JMU
Jurnal Medika Udayana

ISSN: 2597-8012 JURNAL MEDIKA UDAYANA, VOL. 14 NO.10, OKTOBER, 2025

Received: 2025-05-12 Revision: 2025-07-08 Accepted: 30-08-2025

CHARACTERISTICS OF ANEMIA IN PREDIALYSIS CHRONIC KIDNEY DISEASE PATIENTS AT PROF. DR. I.G.N.G. NGOERAH IN 2022

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ABSTRACT

Background: Anemia is a common complication in patients with chronic kidney disease (CKD), especially in the predialysis stage. It mainly occurs due to insufficient erythropoietin production as a result of kidney damage. Anemia worsens with increasing severity of CKD and contributes to reduced oxygen delivery to tissues, decreased quality of life, and increased morbidity and mortality. Determining the characteristics of anemia in predialysis CKD is essential to guide proper management. **Methods:**This study is a descriptive observational design using a total sampling method involving 90 patients with predialysis CKD at Prof. Dr. I.G.N.G. Ngoerah Hospital in 2022. Inclusion criteria included complete medical records with confirmed diagnosis of CKD and documented anemia without undergoing hemodialysis. Data were obtained retrospectively from the hospital information system and included patient demographics, CKD stage, hemoglobin levels, and erythrocyte indices (MCV, MCHC). **Results:**Among 90 patients, 52.2% were male and 48.9% were aged 46–65 years. The most common CKD stage was stage 3 (28.9%). The most frequent anemia severity was mild anemia (67.8%) based on hemoglobin levels. Regarding erythrocyte morphology, normochromic normocytic anemia was the most prevalent, found in 71.1% of the cases. A smaller proportion had microcytic hypochromic anemia (23.3%) and macrocytic normochromic anemia (5.6%). **Conclusion:**The majority of anemia in predialysis chronic kidney disease patients at Prof. Dr. I.G.N.G. Ngoerah Hospital in 2022 was found to be of mild severity with normocytic normochromic morphology. These findings highlight the need for early screening and classification of anemia in CKD patients to optimize treatment.

Keywords: *Chronic Kidney Disease, Anemia, Predialysis*

INTRODUCTION

Chronic Kidney Disease (CKD) is a condition characterized by a progressive decline in kidney function and structural abnormalities with or without a decrease in the glomerular filtration rate (GFR) with various etiologies. CKD can cause kidney damage that can last for more than 3 months. This occurs as a result of toxins that should be excreted not being properly excreted due to kidney impairment, resulting in a disruption of fluid, electrolyte, and acid-base balance due to accumulated metabolic waste[1]

Currently, CKD cases, especially in developing countries, are experiencing a very significant increase. CKD has become a worldwide health problem, apart from being a risk factor for heart and blood vessel disease. CKD also increases the social and economic burden for families of patients[2]. In America, it is estimated that around 35,5 million people, or 14% are estimated to suffer from CKD and as many as 9 out of 10 adults with CKD do not know that they have it[3]**.** Meanwhile, in China between 1990 and 2019, the prevalence of CKD was found to have increased significantly from 6,7% to 10,6%[(4)]. The high prevalence of CKD also occurs in Indonesia.

In Indonesia, based on data from doctors' diagnoses in residents aged ≥ 15 years RISKESDAS (Basic Health Research) in 2018, , the prevalence of CKD cases is 0,38% of the population in Indonesia, and only 0.19% of chronic kidney failure patients who undergo dialysis therapy. The prevalence of CKD was found to increase with age, with the highest increase seen in the 65-74 year age group (0,82%), while for those aged over 74 years it was 0,74%. The prevalence of CKD is lower in females (35,2%) compare to males (41,7%)[5].

