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Factors affecting hemoglobin levels of patients with end-stage kidney disease in the maintenance phase: A prospective observational study

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ABSTRACT

Background: Patients with end-stage kidney disease (ESKD) undergoing hemodialysis almost invariably develop anemia, which can significantly impair their quality of life. It is uncommon to find patients with consistently normal hemoglobin (Hb) levels; therefore, identifying the contributing factors is essential.

Objectives: This study aimed to identify factors affecting Hb levels in ESKD patients during maintenance phase.

Materials and methods: This prospective observational study was conducted at a regional hospital in Yogyakarta. The Hb cutoff point of 10 g/dL was used as the minimum standard for the maintenance phase, based on the Dialysis Consensus of the Indonesian Nephrology Association. The study included ESKD patients aged ≥18 years undergoing hemodialysis. The initial sample comprised 76 patients (38 with Hb >10 gm/dL and 38 with Hb ≤10 gm/dL); however, 65 patients were included in the final analysis after 11 were excluded due to dropout. Samples were matched based on age, sex, duration of hemodialysis, and comorbidities. Data were collected using patient medical record observation sheets, food record sheets, and the brief illness perception questionnaire (B-IPQ). Statistical analyses were performed using chi-square and logistic regression with a backward elimination method.

Results: A total of 65 participants were analyzed (33 patients with Hb >10 and 32 patients with Hb ≤10). Factors that showed significant associations with Hb levels were erythropoietin-stimulating agent (ESA) therapy odds ratio (OR)=7.162, 95% confidence interval [CI]=2.046-25.071, p=0.002), duration of hemodialysis (OR=4.909, 95% CI=1.299-18.551, p=0.019), and vitamin B12 intake (OR=4.238, 95% CI=1.183-15.176, p=0.027).

Conclusion: Erythropoietin stimulating agent therapy, duration of hemodialysis, and vitamin B12 intake were identified as factors influencing the improvement of Hb levels in patients with ESKD. Educational interventions are needed to enhance patients' understanding of the importance of maintaining balanced nutritional intake and adhering to optimal hemodialysis duration.

Introduction

End-stage kidney disease is characterized by a progressive decline in kidney function, which can have detrimental effects and potentially lead to death. End-stage kidney disease has become a major public health concern worldwide. The prevalence of ESKD requiring kidney transplantation continues to increase every year.[1] In Indonesia, the prevalence of active ESKD undergoing routine hemodialysis has increased by 58.9% over the past year.[2]

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Various physical complications arise due to the disease and hemodialysis procedures, one of which is fatigue and weakness caused by low Hb levels. Hemodialysis patients with normal Hb levels are rarely found, as anemia is a common complication among ESKD patients undergoing dialysis, resulting from either the underlying pathology or the dialysis process itself.[3] This condition is one of the major clinical issues in patients undergoing hemodialysis[1] and can have detrimental consequences, such as cognitive and psychological disorders, decreased cardiac function, angina, cardio-renal anemia syndrome, left ventricular hypertrophy, increased healthcare costs, reduced quality of life, worsening of clinical status, accelerated progression of heart disease, and increased risk of mortality.[4-6] It is also one of the major factors contributing to repeated hospitalizations among ESKD patients.[7]

Several studies conducted in different countries have examined the factors associated with anemia in ESKD patients, as reported by Shiferaw *et al*. in their systematic review. However, limited research has focused on the factors that play a critical role in maintaining and improving Hb levels among ESKD patients undergoing hemodialysis.[8] In Indonesia, 22% of ESKD patients receiving dialysis still have normal Hb levels.[2]

Several factors are thought to have a role in maintaining Hb stability in ESKD patients such as energy intake[9] which can increase the effectiveness of erythropoietin;[10] essential amino acids from protein intake, which support the formation of red blood cells;[11] iron, which can increase Hb levels and optimize erythropoietin therapy;[12] and folic acid and vitamin B12, which are essential in the production of healthy red blood cells.[13,14]

In addition, the duration of hemodialysis also affects Hb, as a longer duration of hemodialysis is associated with higher hemodialysis adequacy,[15] which may enhance erythrocyte glucose-6-phosphate dehydrogenase (G6PD) activity, thereby supporting proper red blood cell function.[16] Another factor is erythropoietin therapy which serves as the primary therapy for ESKD patients with anemia.[17] Additionally, patients' perception of their illness is thought to affect Hb levels, as those with a positive perception tend to maintain more stable emotional states and demonstrate greater adherence to recommended dietary and medication regimens.[18,19]

Several studies have analyzed the factors influencing Hb levels in patients with ESKD; however, the findings have been varied and inconsistent across different factors.[20-23] This study aims to identify patient-modifiable factors such as dietary intake, adherence to weekly hemodialysis regimens, and perceptions of their illness that may affect Hb levels. It is expected that the findings of this research will provide clinical implications for identifying factors that can help minimize the risk of anemia among ESKD patients.

