomic level and health system[9,10] The differences in socioeconomic status level between CKD patients in developed countries compared with those in emerging countries such as Indonesia, may play significant role particularly in nutritional status and dietary intake. Those factors may have effects on hemoglobin and albumin levels. The optimal management of anemia in CKD requires intravenous iron preparation and erythropoietin stimulating agent, which may not always available in all Indonesian hospital, and may thus be unmeet need. Based on those considerations, we want to investigate the effect of albumin dan hemoglobin levels on hospitalization, especially for patients with stage 5 chronic kidney disease undergoing hemodialysis in Indonesia;

Therefore, we aimed to investigate the impact of anemia and hypoalbuminemia on risk of hospitalization over 6 months follow up period in patients with stage 5 chronic kidney disease undergoing hemodialysis. We believe the findings may serve as evidence for the importance of hypoalbuminemia and anemia management to reduce risk of hospitalization over the next 6 months in CKD patients.

METHODS

Study Design and Participants

This is a retrospective cohort study. The study enrolled CKD patients undergoing regular hemodialysis at the Prof. dr. R. D Kandou Hospital, Manado, Indonesia. We screened eligible patients and collected data on their albumin and hemoglobin levels. We enrolled patients aged 18 years or older who underwent regular hemodialysis for at least 3 months with a duration of 8-10 hours per week (divided into two sessions). We excluded patients with malignancy. Patients who met the inclusion criteria and agreed to sign the informed consent form would be asked several questions, including age, sex, education, occupation, and ethnicity. Interviews were conducted by trained interviewers. If the patient did not show up for follow-up or the routine HD schedule, we contacted patient's family member following to find out the reason for the patient's absence, whether the patient had died, been admitted to the hospital, or been converted to CAPD therapy or a kidney transplant. If the patient is admitted to the hospital, the investigator searched the time of admission, as well as the primary and secondary diagnoses. For the next 6 months, we observed the hospitalization incidence as recorded in medical record. (January 1 to June 30, 2021). We did not include hospitalization caused by elective procedure (e.g. hospitalization for arteriovenous fistula operation). Hypoalbuminemia was defined as albumin level lower than 3.5 g/dL. Meanwhile, anemia was defined as hemoglobin level below 10g/dL. We used flowcytometry, method to measure hemoglobin level, and dye bromcresol green to measure the albumin serum level. Both

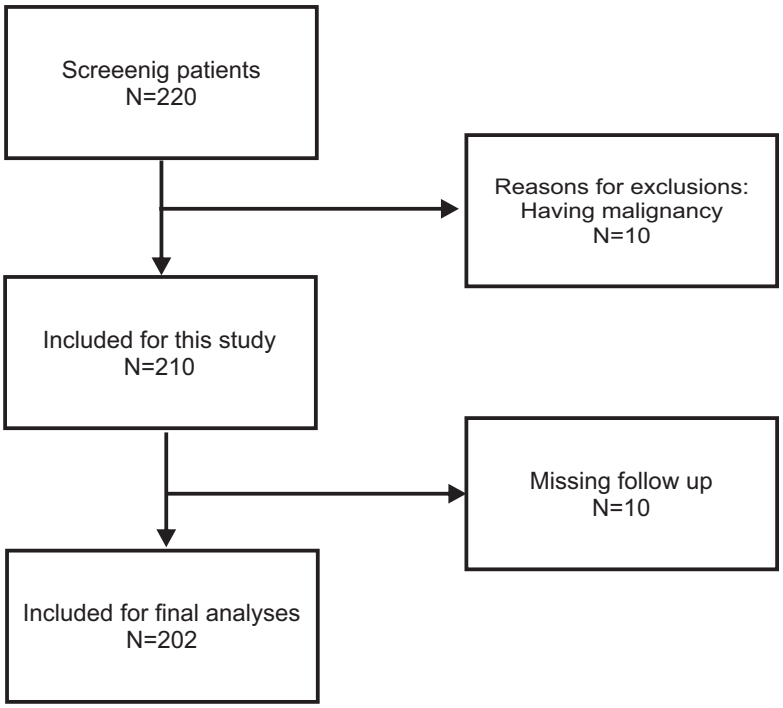

Figure 1. Flowchart of Patients Selection.

tests were carried out in the Clinical Pathology Laboratory of Prof R. D. Kandou Hospital.This study was approved by the Ethics Committee of Prof. Dr. R. D. Kandou Hospital Manado (Reference Number 152/EC/KEPK-KANDOU/IX/2021).

Statistical Analysis

We analyzed the collected data using Statistical Package for Social Sciences (SPSS) program Version 25.0. To determine the association between albumin and hemoglobin levels with hospitalization, we used Chi-square test. If one of the cells had an expected count value less than 5, the *Fisher exact* test was used. The p-value less than 0.05 was considered statistically significant. We also measured the effect size, presented as a relative risk and its corresponding 95% confidence interval.