In several studies, it is stated that CKD can cause several complications. A frequent complication of CKD is anemia, especially in end-stage CKD patients. Management of CKD focuses on treating underlying causes CKD as well as option such as dialysis or kidney transplantation if it is in the final stage. Therefore, it is necessary to manage the anemia that occurs in CKD. Anemia in CKD is usually caused by erythropoietin deficiency, but can also be caused by iron deficiency, acute and chronic inflammation, and blood loss[6]. Where 80%-90% of

anemia is caused by erythropoietin deficiency. Arround 90% of the erythropoietin hormone is formed in the kidneys, with the stimulus of oxygen pressure (O2) in the kidney tissue which is used to stimulate erythropoiesis. If the oxygen pressure is low in the kidneys, the formation of erythropoietin as a hormone that stimulates erythropoiesis will be hampered, thereby reducing the number of red blood cells formed and causing anemia. This anemia condition can cause a decrease in the blood's ability to carry sufficient oxygen to peripheral tissues. Apart from that, anemia also occurs due to a decrease in Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC).[6] A person is said to be anemic if Hemoglobin (Hb) in men Hb <13 g/dl and Hb <12 in women[7].

The prevalence and severity of anemia in CKD will increase along with the increase in the severity and stage of CKD[8]. Research conducted in the Bali region, specifically at Sanglah General Hospital, based on hemoglobin levels obtained from 54 patients, found that 96,3% or around 52 patients were had cases of anemia, of which 13,46% had mild anemia, 51,92% had moderate anemia, and 34,62% had severe anemia. In addition, the percentage of CKD patient who experienced anemia was higher in males than in females[9].

Another research study on CKD cases with anemia found that out of 81 cases, 50.6% showed normocytic normochromic, 39,5% showed macrocytic normochromic and 9,9% showed microcytic hypochromic[10]. It is necessary to know the type of anemia based on erythrocyte morphology to evaluate anemia and determine appropriate therapy to reduce morbidity and mortality rates, thus improving the quality of life of CKD patients. Based on the background mentioned above, the purpose of this study is to determine the characteristics of anemia in predialysis chronic kidney disease patients at Prof. Dr. I.G.N.G. Ngoerah Hospital in 2022.

Anemia in Chronic Kidney Disease

Functional anemia is a decrease in the number of red cell masses, resulting in a decrease in the oxygen carried by peripheral tissues[11]. Low hemoglobin levels in the blood are a sign of anemia, due to too few red blood cells, which result in anemia[1]. Anemia occurs in 80-90% of patients with chronic kidney disease and is a frequent complication[12]. Research conducted in China showed that 51,5% of patients with chronic kidney disease grades 1-5 experienced anemia[13].

Etiology Anemia in Chronic Kidney Disease

Erythropoietic Stimulating Factors (ESF) deficiency is the main cause of anemia in chronic kidney disease. Erythropoietin, which stimulates erythroid precursors to undergo proliferation, differentiation, and maturation, can influence erythrocyte production. Reduced renal parenchymal function will reduce erythropoietin production by peritubular cells, resulting in anemia. Erythropoietin will increase to 26,100 times if the hematocrit is less than 20%. In patients with chronic kidney disease, the renal peritubular response that produces erythropoietin will be disrupted, resulting in erythropoietin deficiency and anemia[6].

Pathophysiology of Anemia in Chronic Kidney Disease

Erythropoietin deficiency is the main cause of anemia in chronic kidney disease, which can increase the risk of death. Proinflammatory cytokines, which are erythropoietin antagonists work by inhibiting erythroid progenitor cells and inhibiting iron metabolism. Around 90% of the erythropoietin hormone is produced by progenitor cells, which stimulate the production of red blood cells. A reduction in nephron mass in chronic kidney disease will result in decreased erythropoietin production. Apart from that, the development of anemia in chronic kidney disease is also influenced by several factors such as iron deficiency, blood loss, and hemodialysis, which also influence the development of anemia in patients with chronic kidney disease[14].

