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Type of anemia correlate with ferritin levels in patients with Chronic Kidney Disease (CKD): a cross sectional study

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ABSTRACT

Background: Anemia is the most common complication due to CKD. Normocytic normochromic is the most common type of anemia in CKD is, but there is also some microcytic hypochromic. Clinical examination such as erythrocyte indices examination and monitoring serum ferritin levels can help diagnose anemia in CKD. The purpose of this study is to determine the correlation between erythrocyte indices and ferritin levels in CKD patients in the hemodialysis unit of PKU Hospital Bantul.
Methods: This research involved 50 CKD patients at PKU Hospital Bantul. Blood samples were taken to check ferritin levels and erythrocyte indices consisting of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC). This study was conducted by cross-sectional study design. Data were analyzed using SPSS version 20 for Windows.
Results: The average hemoglobin level was 8.46±1.31 g/dL in males and 7.92±0.90 g/dL in females. Most of the hematological profile was predominant in male patients such as in MCV (89.36±6.72 fl), MCH (29.12±2.76 pg), and MCHC (32.95±0.96 g/dL). However, the average ferritin level (352.51±544.74 ng/mL) was predominant in female patients (399.99±680.96 ng/mL). There was a significant correlation between MCH and ferritin levels ($r = 0.364$; $p = 0.009$) and MCHC with ferritin levels ($r = 0.295$; $p = 0.038$). However, there was no significant correlation between MCV and ferritin levels ($r = -0.059$, $p = 0.683$).
Conclusion: There is a significant correlation between MCH and MCHC levels with ferritin levels. In addition, the patients had normal MCV, MCH, and MCHC values with normocytic normochromic anemia.

Keywords: Anemia, Chronic Kidney Disease, Erythrocyte Indices, Ferritin.
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INTRODUCTION

One of the world's most serious health problems is Chronic Kidney Disease (CKD). Based on the Global Burden Disease study results, it was found that at least 750 million people in the world have kidney disease.[1] This study also stated that CKD was the 12th leading cause of death globally in 2015.[2]

CKD is divided into 6 stages based on Kidney Disease: Improving Global Outcomes (KDIGO).[3] Patients with stage 5 chronic kidney disease or special conditions should receive kidney replacement therapy. Hemodialysis is one type of kidney replacement therapy most often performed in patients with CKD stage 5 or end-stage renal disease (ESRD).[4] The condition of CKD, especially for those who have undergone hemodialysis, will generally cause various complications. Anemia is the most common complication caused by hemodialysis. Anemia in CKD is confirmed when the hemoglobin (Hb) level in adult men is <13 g/dL and in non-pregnant adult women <12 g/dL.[5]

Usually, the type of anemia in CKD is normocytic normochromic; this is due to CKD, there's only a decrease in the quantity of erythrocyte production. However, anemia in CKD can be microcytic hypochromic in some conditions, although in a small prevalence.[6] Anemia in CKD is caused by an insufficient amount of erythropoietin (EPO). EPO has a role in increasing the proliferation and differentiation of erythrocytes.[7]

Complete Blood Count (CBC), including the erythrocyte index consisting of Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), and iron status, is an example of laboratory examination that can be used to help enforce the diagnosis of anemia in CKD, one of iron status examination can be done by examining ferritin.[8] Ferritin is one of the iron storage proteins in the body which generally accumulates in reticuloendothelial cells, kidneys and almost all other cells.[9]

The role of laboratory tests is very important to diagnose the type of anemia. This diagnosis will affect the treatment that will be given. Based on those mentioned above, this study aims to evaluate the

correlation between the erythrocyte index, namely MCV, MCH and MCHC, on ferritin levels in CKD patients undergoing hemodialysis.

METHODS

This is a cross-sectional study with the type of analytical observational. We observed erythrocyte index including MCV, MCH, MCHC, and from blood samples, we obtain ferritin levels of patients with chronic kidney disease with hemodialysis. The study was conducted at the hemodialysis unit of the PKU Bantul Hospital in June - July 2020 by taking 50 study samples based on inclusion and exclusion criteria.