Materials and methods

Study design

This prospective observational study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[24] The research was conducted at Dr. Sardjito General Hospital, Yogyakarta, over a four-week period. The study subjects were determined based on Hb concentrations measured between June 16 and 18, 2022, and were followed for four weeks, starting from June 20 to July 19, 2022.

Sample

The sample size was calculated using the Lemeshow's formula, resulting in a minimum of 32 participants. Considering a 10% predicted dropout rate, the required minimum sample was 35. However, 38 patients in each group met the criteria, yielding a total sample of 76 participants (38 with Hb >10 gm/dL and 38 with Hb ≤10 gm/dL). However, 11 participants were excluded, resulting in 65 patients included in the analysis (33 with Hb >10 gm/dL and 32 with Hb ≤10 gm/dL). The Hb cutoff of 10 gm/dL was used as the minimum target for the maintenance phase in dialysis patients, based on the Dialysis Consensus of the Indonesian Nephrology Association.[25] The inclusion criteria were ESKD patients undergoing hemodialysis twice a week, aged ≥18 years, and having received hemodialysis for at least six months. The exclusion criteria were patients with human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), liver cirrhosis, spinal cord malignancy, renal carcinoma, a history of kidney transplantation, or prior chemotherapy. The dropout criteria were critical illness, failure to undergo hemodialysis twice a week, withdrawal from the study, additional iron therapy, or death.

Data collection

Data were obtained from food record sheets documenting calorie, protein, iron, folic acid, and vitamin B12 intake, collected three days per week over four weeks.[26] The records were entered into the Indonesian version of NutriSurvey software to analyze nutritional content consumed by each patient. The B-IPQ was used to assess patients' perceptions of illness,[27] and had been validated in ESKD patients, showing validity values of 0.328-0.844 and a reliability coefficient of 0.755.[28] Data on body mass index (BMI), duration of hemodialysis, adequacy of hemodialysis with clearance time volume (Kt/V), and ESA therapy were recorded using an observation sheet prepared by the researchers.

The accuracy of the data on food and beverages consumed depended on the ability and honesty of the participants in reporting. To minimize bias, the researchers reconfirmed participants' dietary information upon submission of the completed food record forms.

Data analysis

Data were analyzed using the statistical package for the social sciences (SPSS) version 22 (IBM Corp. Armonk, NY, USA). Bivariate tests were first conducted to determine candidate variables for logistic regression, defined as those with a $p<0.05$. Logistic regression analysis was then performed to identify factors influencing Hb levels, using the backward method to determine OR with 95% CI. The variables included in the logistic regression analysis were iron intake, vitamin B12 intake, hemodialysis duration, Kt/V, and ESA therapy (Table 1).

Table 1. Factors affecting normal Hb levels.

Variable	Coefficient	*p* value	OR	95% CI
Model 1				
Intake iron	0.532	0.442	1.702	0.439-6.596
Vitamin B12	1.054	0.148	2.870	0.689-11.953
Duration of hemodialysis	1.561	0.026*	4.761	1.206-18.801
Kt/V	0.794	0.296	2.212	0.499-9.800
ESA therapy	1.446	0.046*	4.245	1.023-17.617
Constant	-7.834	0.000	0.000	
Model 2				
Vitamin B12	1.066	0.140	2.905	0.705-11.976
Duration of Hemodialysis	1.484	0.031*	4.411	1.143-17.019
Kt/V	0.917	0.214	2.503	0.589-10.638
ESA therapy	1.580	0.025*	4.854	1.216-19.380
Constant	-7.324	0.000	0.001	
Model 3				
Vitamin B12	1.444	0.027*	4.238	1.183-15.176
Duration of Hemodialysis	1.591	0.019*	4.909	1.299-18.551
ESA therapy	1.969	0.002*	7.162	2.046-25.071
Constant	-7.301	0.000	0.001	

Note: Logistic regression backward method; *significant at $p<0.05$

Results

The recruitment and sample group determination process was conducted on June 18, 2022. A total of 191 patients underwent routine hemodialysis twice a week. In the first step, 26 were excluded (21 with hemodialysis for less than one month, 2 had HIV/AIDS, and 3 did not have the latest Hb test results). Of the 165 patients, 42 had Hb levels >10 gm/dL; however, 4 were excluded (3 declined to participate and 1 was scheduled for kidney transplantation), resulting in a group of 38 respondents with Hb levels >10 gm/dL, resulting in a group of 38 respondents with Hb levels >10 gm/dL. Another 38 patients with Hb levels ≤10 gm/dL were selected through matching on age, sex, length of hemodialysis, and comorbidities.