Erythropoietin is a glycoprotein hormone that stimulates the production of red blood cells by binding to the homodimer Erythropoietin Stimulating Agent (ESA) receptor, which consists of a 165 amino acid buffer protein and 4 complexes. This homodimer ESA receptor is generally located on early erythroid progenitor cells, Burst Forming Units-erythroid (BFU-e), and Colony Forming Units-erythroid (CFU-e). In the pathogenesis of anemia in chronic kidney disease, inhibited red blood cell production due to decreased uremic erythropoiesis may contribute, but there has not been a clear identification of this[15].

Management of Anemia in Chronic Kidney Disease

Anemic patients with chronic kidney disease will receive ESA therapy, to increase erythropoiesis. Folic acid is also given to chronic kidney disease patients with anemia to increase folic acid levels in the body. In addition, cell transfusions or Packed Red Cells (PRC) can also be given to Hb patients with chronic kidney disease who have low Hb Levels. If Hb patients with chronic kidney disease fall too low, they can receive cell transfusions or PRC[16].

In patients with non-dialysis chronic kidney disease and pre-dialysis chronic kidney disease with iron deficiency anemia, oral iron therapy can be given. If ST is less than 20% after three months of oral administration then parenteral iron therapy can be performed. Patients with chronic kidney disease on hemodialysis will usually be given parenteral iron therapy. There are two phases in iron therapy, namely the correction phase and the maintenance phase. The correction phase aims to correct the iron status in iron deficiency anemia until the iron status is sufficient. Before starting intravenous iron therapy, a dosing trial is carried out to determine if there is iron hypersensitivity. In the correction phase, the dose of iron therapy given is 100 mg 2x per week, and during hemodialysis the total dose requirement is 1000 mg with 10x administration. The next maintenance phase aims to maintain sufficient iron levels for the erythropoiesis process during ESA therapy. Iron status is checked every 1-3 months, and iron therapy doses are given based on ST and FS levels. If ST is greater than 50%, then ESA therapy is continued. If ST is between 20-50%, then ESA therapy is continued[17].

ESA therapy is started if Hb is less than 10 g/dl and factors that aggravate anemia have been excluded. Iron status should be adequate and there should be no iron deficiency anemia or severe infections. ESA therapy should be considered, especially when reducing the need for transfusions and correcting anemia with a high risk of stroke, vascular access thrombosis, and hypertension. Contraindications for ESA therapy are hypersensitivity to ESA and caution should be taken with high blood pressure and hypercoagulation, as it can cause increase blood pressure if Hb rises quickly or the ESA dose is high[17].

MATERIALS AND METHODS

This research is of the descriptive observational type, using the total sampling method. The total sampling technique involves selecting a sample that includes all the individuals in the population who meet the inclusion and exclusion criteria. Ethical compliance No:371/UN14.2.2.VII.14/LT/2023 is followed. The inclusion criteria for this study are patients who have complete medical records, a diagnosis of chronic kidney disease without hemodialysis and recorded anemia at RSUP Prof. Dr. I.G.N.G Ngoerah in 2022. The data required for this research include patient name, medical record number, age, gender, degree of CKD, hemoglobin level, degree of anemia, MCV, and MCHC values. Patient data were identified through medical records using hospital information systems. Patients were filtered according to inclusion criteria: diagnosis of CKD, no hemodialysis, and documented anemia. Data were collected retrospectively by trained reviewers.

RESULT

In this study, the number of samples that met the inclusion criteria was 90 cases. According to the inclusion criteria used, the sample for this study consisted of patients who had complete medical records and a diagnosis of chronic kidney disease without hemodialysis and anemia recorded at RSUP Prof. Dr. I.G.N.G Ngoerah 2022.