RESULTS

We enrolled 202 patients with stage 5 CKD who underwent routine hemodialysis. The mean age in this study was 60.2±9.3 years, with 61.8% of total participants were men and 38.2% were women samples. In this study, the mean hemoglobin was 9.43±1.75 g/dl, while the mean albumin was 3.29±0.63 g/dl. Most patients aged 60 years or younger who were hospitalized had hypoalbuminemia and did not have anemia. The **Table 1** presented the baseline characteristics of the study participants.

Table 1. The baseline characteristics of the study participants.

Characteristics	
Men , n (%)	125 (61.8)
Age, mean±SD	60.21±9.32
Age >60 years old, n (%)	96 (47.5)
Hospitalized patients, n (%)	120 (59.4)
Length of hospitalization stay, mean±SD (days)	6.97±18.15
Anemia n(%)	91 (45)
Hypoalbuminemia, n (%)	127 (62.9)
Hemoglobin, mean±SD	9.43±1.75
Albumin, mean±SD	3.29±0.63

There were 120 participants who had been hospitalized within 6 months follow up period. **Table 2** showed the associations as well as the effect sizes between anemia, hypoalbuminemia, and hospitalization in patients with CKD stage 5 on hemodialysis. We found statistically significant association between both anemia and hypoalbuminemia with hospitalization, with p-values 0.007 and 0.001, respectively. The relative risk for being hospitalized over 6 months follow up period in patients having

anemia was 2.32 (95% CI 1.29-4.17), and for hypoalbuminemia was 2.77 (95% CI 1.54-4.99).

Table 2. The associations and effect size measurements between anemia and hypoalbuminemia with 6-months hospitalization in stage 5 CKD patients undergoing hemodialysis.

Variables		Hospitalization		RR (95%CI)*
		Yes	No	
Anemia	Yes	64	27	2.328 (1.299-4.174)
	No	56	55	
Hypo-albuminemia	Yes	87	40	2.768 (1.535-4.994)
	No	33	42	

* Pearson Chi-Square

DISCUSSION

The mean age of the subjects in this study was 60.2 years. Data from the Indonesian Renal Registry shows that CKD occurs most often between the age of 60-70 years old. In addition, CKD patients who undergo hemodialysis are usually aged 45-54 years. This shows that CKD patients undergoing hemodialysis have varied age ranges. This is related to the decline in nephron function, which is physiologically starting at this age (45-54 years). This study found that in CKD patients undergoing hemodialysis, the majority (61.8%) were men. This is congruent with the data from the Indonesian Renal Registry in 2018, showing more male HD patients than female patients. Based on IRR data, out of 30,831 new patients undergoing HD in Indonesia, 17,133 (56%) were men, and the remaining 13,698 (44%) were women. Several factors are associated with increased CKD progression in men compared to women, such as a higher risk of causing diabetic nephropathy, hypertension, hyperglycemia, albuminuria, dyslipidemia, an increased body mass index, lifestyle factors, kidney structure, and sex hormones.[11]

This study's hospitalization incidence was 59.4% in patients undergoing routine HD. Arif et al. revealed that 48,621 patients started hemodialysis, of whom 22,338 (46%) performed routine hemodialysis as inpatients. The length of stay of patients starting hemodialysis was 10 (7-17 days). Hemodialysis was initiated at a median of 3 (2-7 days) after hospital admission, and patients were discharged from the hospital 6 (3-10 days) after the first hemodialysis. Based on a national retrospective cohort in the US, older inpatients can be found to have congestive heart failure and dementia. In addition, they experienced longer hospitalizations during hemodialysis.[12] Medical indications for hospitalization for hemodialysis include patients with congestive heart failure who experience fluid overload or older patients who experience severe consequences of uremia. Li et al investigated the cause of CKD patients who were already on hemodialysis 1-2 years after their hemodialysis initiation. They found that infectious diseases such as pneumonia and urinary tract infection were s the most common indications for admission. Comorbidities also played significant roles in increasing hospitalization risk with cardiovascular diseases being the most significant.[13] Tanmoy et al. analyzed the data of patients on maintenance hemodialysis who were hospitalized in India. They found that the mean length of stay was 10.31±6.07 days, which was longer than our finding. They also found that the most common cause of admission was left ventricular failure (59.18%) and respiratory tract infection (14.29%).[14] We found in our study that anemia increased the risk of hospitalization by 2.3 times ($p = 0.007$). A systematic review by Palaka et al. found that significant association between anemia and hospitalization in CKD stage 5 patients undergoing hemodialysis. They found that hospitalization risk among CKD 5 patients undergoing HD was inversely correlated with hemoglobin level. They found that the hazard ratio of hospitalization in patients on dialysis with Hb 10–12 g/dL was 1.09 (1.07-1.11) and >12 g/dL was 0.91 (0.87–0.96).[15]

