

Hospital-Acquired Anemia In Chronic Kidney Disease

Mehmet Nur Kaya, Burcu Caner, Ömer Toprak

Abstract: Chronic kidney disease (CKD) has become an important public health problem with the increasing incidence and prevalence of life with increasing life expectancy in developed countries and increasing the life expectancy in our country as well as facilitating access to health services. There was no study on hospital-acquired anemia (HEA) in patients with CKD. The aim of our study was to determine the prevalence of HEA and the factors affecting the development of HEA in patients with chronic renal failure who did not undergo hemodialysis. This study was performed prospectively between March and September 2014 at the Nephrology Clinic, Faculty of Medicine, Balıkesir University. Patients aged between 18- 80 years and 100 without any renal replacement therapy were included in the study. Of the 100 patients included in the study, 48 were female and 52 were male. The mean age in the group was 61.58, the mean age was 62.02 in males and 60.90 in females. Of the patients included in the study, 47 had diabetes mellitus, 73 had hypertension, 18 had atherosclerotic heart disease, 8 had heart failure, 11 patients had hypothyroidism, 2 had hyperthyroidism, 6 had chronic obstructive pulmonary disease, 59 had metabolic syndrome was detected. The patient's hemoglobin level decreased by 0.5 g/dl after the hospitalization was defined as HEA positive, and the reduction of less than 0.5 g/dl was defined as HEA negative. According to our study, hypothyroidism and CKD stage were found to be significantly related to the presence of HEA in the HEA positive group. All 11 patients with hypothyroidism developed HEA. The increase in the number of patients with HEA with an increased CKD stage is evident (for hypothyroidism and CKD stage $p=0.021$). Anticoagulant use and CKD were significantly associated with the presence of HEA ($p=0.025$ for anticoagulant use and $p=0.002$ for CKD). The prevalence of HEA was found to be high in CKD. When we investigated the factors that may affect HEA development in CKD patients, only CKD stage and hypothyroidism were significantly associated with HEA development. Comparison of these results with healthy individuals; To investigate the effect on prognosis, mortality, and morbidity, we think that a large patient series should be studied.

Index Terms: chronic kidney disease, anemia, hospital

1. INTRODUCTION

Hospital-acquired anemia (HAA) is anemia that develops in the absence of apparent blood loss in hospitalized patients. HAA was first recognized by the end of the year 1970, and it was thought that it resulted from diagnostic tests and interventions performed in patients during the hospital stay. Although it has been almost 4 decades since that time and the amount of patient blood either taken for laboratory tests or lost due to interventional procedures has reduced significantly; HAA is still observed in patients. In our country, no studies have been conducted about this clinical condition yet. Various studies conducted abroad report the prevalence of HAA in the range from 40 to 75% [1]. It has been demonstrated that HAA prolongs the duration of hospital stay, and increases several other untoward consequences including medical expenses, the need for transfusions, and the risk of immune reactions and infections, as well as being associated with increased mortality and morbidity in patients. Patients with HAA have been shown to have a poorer health status than patients without HAA in the follow-up period after hospital discharge [2]. Various factors such as risk factors and high-risk patients, along with other factors associated with acquiring HAA have been studied; however, no definite factors have been clearly identified yet except diagnostic phlebotomy. Recognition of HAA will have a positive impact on patients' health status by ensuring the delivery of

sufficient quality of care to prevent HAA and it will reduce medical expenses by eliminating the need to perform irrelevant investigations or interventions.

Chronic Kidney Disease (CKD) has become a major public health issue with increases in life expectancy in developed countries. In our country, along with the increased life expectancy, facilitation of patient access to healthcare services, consequently resulted in HAA to become a significant public health issue with growingly incidence and prevalence rates. There are no studies in the literature about HAA in patients with CKD. The aim of our study was to determine the prevalence of HAA and to determine the factors involved in the development of HAA in patients with CKD, who do not undergo hemodialysis.

2. MATERIAL AND METHODS

The study was carried out prospectively in the period from March to September in 2014 in the Nephrology Clinic of Balıkesir University's School of Medicine Hospital. A total of 100 patients with CKD, who were in the age range from 18 to 80 years and who did not receive renal replacement therapy were included in the study.