The number of samples analyzed was 65 (33 patients with Hb >10 gm/dL and 32 with Hb ≤10 gm/dL), since 11 participants were considered dropped out by the researchers because one participant resigned, one participant had to get special treatment in the Intensive care unit, one participant undergo hemodialysis less than two times a week because there were problems with vascular access, seven participants received additional iron intravenous therapy, and one participant died.

Table 2 shows that 58% of patients with Hb >10 gm/dL and Hb ≤10 gm/dL are aged 48.03±12.00 and 48.78±14.07 years, respectively. Among patients with Hb >10 gm/dL, 54% are male, whereas in the Hb ≤10 gm/dL group, 59% are female. The most recent education level in both groups was higher education. Regarding occupation, 33% of patients with Hb >10 work as government or private employees, while 31% of patients with Hb ≤10 gm/dL are housewives. Patients in both groups have been undergoing hemodialysis for 1-5 years. The most common eating disorder reported in both groups was decreased appetite. Hypertension was the most prevalent comorbidity among patients with Hb >10 gm/dL and Hb ≤10 gm/dL. Folic acid was the most frequently consumed vitamin or supplement. Patients with Hb >10 gm/dL were more likely to consume additional vitamins or supplements

such as Neurobion™, become C™, Albuvit™, and iron tablets, compared to patients with Hb ≤10. The results of regression analysis (Table 1) indicated that ESA therapy (OR=7.162, 95% CI=2.046-25.071, *p*=0.002), duration of hemodialysis (OR=4.909, 95% CI=1.299-18.551, *p*=0.019), and vitamin B12 intake (OR=4.238, 95% CI=1.183-15.176, *p*=0.027) were significantly associated with Hb levels in patients with ESKD.

Table 2. Characteristics of patients with ESKD.

Characteristic		**Hb >10 gm/dL N (%)**	**Hb ≤10 gm/dL N (%)**	***p* value**
Age[a]		48.03 ± 12.00	48.78 ± 14.07	0.646
Gender[b]	Male	18 (54)	13 (41)	0.261
	Female	15 (46)	19 (59)	
Education[c]	Primary school	4 (12)	7 (22)	0.078
	Secondary school	2 (6)	6 (19)	
	Higher education	15 (46)	12 (37)	
	Associate degree/bachelor	10 (30)	5 (16)	
	Master's degree	2 (6)	2 (6)	
Occupation[c]	Farmer/ laborer	2 (6)	2 (6)	0.641
	Housewife	7 (21)	10 (31)	
	Self-employed	7 (21)	6 (19)	
	Government/private	11 (33)	7 (21)	
	employee	1 (3)	1 (3)	
	Student	5 (16)	6 (19)	
	Retired			
Hemodialysis period[c]	6 - <12 months	2 (6)	1 (3)	0.120
	1 – 5 years	14 (42)	23 (71)	
	6 - 10 years	13 (39)	4 (13)	
	>10 years	4 (13)	4 (13)	
Eating disorders[c]	Nausea	2 (6)	4 (13)	0.630
	Anorexia	8 (25)	7 (21)	
	None	23 (69)	21 (66)	
Comorbidities[c]	Hypertension	31 (94)	31 (97)	0.407
	Diabetes	14 (42)	8 (25)	
	Gout	2 (6)	3 (9)	
Vitamins/supplements[c]	Used	25(76)	25 (75)	0.821
	Folic acid	25(76)	24 (75)	
	Neurobion™	8 (24)	4 (12)	
	Albuvit™	3 (9)	2 (6)	
	Becom C™	2 (6)	0 (0)	
	Iron tablets	1 (3)	0 (0)	
	None	8 (24)	7 (22)	
Intake Calories[b]	≥35 kkal/kg body weight/day	12 (36)	7 (22)	0.199
	<35 kkal/kg body weight/day	21 (64)	26 (78)	
Intake Protein[b]	≥1 g/kg body weight/day	19 (58)	16 (50)	0.540
	<1 g/kg body weight/day	14 (42)	16 (50)	
Intake Iron[b]	≥10 mg/day	21 (64)	11 (34)	0.018*
	<10 mg/day	12 (36)	21 (66)	
Intake Folic acid[b]	≥0,8 mg/day	25 (76)	24 (75)	0.943
	<0,8 mg/day	8 (24)	8 (25)	
Intake Vitamin B12[b]	≥3 µg/day	20 (61)	10 (31)	0.018*
	<3 µg/day	13 (39)	22 (69)	
BMI[b]	Normal	20 (62)	18 (56)	0.722
	Abnormal	13 (38)	15 (44)	

Table 2. Characteristics of patients with ESKD (continued).