Table 1. Frequency distribution based on the age of predialysis chronic kidney disease patients with anemia

Age range (Year)	Mean 55,69 18±85 (± SD 15,1)	
	Frequency (n=90)	Percentage (%)
18-25	5	5,6
26-45	16	17,8
46-65	44	48,9
>65	25	27,8

Table 1 shows the frequency distribution of general characteristics of CKD patients with anemia who did not undergo hemodialysis at the nephrology clinic at Prof. Hospital. Dr. I.G.N.G Ngoerah in 2022. Out off the total 90 cases, the age group with the highest frequency is the 46-65 year age range, which has 44 cases (48,9%), followed by the >65 year age range with 25 cases (27,8%), the 26-45 years age range with 16 cases (17,8%), and the lowest number of cases is in the 18-25 years age range, with 5 cases (5,6%). The average age of patients suffering from chronic kidney disease was 55,69 years (±SD 15.1) with the youngest being 18 years and the oldest being 85 years.

Table 2. Frequency distribution based on the gender of predialysis chronic kidney disease patients with anemia

Gender	Frequency (n= 90)	Percentage (%)
Male	47	52,2
Female	43	47,8

The next general characteristic is gender. It can be seen in Table 2 that there were 47 cases (52,2%) of male gender in CKD patients with anemia without hemodialysis, and 43 cases (47,8%) of female gender. Based on the data above, there are more male than female CKD patients with anemia without hemodialysis.

Table 3. Frequency distribution based on the degree of CKD in predialysis chronic kidney disease with anemia

Degree of CKD	Frequency (n= 90)	Percentage (%)
Stage 1	7	7,8
Stage 2	16	17,8
Stage 3	26	28,9
Stage 4	23	25,6
Stage 5	18	20

Table 3 shows the frequency distribution of CKD stages with anemia in predialysis CKD patients at the nephrology polyclinic at Prof. Hospital. Dr. I.G.N.G Ngoerah in 2022. Based on the data obtained, out of the 90 cases of CKD, the most cases were at stage 3 with 26 cases (28,9%), followed by stage 4 with 23 cases (25,6%), stage 5 with 18 cases (20%), stage 2 with 6 cases (17,8%), and the lowest was stage 1 with 7 cases (7,8%).

Table 4. Frequency distribution based on the degree of anemia in predialysis chronic kidney disease patients with anemia

Degree of Anemia	Frequency (n= 90)	Percentage (%)
Mild	61	67.8
Moderate	23	25.6
Severe	6	6.7

Table 4 displays the frequency distribution based on the degree of anemia in predialysis CKD patients at the nephrology clinic at Prof. Hospital. Dr. I.G.N.G Ngoerah in 2022. In this study, hemoglobin levels were used to determine the degree of anemia with the following range of values: Hb 8-10 mg/dl for mild degree, Hb 6-8 mg/dl for moderate degree, Hb <6 mg/dl for severe degree. From the data obtained, it can be seen that the degree of anemia with the highest frequency is mild with 61 cases (67,8%), followed by moderate with 23 cases (25,6%), and the lowest is severe with 6 cases (6,7%).

Table 5. Frequency distribution based on erythrocyte morphology in predialysis chronic kidney disease patients with anemia

Erythrocyte Morphology	Frequency (n=90)	Percentage (%)
Normochromic normocytic	64	71,1
Hypochromic microcytes	21	23,3
Macrocytic normochromic	5	5,6

The data in Table 5 shows the frequency distribution of the anemia erythrocyte morphology in predialysis CKD at Prof. Hospital. DR. I.G.N.G Ngoerah in 2022. It was found that the highest frequency of erythrocyte morphology was normocytic normochromic, with 64 cases (71,1%), followed by microcytic hypochromic, with 21 cases (23,3%), and macrocytic normochromic, with 5 cases (5,6%).