The laboratory tests were carried out daily in the blood samples of the patients, which were collected in the

time period from 06.00 to 08.00 am. In these blood samples; complete blood count, and the levels of serum creatinine, urea, sodium, potassium, calcium, phosphorus, alanine aminotransferase (ALT), aspartate aminotransferase (AST), INR (International Normalized Ratio), uric acid, total bilirubin, conjugated bilirubin, albumin, glucose, free T4, and thyroid-stimulating hormone (TSH) were studied. The complete blood count was studied using an LH 750 Beckman Coulter Analyzer. Body mass index (BMI) and waist circumference of the patients were measured and recorded at the time of admission. Cockcroft-Gault formula was used for calculating the glomerular filtration rate (GFR) (Creatinine clearance = $(140 - \text{Age}) \times (\text{body weight}) (\text{ml} / \text{min}) / \text{Serum creatinine} (\text{mg} / \text{dl}) \times 72$). The value derived from this formula was multiplied by 0.85 to calculate the respective values for women. CKD staging of the patients was carried out based on the Kidney Disease Outcomes Quality Initiative (KDOQI) Guideline (Table-1). A diagnosis of HAA was made in the patients, whose hemoglobin values decreased by 0.5 g/dl or more after hospitalization.

Table 1. KDOQI Classification In Chronic Kidney Disease

Category	GFR (ml/min/1.73m ²)	Terms
Normal	≥90	Apply the action plan if there are risk factors for CKD.
1	≥90	Known renal damage with normal or decreased GFR
2	60-89	Kidney damage with a slight decrease in GFR

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3	30–59	Moderately decreased GFR
4	15-29	Severely decreased GFR
5	<15(or dialysis)	Renal Failure

2.1. Exclusion Criteria

The exclusion criteria used in our study were being younger than 18 years old or older than 80 years old; undergoing renal replacement therapy such as hemodialysis, peritoneal dialysis, and renal transplantation; hypervolemia or hypovolemia detected in the physical examination; receiving blood transfusion or intravenous fluid therapy during the hospital stay; no known malignancies; active bleeding, scheduled or performed surgical interventions; being in need for emergency hemodialysis; starting hemodialysis; pregnancy; being in shock, hemolytic anemia, or known hematological malignancies in the patients.

2.2. Statistical Analyses

The statistical analyses were carried out using the SPSS (Statistical Package for the Social Sciences) version 17.0 software. The qualitative measurements were defined as actual numbers and percentages, and the quantitative variables were expressed as mean \pm standard deviation. The χ^2 test was used for comparing the qualitative variables between the groups. The results were considered statistically significant within the 95% confidence interval and at a p-value < 0.05. Patients with a decrease in the hemoglobin levels by 0.5 g/dl or over after the admission to the hospital were categorized as HAA positive. Patients with no reduction in the hemoglobin levels or patients with a decrease in the hemoglobin levels by less than 0.5 g/dl were grouped as HAA negative. A third group included patients with a decrease in the hemoglobin levels by 1 g/dl or over after admission to the hospital.

3. RESULTS

Of the 100 patients included in the study, 48 were

women and 52 were men. The mean age of the study patients was 61.58 years. The mean age was 62.02 years in men and it was 60.90 years in women (Figure 1).

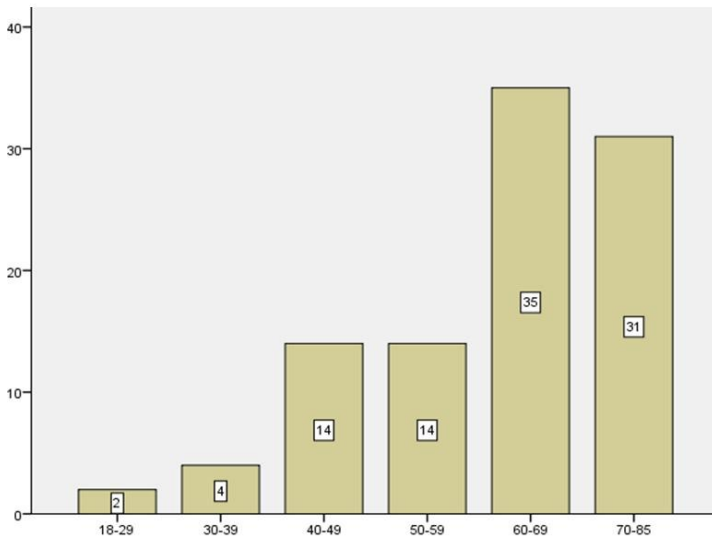


Figure 1. Distribution of patients by age groups

The mean BMI of the patients was 28.40. The mean BMI was 26.57 in men, and it was 30.40 in women. The mean waist circumference was 97.46 cm in men and 101.27 cm in women. Thirteen of the patients were smokers (8 males, 5 females). None of the patients had habitual alcohol use. The distribution of the patients by the CKD classification included 10 patients (2 men, 8 women) in category 1; 16 patients (8 men, 8 women) in category 2; 24 patients (12 men, 12 women) in category 3; 21 patients (12 men, 9 women) in category 4, and 29 patients (18 men, 11 women) in category 5 (Figure 2).