Medical records and the Indonesian Renal Registry (IRR) are used to completing research data. There are several inclusion criteria used in this study. The subject is a patient with chronic kidney disease who underwent hemodialysis at PKU Bantul for at least 3 months and at least twice a week, aged ≥ 18 years, and patients willing to participate in the study. After initial screening, the patients were included in the anemia category. Female patients who were pregnant, patients who received iron therapy in the last 3 weeks and patients with a history of transfusion in the previous 3 months are the exclusion criteria in this study. The tools and materials needed in this study were respondent data, a consent form for the study, a 3-cc syringe, an EDTA tube and serum tube, alcohol swab, Sysmex XN-550, Cobas-6000, and cooler box.

Coordination with PKU Bantul Hospital does determine the research topic and then determine the research sample based on inclusion and exclusion criteria. Informed consent was done after determining the sample criteria. We ask the study patient to sign a study approval letter if they are willing to participate in the study at PKU Bantul Hospital.

Data were obtained by searching for patient information through the Indonesian Renal Registry (IRR) and taking 2 tubes of blood samples from patients per patient with 1 EDTA tube and 1 serum tube. Complete blood counts examine with Sysmex-XN 550 by using the EDTA tube and blood samples from serum tubes were used for ferritin tests with Cobas-6000.

There are two types of variables observed in this study. Erythrocyte index includes MCV, MCH, and MCHC, the independent variables in this study, while the ferritin level is the dependent variable. Interfering variables in the study were inflammation factors and the amount of iron intake in patients. The analysis technique in this study used univariate and bivariate analysis. The Pearson correlation test was used in this study. The correlation test is significant if the p-value is <0.05.

RESULTS

This table shows that research respondents consist of 26 males (52.0%) and 24 females (48.0%). In addition, most of the respondents were found in the 45-49 years age range (58.0%), ≤ 36 months of hemodialysis period (62.0%), and having hypertension comorbidity (76.0%) (Table 1).

The mean value of hemoglobin patients indicated that the hemoglobin of the patient subjects was in the anemia category (8.20±1.16 g/dL) (Table 2). The average hemoglobin level was 8.46±1.31 g/dL in males and 7.92±0.90 g/dL in females. Most of the hematological profile was predominant in male patients, such as in MCV (89.36±6.72 fl), MCH (29.12±2.76 pg), and MCHC (32.95±0.96 g/dL). However, the average ferritin level (352.51±544.74 ng/mL) was predominant in female patients (399.99±680.96 ng/mL) (Table 2). The group has a Standard Deviation (SD) greater than the average value, which means that ferritin has a large data distribution and a large variation gap.

The outcomes showed that most MCV was in the normocytic category with a total of 36 (72.00%), 10 (20.00%) patients with microcytic and 4 (8.00%) patients with macrocytic (Table 3). Similar results were also found in the MCH and MCHC categories. In contrast, a total of 41 (82.00%) subjects had MCH in the normochromic category and 9 (18.00%) other subjects were in the hypochromic category (Table 3). The results of the MCHC frequency distribution analysis showed that 36 (72.00%) patients were categorized as normochromic and 14 (28.00%) patients were considered hypochromic (Table 3).

Bivariate analysis using the Pearson Correlation test showed that MCH and MCHC are 2 variables related to ferritin levels. MCV has no significant correlation to the ferritin levels (r=-0.059; p=0.683) (Table 4). However, there is a moderate significant correlation between MCH and ferritin levels (r=0.364; p=0.009) and a low significant correlation between MCHC and ferritin levels (r=0.295; p=0.038) (Table 4).