DISCUSSION

In this study, the number of samples that met the inclusion criteria was 90 cases. According to the inclusion criteria used, the sample for this study consisted of patients who had complete medical records and a diagnosis of predialysis chronic kidney disease and anemia recorded at RSUP Prof. DR.I.G.N.G Ngoerah 2022.Based on Table 1, it can be seen that the age group with the highest frequency is the elderly with an age range of 46-65 years where there are 44 cases (48,9%). According to data on the prevalence of chronic kidney disease from Riskesdas RI in 2018, it was found that CKD cases increased with increasing age. The increase in age is quite significant when entering >34 years of age[5]. Similar to the research conducted by Sanjaya et al. where the highest frequency of cases was found in the age range of 46-65 years[9]. This happens because in the aging process, GFR decreases and the risk of developing comorbid diseases increases. A decrease in GFR will result in fewer functioning neurons, including the production erythropoietin which causes anemia[18]. The presence of physical or biological deterioration caused by predisposing factors also means that the elderly category has more cases of CKD. Predisposing factors can be biological disorders in the central nervous system that cause disturbances in body function, one of which is kidney function which will result in CKD[19].

In Table 2, it can also be seen that the frequency of males is 47 cases (52,2%) higher than females with 43 cases (47,8%). Prevalence data from Riskesdas can be used as a reference regarding the results of this study, where CKD patients with anemia without hemodialysis obtained data on the higher frequency of males compared to females[5]. Previous research conducted by Sanjaya et al. found that men (59,3%) had a higher number of cases than women (40,7%)[9].

There is no definite mechanism for explaining the influence of gender on the progression of CKD, whether there is a relationship or not. However, several theories suggest that male are more at risk of developing CKD. Research theorizes that estrogen is a protective agent for CKD, preventing apoptosis due to estrogen receptors in female podocytes. This makes the risk of CKD lower for female compared to men, who have testosterone that triggers apoptosis[18]. Ipo et al. conducted research that more male experience CKD than female due to poor lifestyles and quality of life. Lifestyles such as smoking, consuming alcohol, coffee and drinking supplements can trigger systemic diseases that impact kidney function damage[20].

CKD patients often experience anemia, with the prevalence and severity increasing as the severity as the disease progresses. According to a study conducted by Adera et al. in 162 cases, the prevalence of anemia in CKD was found to increase with the severity of the disease. For stage I, there were 2 cases, and this number increased to 61 cases for stage V[21]. However, the results of this study presented in Table 3 show a different pattern. The lowest frequency was found in stage 1 with 7 cases (7,8%), followed by stage 2 with 16 cases (17,8%), stage 5 with 18 cases (20%), stage 4 with 23 cases (25,6%), and the highest was in stage 3 with 26 cases (28,9%). This discrepancy may be because the study sample consisted of CKD patients who had not undergone hemodialysis. Routine hemodialysis therapy is typically given to stage V CKD or chronic renal failure patients. It serves to replace the kidney function in maintaining electrolyte balance and removing metabolic waste from the body[8]. These results are similar to research conducted by Alemu et al. At Addis Ababa Hospital, it was found that the highest frequency of CKD with anemia was stage III at 45,2%, followed by stage IV at 24,5% and stage V at 14,2% compared to stage I[22]. Research related to the prevalence of anemia in predialysis CKD was conducted by Alagoz et al. in Turkey, stage 3 results also had the highest frequency, namely 694 cases (65,1%)[23].

Table 4 displays the frequency distribution of degrees of anemia in predialysis CKD patients at Prof. Hospital. Dr. I.G.N.G Ngoerah in 2022. In this study, the highest frequency was found, namely in the mild degree with a Hb range of 8-10 g/dl as many as 61 cases (67,8%). These results are similar to research conducted by Maulidya et al, from 100 cases of CKD with anemia without hemodialysis, it was found that hemoglobin levels of 7,0-9,8 g/dl or mild grade had the highest frequency in chronic kidney failure patients at Ulin Regional Hospital, Banjarmasin[24].

Anemia can occur in CKD patients before hemodialysis because the kidneys experience a decrease in work to 20-50% of normal kidney function, as a result, there will be a decrease in fluid and sodium excretion, and this decrease in fluid amount will cause dilution, resulting in low hemoglobin. The function of the kidneys is to regulate the amount of fluid in the body, filter toxins, balance acids and bases, produce the hormones erythropoietin and renin, and activate vitamin D. If the kidneys begin to lose their function, the accumulation of fluid and toxins in the body will damage the kidneys[19]. When kidney damage begins to occur, erythropoietin (EPO) production will become deficient. Erythropoietin is a hormone that stimulates the bone marrow to produce red blood cells. Erythropoietin deficiency causes the production of fewer red blood cells, leading to anemia[15]. The degree of anemia is also related to the degree of kidney damage, so the more damaged the kidney function, the lower the hemoglobin, and the anemia will tend to get worse[25].