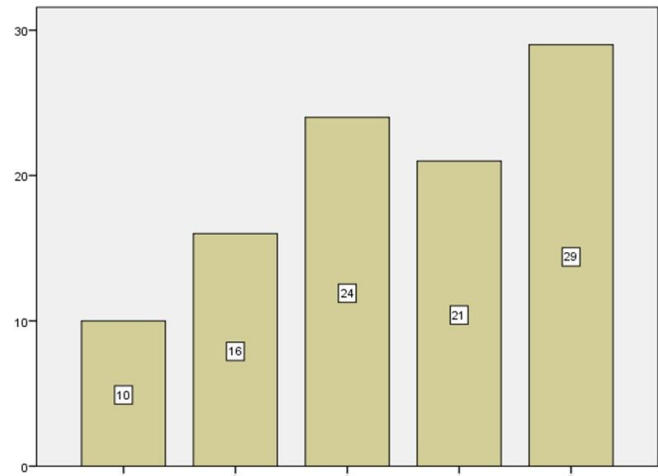


Figure 2. Distribution of patients according to CKD stages

Of the patients included in the study; 47 patients had diabetes mellitus (DM), 73 patients had hypertension, 18 patients had atherosclerotic heart disease, 8 patients had heart failure, 11 patients had hypothyroidism with normal TSH levels, 2 patients had hyperthyroidism, 6 patients had chronic obstructive pulmonary disease, and 59 had metabolic syndrome. Patients with a decrease in the hemoglobin levels by 0.5 g/dl or over after the admission to the hospital were categorized as HAA positive; whereas patients with no reduction in the hemoglobin levels or patients with a decrease in the hemoglobin levels by less than 0.5 g/dl were categorized as HAA negative. A third group included patients with a decrease in the hemoglobin levels by 1 g/dl or over after admission to the hospital.

According to our study results, HAA developed in 70 patients but it did not occur in 30 patients. Of the 70 patients who developed HAA, 36 were male and 34 were female. Reduction in hemoglobin levels by 1 g/dl or over was observed in 50 of 100 patients. Of these 50 patients, 27 were male and 23 were female. The mean BMI was 27.69 in the patients with HAA and 30.08 in the patients without HAA. No significant differences were found between these two groups. The total amount of phlebotomy was 61,40 ml. In contrast to other studies, the amount of blood drawn for phlebotomy was not associated with acquiring HAA ($p=0.203$). In our study, the mean length of hospital

stay was 4.66 days. There was no association between the length of hospital stay and acquiring HAA ($p=0.180$). The mean hemoglobin value of the patients at admission was 11.6 g/dl and the mean hemoglobin value at discharge was 11.00 g/dl.

Our study found a significant association of hypothyroidism and the category of CKD with the presence of HAA in the HAA positive group. All 11 patients with hypothyroidism developed HAA. The increase in the number of patients acquiring HAA with advanced categories of CKD is evident (hypothyroidism and CKD category= 0.021) (Figure 3).

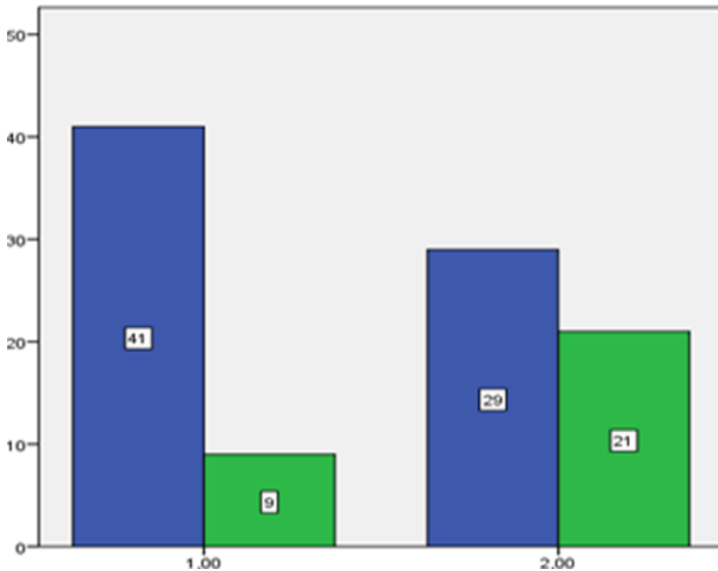


Figure 3. Blue column shows a decrease in hemoglobin levels and green column increases in hemoglobin levels in the distribution of patients who develop HEA according to CKD stages

When the patients were divided into two groups based on the CKD categories as the patients in the categories 4 and 5 in one group and the patients in categories 1, 2, 3 in the other, acquiring HAA was significantly higher in the group having a GFR of <30 ml/min ($p=0.009$) (Figure 4).