Table 1. Baseline characteristics of respondents

Characteristics	Frequency (n = 50)	Percentage (%)
Gender		
Male	26	52.0
Female	24	48.0
Age (Years)		
< 45	2	4.0
45 - 59	29	58.0
60 - 74	17	34.0
75 – 90	2	4.0
Length of Hemodialysis (Months)		
≤ 36 months	31	62.0
> 36 months	19	38.0
Comorbid		
Hypertension	38	76.0
Diabetes Mellitus	18	36.0
Urinary Tract Stone (UTS)	5	10.0

DISCUSSION

Given the consequences of univariate analysis, it was found that the mean MCV of the 50 subjects showed the normocytic type or normal in size. The study results were in line with a previous study by Shastry and Belurkar in 2019, which included 300 patients with CKD with similar outcomes.[8] More than 70% of patients had normal MCV with a mean MCV of 86±7.07 fl.[8] The results of this study are also similar to another study, whereas 90% of patients had normocytic anemia at the time of the blood smear examination prior to hemodialysis.[10] In addition, a previous study conducted by Dmitrieva O et al. was also found that 80.5% of patients with CKD had normocytic anemia.[11]

Table 2. Hematological Profile of Patients

Variable	Total (N=50)	Mean	Minimum	Maximum	SD
Hemoglobin (g/dL)		8.20	5.70	11.30	1.16
Male	26 (52.0)	8.46	6.50	11.30	1.31
Female	24 (48.0)	7.92	5.70	10.20	0.90
MCV (fl)		88.39	65.20	105.70	8.05
Male	26 (52.0)	89.36	71.00	105.70	6.72
Female	24 (48.0)	87.33	65.20	105.10	9.31
MCH (pg)		28.92	23.20	35.30	2.55
Male	26 (52.0)	29.12	23.20	35.30	2.76
Female	24 (48.0)	28.7	24.00	34.00	2.34
MCHC (g/dL)		32.65	30.60	35.00	1.01
Male	26 (52.0)	32.95	30.90	35.00	0.96
Female	24 (48.0)	32.32	30.60	34.50	0.98
Ferritin (ng/mL)		352.51	9.76	2,956.00	544.74
Male	26 (52.0)	308.67	9.76	1,615.00	388.38
Female	24 (48.0)	399.99	27.85	2,956.00	680.96

MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; SD: Standard Deviation

Table 3. Type Anemia of Subjects

Variable	Frequency			Percentage (%)		
	M (n=26)	F (n=24)	Total (N=50)	M	F	Total
MCV (fl)						
Microcytic	3	7	10	11.5	29.2	20
Normocytic	22	14	36	84.6	58.3	72
Macrocytic	1	3	4	3.8	12.5	8
MCH (pg)						
Hypochromic	4	5	9	15.4	20.8	18
Normochromic	22	19	41	84.6	79.2	82
MCHC (g/dL)						
Low	4	10	14	15.4	41.7	28
Normal	22	14	36	84.6	58.3	72

MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; M: Male; F: Female

Table 4. Correlate between erythrocyte index and ferritin levels

Variable	n	r	p
MCV (fl)	50	-0.059	0.683
MCH (pg)	50	0.364	0.009*
MCHC (g/dL)	50	0.295	0.038*

MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; r: Coefficient Correlation; *Statistically significant if p-value less than 0.05 in Pearson Correlation test.

The most often anemia that occurs in patients with chronic disease is normocytic normochromic. The cause of anemia in chronic disease can be multifactorial, but the leading cause of anemia in CKD is a deficiency of erythropoietin (EPO).[8] Kidney damage will increase pro-inflammatory cytokines, leading to suppression of EPO, so that erythrocyte production can be decreased without changes in erythrocyte shape.[12] Meanwhile, microcytic anemia commonly occurs due to a decrease in the amount of iron in the body.[13]

MCH and MCHC mean values showed a normochromic state. A previous study conducted by Shastry I and Belurkar S involved 300 study patients with similar findings where 70% of patients had normal MCH, the average MCH was 28.4±2.59 pg, and the average MCHC was 32.8±1.71 g/dL.[8] Another study also had the same results where the average MCH in the previous study was 31.40 pg and the average MCHC within the normal range with 32.4 g/dL.[14]

