OPEN ACCESS

Nutritional Status Associated to Red Cell Distribution Width, Length of Stay, and Clinical Outcome patient with Chronic Kidney Diseases

Layle Rahmiyanti[1] , Haerani Rasyid[1,2] , Nurpudji Astuti Taslim[1,2]* , Suryani As'ad[1,2] , Agussalim Bukhari[1,2] , Aminuddin Aminuddin[1,2]

[1]Department of Nutrition, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia; [2]Wahidin Sudirohusodo Regional Hospital, Makassar, Indonesia

Abstract

INTRODUCTION: Red cell distribution width (RDW) shows the heterogeneity of erythrocyte size associated with inflammation and various clinical conditions including in patients with chronic kidney disease (CKD). Systemic inflammation and oxidative stress were commonly found in CKD patients.

AIM: This study aimed to examine the relationship of nutritional status, length of hospital stay (LOS), and clinical outcome to RDW in CKD patients.

METHODS: We conducted a retrospective cohort study of 1736 patients CKD patients who admitted from January 2017 to August 2020, aged between 18 and 60 years and were hospitalized at Wahidin General Hospital. From those, 239 were consulted with clinical nutrition specialist, of which 59 patients eligible with the criteria inclusion. Data were collected through medical records and through electronic data (biochemical data). RDW was categorized into normal and high RDW group, nutritional status based on subjective global assessment (SGA), LOS <10 days and clinical outcome based on conditions at the time of hospital discharged. Data were analyzed using SPSS version 25.0.

RESULTS: The data of 59 patients were analyzed, the mean age was 50.42 years (normal RDW) and 47.24 years (high RDW), most of them are women (57.7% vs. 60.6%). There were 42 patients with moderate malnutrition (23 normal RDW and 19 high RDW) and 17 patients with severe malnutrition (3 normal RDW and 14 with high RDW). The study found a significant differences between normal RDW and high RDW (p 0.021), but not significant differences in LOS (p 0.890) and clinical outcome (p 0.968). There were a significant differences in the levels of hemoglobin (p = 0.001), RBG (p = 0.030), and serum sodium level (p = 0.010). Patient with LOS < 10 days had lower sodium levels and more severe anemia when compared with LOS > 10 days and the poor clinical outcome had a heavier degree of anemia compared to the good clinical outcomes.

CONCLUSION: Poor nutritional status was associated with an increase in RDW, degree of anemia, and sodium level.

Introduction

Chronic kidney disease (CKD) is "a general term for a heterogeneous disorder affecting the structure and function of the kidneys with varying clinical presentations, relating to its cause, severity, and rate of progression" [1]. According to the Global Burden of Diseases study, 2016, globally, CKD affects 753 million people, of which 417 million women and 336 million men [2]. In 2017, 1.2 million peoples died from CKD. The CKD mortality rate for all ages increased by 41.5% between 1990 and 2017 [3]. While national data according to the Basic Research Indonesia data (RISKESDAS) 2018, the prevalence of CKD age ≥ 15 years (based on doctor's diagnosis) has increased from 2.0 to 3.8 per mile, meanwhile Sulawesi Selatan ranks in the 19th largest province with the highest prevalence nationally, although the percentage is still below the national average, there was an increase from year to year [4].

CKD patients commonly experience a chronic systemic inflammatory state associated with various underlying factors, such as a higher incidence of infection, uremic environment, presence of extensive arteriosclerosis, and increased levels of proinflammatory cytokines. The results of animal studies in which kidney function was eliminated suggest that the half-lives of serum proinflammatory cytokines, including tumor necrosis factor (TNF-α) and interleukin-1 (IL-1), will be higher. Furthermore, decreased renal function may also affect other inflammatory markers, such as serum C-reactive protein (CRP) and IL-6, which their concentrations were inversely correlating with creatinine clearance [5]. Persistent inflammatory conditions in chronic disease patients using six types of inflammatory markers (leukocytes, CRP, IL-6, IL-8, fibrinogen, and TNF α) showed that there were significant results where inflammatory conditions declined clinically outcome, on exacerbation and mortality rate [6]. Another study related to inflammatory conditions (assessed using CRP and serum albumin ratio) associated with LOS

in hospital showed a significantly positive correlation (r=0.593 and p < 0.001) [7]. Inflammatory conditions and oxidative stress are also often associated as one of the causes of protein-energy wasting (PEW) in CKD patients, the other hand from food restrictions (sodium, potassium, phosphor, and fluids), anorexia, and nutrient loss due to hemodialysis (HD) or peritoneal dialysis (PD) [8]. "Protein-energy wasting is a deficit of energy and/or protein, as well as a deficiency of multivitamins and minerals". In general, malnutrition often occurs in hospitalized patients, possibly related to the heterogeneity of erythrocytes due to nutritional deficiencies (e.g., iron depletion, vitamin B12, or folic acid) which is important in the erythropoiesis [9], [10], [11].

Apart from using markers such as CRP, IL-1, IL-6, IL-8, and TNF α, the inflammatory environment and oxidative stress can also be measured with simple and routine laboratory parameters in daily clinical practice such as red cell distribution (RDW) [7], [8], [9]. Red cell distribution width is still rarely exploited for diagnostic and prognostic purposes during treatment [12]. Red cell distribution width (RDW) is a quantitative marker that measures the heterogeneity of the size of the circulating erythrocytes. The RDW is reported automatically in a complete blood count and obtained by split the erythrocyte standard deviation (SD-RBC) and mean corpuscular volume (MCV) [13]. There are currently many data reporting that increased RDW is associated as a marker of malnutrition and inflammation [14], [15], [16], [17] in various acute and chronic diseases including CKD patients [13], [15], [16], [18].