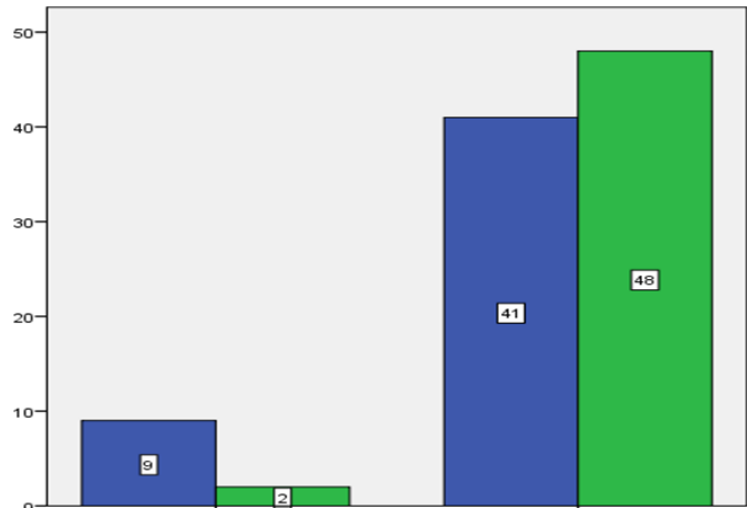


Figure 4. Hemoglobin >1 g/dl decrease in the distribution of patients according to the use of anticoagulant blue column hemoglobin levels decrease, green column hemoglobin levels increase is shown

Anticoagulant use and CKD category were significantly associated with the presence of HAA in patients with reduced hemoglobin levels by 1 g/dl or over after admission to the hospital. Patients using anticoagulants were excluded from the study if their INR levels were higher than the levels in the targeted range. None of the patients using anticoagulant or antiaggregant medications had major bleeding in the gastrointestinal or urinary tract. However, a high INR value may be associated with a hidden loss from the gastrointestinal tract (GIS). ($p = 0.025$ for anticoagulant use; $p=0.002$ for the CKD category) (Figure 5).

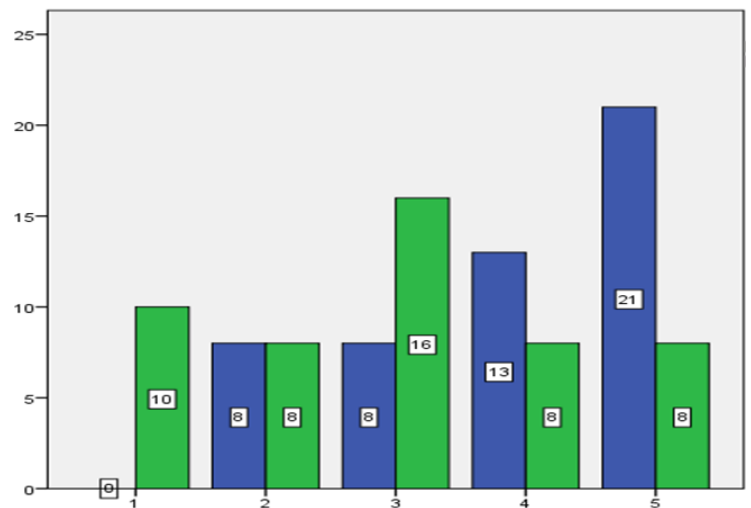


Figure 5. Hemoglobin >1g/dl decline in the

distribution of patients according to CRF stages of blue column hemoglobin levels decrease, green column hemoglobin levels increase is shown

4. DISCUSSION

As far as we know, there are no studies about HAA in the CKD patients not receiving renal replacement therapy. In our study, we found that acquiring HAA was significantly associated with the CKD category and hypothyroidism. In our study, the effect of posture on hemodilution and hemoglobin levels determined the presence of HAA due to variations in hemoglobin levels. Therefore, we did not accept any variations significant, in which the hemoglobin levels reduced by 0.5 g/dl. The posture during phlebotomy was also found to affect laboratory test results even though it was negligible. After the patients sat on a chair for 15 minutes, a 3% increase in the hemoglobin levels was observed in the blood samples, compared to the hemoglobin levels in the blood samples of the same patients staying in a horizontal position during the night. This effect disappeared after the patients remained in the supine position for an hour [3]. In another publication, a 9% decrease in hematocrit was reported in a patient in the supine position, who had nephrotic syndrome and edema [4]. There is a possibility that this condition might have contributed to the initial decrease in the complete blood count parameters on the first day after hospital admission.