Li et al. also found that in their study, the mean hemoglobin level on admission of hospitalized patients with maintenance HD was 7.72±1.82. This finding also showed anemia to be prevalent in CKD patients that were admitted.[13] Anemia is one of the important clinical conditions of dialysis patients. The guideline for treating anemia in Indonesia is to use a limit of 10 g/dL to get supportive therapy. In general, patients with CKD on hemodialysis have Hb levels <10 g/dl, with a percentage of 65.9-100%. This is in accordance with national data, where only 22% of HD patients achieve Hb

≥ 10 g/dl. Meanwhile, the other 78% have Hb < 10 g/dl. Anemia occurs because the kidneys are the main source of erythropoietin. It is one part of the progression of kidney failure. It is independently related to the occurrence of cardiovascular disease in chronic kidney failure. Every decrease in the average hemoglobin of 1 g/dl will increase the risk of heart failure by 25%. More strikingly, the risk of death increases by up to 14%. Signs of anemia appear when GFR falls to 50 ml/minute. The average hemoglobin concentration is 2.3 g/dL. It might be lower in patients with a GFR of 50-25 ml/min compared to those with a GFR >50 ml/min.[16]

In patients with CKD, anemia is an independent predictor of death.[17] In patients with CKD who are not on dialysis, the risk of cardiovascular events, including stroke, is greatly increased when anemia is present.[18] A study in the United States investigated patients with CKD during the predialysis period. The study compared anemic CKD patients who did not use EPO to those who regularly used EPO. The results indicated that the regular use of EPO led to an increase in Hb levels.[19] This is associated with a decrease in hospitalizations, including hospitalizations for CVD. Mortality, morbidity, and CVD were also lower when these EPO-treated patients were eventually on dialysis. In patients already on dialysis, the higher the Hb level, up to 12 g/dL, the lower the patient's mortality and hospitalization rate.[17,20] Correction of anemia with subcutaneous erythropoietin and intravenous iron often results in improved or at least stable renal function. In addition, the patient's quality of life and exercise capacity also improve with anemia correction. In CKD patients, anemia can also play an important role in increasing the risk of death, coronary heart disease, stroke, and developing end-stage kidney disease. Erythropoietin may have direct positive effects on the heart and brain, unrelated to the correction of anemia, by reducing cell apoptosis and increasing neovascularization. Both of which may prevent tissue damage.[21]

We found a significant relationship between albumin and hospitalization in CKD 5 patients who underwent HD by 2.7 times (p = 0.001). Antunes et al. conducted a study to investigate the impact of hypoalbuminemia on the clinical outcome of patients with chronic HD. They observed the patients for 13 months. They found that hypoalbuminemic patients had a significantly higher hospitalization rate and shorter hospitalization free period (p=0.008).[22] Hypoalbuminemia is a poor predictor of worse prognosis for dialysis patients. Many recent studies have shown that serial measurement of serum albumin can even predict chronic inflammation and prognosis well. Based on the results of several studies, it is clear that hypoalbuminemia is associated with mortality in cardio-cerebrovascular and CKD stage 5 patients undergoing hemodialysis. In several studies, the relationship between hypoalbuminemia and cardio-cerebrovascular diseases is a reflection of inflammation-induced malnutrition. The underlying mechanisms behind this are appetite suppression and increased catabolism by inflammatory cytokines. Serum albumin is a potential barrier to free radicals. A decrease in serum albumin levels will lead to a decrease in antioxidant capacity and contribute to the harmful effects of oxidative stress on various tissues, including the arterial walls. These data suggested that hypoalbuminemia can more accurately be viewed as a composite marker reflecting malnutrition and increased acute phase inflammation, given that albumin is also a negative acute phase reactant.[23, 24]

Based on our study, hypoalbuminemia and anemia may play a significant role in increasing the hospitalization risk. However, in this study we did not analyze other hospitalization risk factors as confounding variables, such as the patients' comorbidities. Future studies are also needed to assess the effectivity of hemoglobin and albumin correction in reducing hospitalization incidence among patients with chronic hemodialysis.

CONCLUSION

In conclusion, we found a significant association between anemia and hypoalbuminemiaemia with hospitalization within 6 months of follow up in patients with stage 5 chronic kidney disease who undergo chronic hemodialysis. Optimizing anemia and hypoalbuminemia conditions are required to

reduce the risk of hospitalization over the next 6 months.

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COMPETING INTEREST

The authors declare no conflict of interest.

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