Characteristic		Hb >10 gm/dL N (%)	Hb ≤10 gm/dL N (%)	*p* value
Adequation of hemodialysis (Kt/V)[b]	≥1.8	26 (79)	10 (31)	0.000*
	<1.8	7 (11)	22 (69)	
Duration of hemodialysis[b]	≥4.5 hours	28 (85)	15 (47)	0.001*
	<4.5 hours	5 (15)	17 (53)	
ESA therapy[b]	Appropriate	25 (76)	9 (28)	0.000*
	Inappropriate	8 (24)	23 (72)	
Perseption of disease[b]	Positive	21 (64)	15 (47)	0.174
	Negative	12 (36)	17 (53)	

Note: *significant at $p<0.05$, [a]mann whitney, [b]chi-square, [c]spearman rank.

Discussion

The factors influencing Hb levels in ESKD patients undergoing hemodialysis include ESA therapy, hemodialysis duration, vitamin B12 intake, and education. The dosage of alpha and beta ESA was categorized as 2000-5000 international units (IU) administered twice weekly or 80-120 IU/kg body weight per week. Continuous erythropoietin receptor activator (CERA) was administered at 0.6 µg/kg body weight or 50-75 µg every two weeks.[29] Erythropoiesis-stimulating agent therapy was identified as the dominant factor affecting Hb levels in patients with ESKD undergoing hemodialysis. Patients who received appropriate ESA therapy had a 7.162-fold higher likelihood of achieving Hb levels >10 gm/dL. In this study, the frequency of ESA therapy differed between the groups: patients with Hb >10 gm/dL received ESA therapy once weekly, whereas those with Hb ≤10 gm/dL received therapy twice weekly. Some patients with low Hb received ESA therapy cautiously due to post-dialysis increases in blood pressure, which could exacerbate hypertension.[30] In line with previous studies, regular administration of ESA therapy significantly increased Hb levels in patients with ESKD.[17]

Each hemodialysis session lasted 4-5 hours and was performed 2-3 times per week with the ideal total duration being 10-15 hours per week. However, most health insurance providers in Indonesia only cover an average of two sessions per week, and patients spending 5 hours per session are rare. Therefore, the maximum average duration per patient was set at 4.5 hours.[25] In this study, patients with an average hemodialysis duration of 4.5 hours had a 4.909 times chance of Hb levels compared to patients with an average hemodialysis duration of <4.5 hours. In line with the results described in Table 1, 85% of patients with a mean duration of hemodialysis of 4.5 hours had Hb levels of >10 gm/dL. Previous studies have also reported that patients undergoing hemodialysis for 12 hours per week had higher average Hb levels than those dialyzed for 8-10 hours per week.[31] Longer hemodialysis sessions improve dialysis adequacy, allowing for more effective removal of toxins.[15] Elevated blood urea nitrogen (BUN) levels have been shown to indirectly affect Hb levels; patients with high BUN have a 1.02-fold higher risk of developing anemia.[32]

Patients with adequate vitamin B12 intake had a 4.238-fold higher likelihood of achieving target Hb levels compared to those with lower intake, which aligns with previous research.[33] Vitamin B12 is a nutrient that functions as one of the main ingredients that play a role in the production of red blood cells.[34] Vitamin B12 is essential for red blood cell production and is a key marker in megaloblastic anemia, which arises from deficiencies in vitamin B12 and folic acid. Appropriate intake of vitamin B12 supports stable Hb levels in patients undergoing hemodialysis.[13] In this study, patients with Hb >10 gm/dL had higher average vitamin B12 intake than those with Hb ≤10 gm/dL; however, as shown in Table 1 , vitamin B12 intake was not a statistically significant predictor of Hb levels. Consistent findings have been reported in previous studies.[35] Only a small proportion of patients regularly consumed iron-rich foods, such as red meat, liver, green vegetables, and fish, and the variety of diet was limited. Adequate iron intake is crucial for increasing serum Hb levels and optimizing treatment response.[36]