Normochromic anemia is a type of anemia that most often occurs in chronic kidney disease conditions.[15] Patients CKD with normochromic anemia has a lower EPO production that is not accompanied by iron deficiency, so the erythrocytes are still red and make the type of anemia is normochromic anemia.[16] However, in a particular condition, severe chronic inflammation can induce hepcidin accumulation and decrease plasma transferrin used for the erythropoiesis process.[17] This condition can reduce the iron, so the production of hemoglobin chains will decrease. The hemoglobin concentration in erythrocytes will also decrease and cause the color of the erythrocytes to become paler or called hypochromic.[18]

The ferritin mean (352.51 ng/mL) cannot be directly used to determine the type of anemia. The type of anemia in

renal disease is determined based on two components: ferritin levels and transferrin saturation. The result indicated that the sample patients had values above the cut-off of absolute iron deficiency anemia (≥200 ng / mL). This study's results are similar to a previous study by Iyawe IO et al., that found a ferritin level was 223.23 ng/mL, which means that the ferritin value is still above the cut-off of absolute iron deficiency anemia.[19]

Bivariate analysis showed that there was no significant relationship between MCV and ferritin levels. The results of this study are similar to a previous study which found no significant correlation between serum ferritin levels and MCV.[20] Similar results were also found in a study conducted by Takasawa K et al. where no significant correlation between MCV and serum ferritin levels (r = 0.05; p = 0.3512).[21] Based on Sysmex XN-550, the mean of MCV in male and female patients was still in the normal category because of the value at 82 - 99 fl.

This research showed that there was a significant correlation between MCH and ferritin. This study's result is similar with a previous study that found a positive correlation between MCH and serum ferritin (r = 0.616; p = <0.001).[22] Referring to the normal value of the MCH examination using the Sysmex XN-550, the value also still in the normal category because it is still in the range of 27-32 pg based on the previous study. The average MCH in the male patient group was 29.12 pg and 28.7 pg in the female group.[23]

This study's results showed that there was a significant correlation between MCHC and ferritin levels. The results of this study are different according to the previous study where there was no significant correlation between MCHC and serum ferritin in chronic kidney patients at DR. Sardjito Public Hospital (p=0.528; r = 0.058).[24] This difference can be influenced by several factors, including differences in the number of subjects used in the study. This research was conducted by involving 50 research subjects, while the previous research was conducted by involving 119 research samples.[24] Difference number of subjects could provide different statistical results.

However, this study also has several limitations. The iron status assessment was done in this research using ferritin levels; however, the gold standard assessment to evaluate the iron reserve levels is the hemosiderin assessment. It is important to do extra iron status assessment, commonly transferrin examination done to decide the type of anemia in CKD patients. Furthermore, due to this research was a cross sectional study, the scientist could not get definite data on the patient's history, like the patient's food diet and the patient's history of anemia which could cause various types of anemia in the patient subject.

CONCLUSION

There is a significant correlation between MCH and ferritin levels and MCHC with ferritin levels and there is no significant relationship between MCV and ferritin levels. The average values of MCV, MCH and MCHC of CKD patients at PKU Bantul Hospital were in the normal category. The mean ferritin in CKD patients at PKU Bantul Hospital was included in the above category of the ferritin level cut-off to determine absolute iron deficiency anemia.

CONFLICT OF INTEREST

There is no competing interest regarding the manuscript.

ETHICS CONSIDERATION

The research was approved by the Ethics Committee, Faculty of Medicine, Universitas Islam Indonesia, with the letter-number 3/Ka.Kom.Et /70/KE/ VIII/2020.

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AUTHORS CONTRIBUTION

Conceptualization and methodology, LR, NJ, BD, TR; data collection, LR, NJ, BD, TR, US; analysis and writing, LR, NJ, RY; review, LR All authors have read and agreed to publish the manuscript.

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