The main cause of anemia is disruption of red blood cell production due to erythropoietin deficiency by the kidneys, one of which is uremia poison. Uremia toxins can suppress the bone marrow response to erythropoietin. Every 10 mmol/L increase in

urea in the blood can reduce hemoglobin by 2 g/dL. Another factor contributing to anemia is the shortened lifespan of erythrocytes, which is half that of normal erythrocytes. Abnormalities in the blood plasma environment will increase erythrocyte hemolysis, resulting in anemia[26].

Based on Table 5, it can be seen that the highest frequency of erythrocyte morphology is normocytic normochromic with 64 cases (71,1%). In line with the results of research at Ulin Regional Hospital, Banjarmasin regarding the types of anemia in chronic kidney failure by Maulidya et al. It was found that the highest frequency of anemia type based on the MCH value was normochromic anemia at 70%[(24)]. Normochromic anemia is anemia with normal colored erythrocytes in the cells. Chronic kidney failure does not cause bleeding so the erythrocyte coloring substance (Fe or iron) is still present in the body, which will cause the color to remain red or what is called normochromic anemia[27].

Normocytic normochromic anemia is characterized by normal MCV and MCHC values but the patient still experiences anemia. This type of anemia occurs due to uremia syndrome in CKD patients. Uremia syndrome can inhibit erythropoietin and the proliferation of erythroid precursor cells in producing red blood cells. In normochromic normocytic anemia, erythropoietin production will be deficient but there will be no iron deficiency This causes the size, shape, and color of erythrocytes to remain normal[28].

From the research results in Table 5, it was also found that 21% of CKD patients had anemia with microcytic hypochromic erythrocyte morphology. Microcytic hypochromic anemia is characterized by a decrease in MCV and MCHC due to iron deficiency in CKD patients[27]. If the amount of iron bound to protoporphyrin is small, cell division will occur during several additional cycles and the erythrocyte cells will become smaller. Failure of iron to reach erythroblasts due to lack of iron will cause erythrocytes to contain less hemoglobin or be called hypochromic[29].

Iron deficiency in CKD patients is usually found in patients undergoing hemodialysis. During the hemodialysis process, the body will lose 3-5 grams of iron per year, or about 10-20 times more than normal people[30].

In Table 5, it can be seen that the lowest frequency of erythrocyte morphology in predialysis CKD patients is normochromic macrocytic morphology at 5,6%. Macrocytic normochromic anemia occurs due to impaired cell maturation due to deficiency of folic acid and vitamin B12 resulting in a decrease in DNA synthesis which causes cell size to become larger[29]. This type of anemia is more common in CKD patients who have undergone hemodialysis because, during the hemodialysis process, the patient will lose folic acid and vitamin B12 through the dialysis membrane[31].

CONCLUSIONS AND SUGGESTIONS

Based on the results of research on the characteristics of anemia in predialysis chronic kidney disease at RSUP Prof. Dr. I.G.N.G.Ngoerah in 2022, 90 cases met the inclusion and exclusion criteria.

The frequency distribution based on age group was found to be highest in the elderly group with an age range of 46-65 years (48,9%), and the frequency distribution based on gender found that men (52,2%) had more cases than women (47,8%).

The distribution based on the degree of chronic kidney disease was mostly stage 3 (28,9%), and the frequency distribution based on the degree of anemia found that mild anemia had the greatest frequency of 25 cases (67,8%).

Frequency distribution based on erythrocyte morphology found that the erythrocyte morphology that had the highest frequency was normocytic normochromic (71,1%).

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