Accepting reduction in the hemoglobin levels by 0.5 g/dl significant after hospital admission, we found the frequency of HAA as 70% in individuals with CKD. This rate is slightly higher than the rates of HAA acquisition found in previous studies. Wong et al. followed up 98 patients and found that 64 patients (65.3%) developed HAA [5]. In 1973, Elaine Eyster et al. followed up 93 patients, observing that hematocrit levels decreased by 5.7% in 75 patients without any findings of hemorrhage. They also observed that 26 patients (40%) out of 64 without anemia at admission developed anemia with no apparent causes. Salisbury et al. followed up 17676 patients with normal

hemoglobin levels at admission, who were hospitalized with acute myocardial infarction. They observed that 57.5% of the patients acquired HAA [6]. The largest study about this subject was the study carried out in 2013 at Cleveland Clinic on 188447 patients. When the results of 188447 patients were examined, it was reported that HAA developed in 139807 patients (74%). However, this study was performed based on electronically recorded data and the patient selection was not meticulous [7].

Anemia is common in CKD due to several factors including erythropoietin deficiency, short survival of erythrocytes, circulating erythropoiesis inhibitors, iron and vitamin deficiencies, and bleeding. These patients carry risks to develop anemia. However, there are no studies available about HAA in CKD patients. In this study, we determined that HAA development in CKD patients occurred at a higher rate compared to other patient groups. As the CKD category advances, the risk of acquiring HAA increases, too.

Examination of the patients with HAA revealed the involvement of hypothyroidism and the CKD category in acquiring HAA. All 11 patients with hypothyroidism in the study were diagnosed with HAA. Untreated hypothyroidism is associated with mild macrocytic anemia and rarely hemolysis due to bone marrow suppression. However, in patients with normal TSH levels, the acquisition of HAA may be due to the current CKD. Of the 11 patients with hypothyroidism; 1 patient was in category 1, 2 in category 2, 3 in category 3, 1 in category 4, and 4 in category 5 based on CKD classification. A further study to be conducted on a higher number of patients will be more guiding.

The length of hospital stay and the phlebotomy volume were associated with the development of HAA in the previous studies about HAA. Thavendiranathan et al. found that phlebotomy performed for diagnostic tests was associated with the development of HAA. In their study on the patients hospitalized in the general internal medicine clinic, they found the mean changes

in hemoglobin and hematocrit levels as 7.9 g/L and 2.1% respectively in the period from hospital admission to discharge. They reported that every 1 ml of blood taken for phlebotomy resulted in a mean decrease by 0.07 g/L in the hemoglobin levels and by 0.019% in hematocrit levels [8]. Salisbury et al. reported that every 50 ml of phlebotomy volume increased the risk of developing moderate and severe HAA by 18% [9]. Chant et al. demonstrated in their study that a daily increase of 3.5 ml in the phlebotomy volume doubled the likelihood of receiving a blood transfusion at the end of a period of 21 days. Weisbach et al. demonstrated in their study that a healthy person can tolerate a phlebotomy amount of 10 ml per day [10]. We did not detect this relationship in our study. The shortest duration of hospitalization was 2 days and the longest was 11 days in our study. The effect of the length of hospital stay on acquiring HAA might be apparent in the longer term. The mean amount of phlebotomy was 61.40 ml (minimum 31 ml, maximum 116 ml) in our study. The volume of phlebotomy was not found to be associated with acquiring HAA in CKD patients. When the patients with a decrease of 1 g/dl and over in hemoglobin levels were examined, the category of CKD and using anticoagulants were found to be associated with developing HAA. None of the patients using anticoagulant or antiaggregant medications had major bleeding in the gastrointestinal or urinary tract. However, a high INR level may be associated with occult bleeding in GIS.

Our study had some limitations. We should note that the number of patients in our study was low because we included inpatients in the nephrology service, who did not receive renal replacement treatment and who did not have hypervolemia. In addition, we suggest that the results might have been affected by significant phenotypic and genotypic differences of the patients and this is a point not to be overlooked.

In conclusion, we found that the incidence of HAA was high in CKD. When we investigated the potentially involved factors in acquiring HAA in CKD patients, we observed that only the CKD category and the hypothyroidism were significantly associated with

developing HAA. We are of the opinion that the results of this study should be further investigated for prognosis, mortality, and morbidity in large patient series, comparing the results with those obtained from healthy individuals.

5. REFERENCES

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