This study found no significant effect of caloric, protein, or folic acid intake on Hb levels in ESKD patients undergoing hemodialysis. Both the Hb >10 gm/dL and Hb ≤10 gm/dL groups had average caloric intake within the lower category, which contrasts with previous studies on energy intake.[9] Patients must also restrict food intake to prevent excessive potassium and phosphate levels and to avoid fluid overload.[10] In line with previous research there was no significant relationship between protein intake and Hb levels.[35] In general, Essential amino acids from protein intake are generally necessary for red blood cell formation, as they play a crucial role in iron transport and utilization in the body.[37] Similarly, folic acid intake was not significantly associated with Hb levels in this study.[35] Most patients had taken daily folic acid as recommended, yet some still had Hb ≤10 gm/dL. Folic acid, a water-soluble vitamin, is essential for the production of healthy red blood cells.[14] Therefore, the intake of foods containing folic acid in patients with ESKD must adequate, as the human body cannot synthesize folic acid and must

obtain it through daily dietary intake.[38] This finding contrasts with previous studies on BMI.[39] In this study, less than half of the patients had comorbid diabetes mellitus. Patients with diabetes typically exhibit lower Hb levels than those without diabetes because blood glucose levels can influence Hb levels in individuals undergoing hemodialysis. On average, ESKD patients with controlled blood glucose levels maintained more stable Hb levels.[40]

Almost all patients in this study underwent hemodialysis twice weekly, and therefore, a Kt/V standard of 1.8 was applied. According to the dialysis consensus of the Indonesian Nephrology Association, the ideal Kt/V target is 1.2 for patients undergoing hemodialysis three times per week, whereas the target for those dialyzed twice weekly is 1.8.[25] In this study, hemodialysis adequacy was not significantly associated with Hb levels. Ginting *et a*l. also reported that patients achieving a Kt/V of 1.8 exhibited higher Hb levels than those with Kt/V <1.8.[41] Adequate hemodialysis is crucial for reducing anemia, morbidity, and mortality in patients with ESKD.[42] Additionally, another study reported that patients receiving adequate hemodialysis had higher erythrocyte G6PD activity.[16] Low G6PD activity is associated with reduced red blood cell survival, leading to decreased Hb levels.[43]

This study also examined patients' perceptions of illness, including both positive and negative beliefs, and their potential influence on health-related decision-making.[44,45] Most patients (64%) with Hb levels >10 gm/dL reported a positive perception of their disease compared to patients with Hb ≤10 gm/dL; however, no significant effect on Hb levels was observed. Research on the relationship between disease perception and Hb levels in hemodialysis patients remains limited. Patient perceptions in ESKD are often related to hopelessness, self-management, medication adherence, and dietary compliance. Patients with a positive perception tend to maintain more stable emotional status and follow self-management, medication, and dietary recommendations, which may have a favorable impact on Hb level.[18,19,46]

Limitations

This study has several limitations. First, including its cross-sectional design and relatively small sample size may limit the generalizability of the findings. Second, monitoring was conducted for only one month, with Hb measurements taken only twice, at baseline and at the end of the study. Third, other potentially influential factors, including infection, pure red cell aplasia (PRCA), dialysis access, smoking, drinking, and laboratory tests such as albumin levels, were not monitored. Fourth, the accuracy of dietary intake depended on the participants' ability and honesty in reporting, which was beyond the researchers' control. All participants were not willing to maintain food intake records for four weeks, as the types and portions consumed were not substantially different from previously recorded data. Consequently, dietary intake variables were analyzed using data recorded by patients for 2-3 weeks. Therefore, the results of this study should be interpreted with caution.

Conclusion

Erythropoietin stimulating agent therapy, duration of hemodialysis, and vitamin B12 intake were identified as factors influencing the improvement of hemoglobin levels in patients with ESKD. Enhanced education programs are needed to increase patient awareness of the importance of maintaining a balanced nutritional intake and completing hemodialysis sessions of adequate duration to sustain and enhance the hemoglobin levels. In this study, dietary intake data were obtained solely from patient-completed food records, which may have introduced variability due to individual perceptions of portion sizes. Additionally, hemodynamic variables were not assessed, highlighting the need for further research to validate and extend these findings.

Ethical approval

This study has approved by Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (KE/FK/0750/EC/2022).

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Conflict of interest

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CRediT authorship contribution statement

Maryadi M: conceptualization, methodology, data collections, data curation, writing original draft, review and editing, analyzed the data, and drafted the manuscript; **Khudazi Aulawi:** conceptualization, methodology, data curation; and supervision; **Uki Noviana:** conceptualization, methodology, and validation, and supervision.

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