The mechanism increases of RDW in CKD patients are related to clinical outcomes in term nutritional status, LOS, and mortality that are not known with certainty, but are associated with proinflammatory conditions and oxidative stress. Due to limiting data regarding this in CKD patients in Makassar, we conducted a study to examine the relationship between RDW levels and nutritional status, LOS, and clinical outcome in CKD patients.

Materials and Methods

The study is a retrospective analysis of 1736 patients who were admitted between January 2017 and August 2020 and were hospitalized at Wahidin General Hospital aged 18−60 years, of which 239 CKD patients have been treated together with the clinical nutrition physician, from those patients, only 59 patients have completed data and met the criteria. The exclusion criteria: If within 2 weeks before admission received a blood transfusion, there was active bleeding or severe infection (sepsis) on admission, there was a blood disorder or had just undergone a major surgical procedure, readmissions during the study period, pregnancy and delivered, documents, or data were not found/complete. General characteristics data were collected through medical records and biochemical data were collected through SIRS.

The etiology of CKD in our study was as follows: HT (n = 48), DM (n = 15), malignancy (n = 12), chronic pyelonephritis (n = 16), urinary tract stones (n = 6), and other (n = 15). We grouped the 59 patients into two groups according to the RDW ≤14.5% and RDW >14.5% categories. Nutritional status was based on SGA, LOS ≤10 days, and >10 days and clinical outcome was based on conditions at the time of hospital discharge.

This ethical approval recommendation has been performed from the Health Research Ethics Commission, Faculty of Medicine, Hasanuddin University (Number: 427/UN4.6.4.5.31/PP36/2020) and a research permits from the Education and Research Division of Dr. Wahidin Sudirohusodo Hospital, Makassar (Number LB.02.01/2.2/13910/2020).

Results

The flow of study is shown in Figure 1. The potential participants were 1736 patients, 239 patients eligible with inclusion criteria, there were excluded because they did not have Ferin, TIBC, and ferritin test; active bleeding and sepsis on admission; readmission; and medical record that were not found. The general characteristics, etiology, and therapy of CKD patients according to their RDW group are summarized in Table 1. The mean age was 48.64 ± 9.13 years and about 35 (59.3%) patients were female. Of the 59 patients, the analysis was divided into two groups based on RDW ≤ 14.5% and RDW > 14.5%. There were no significant differences in age, sex, smoking habits, MAP, MUAC, CKD etiology, comorbidities, and hemodialysis between the two study groups (Table 1).

The biochemical characteristics of the two groups are shown in Table 2. There were a significant differences in the levels of hemoglobin (p = 0.001), RBG (p = 0.030), and serum sodium level (p = 0.010) of both study groups, but there was no significant difference
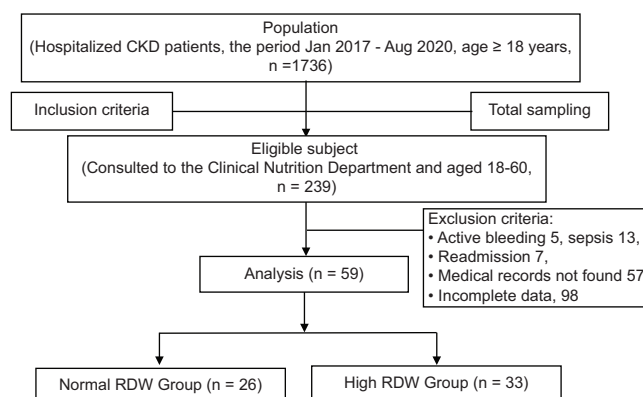

Figure 1: Data collection flow

Table 1: General characteristics, etiology, and therapy of CKD patients with normal and high RDW groups

Characteristics	n	RDW				p value
		Normal group (26)		High group (33)		
		n/mean	%/SD	n/mean	%/SD	
Age (years) (mean ± SD)	48.64 ± 9.13	50.42	8.62	47.24	9.40	0.166**
Sex						1.000***
Male (n, %)	24 (40.7)	11	42.3	13	39.4	
Female (n, %)	35 (59.3)	15	57.7	20	60.6	
Cigarette						0.890***
Yes (n, %)	20 (33.9)	8	30.8	12	39.4	
No (n, %)	39 (66.1)	18	69.2	21	63.6	
MAP (mmHg) (mean ± SD)	99.56 ± 18.76	94.88	22.74	103.24	14.22	0.089*
eGFR ((mL/min/1.73 m^2) (mean ± SD)	7.36 ± 5.48	6.93	4.79	7.70	6.01	0.766**
MUAC (cm) (mean ± SD)	22.26 ± 4.29	22.17	3.02	22.33	5.12	0.882*
Etiology						
Hypertension (n, %)	48 (81.4)	20	76.9	28	84.8	0.511***
Diabetes (n, %)	15 (25.4)	6	23.1	9	27.3	0.947***
Malignancy (n, %)	12 (20.3)	6	23.1	6	18.2	0.890***
Chronic pyelonephritis (n, %)	16 (27.1)	6	23.1	10	30.3	0.745***
Urinary tract stones (n, %)	6 (10.2)	2	7.7	4	12.1	0.685***
Others (n, %)	15 (25.4)	5	19.2	10	30.3	0.504***
Comorbidities						
Pneumonia (n, %)	8 (13.6)	3	11.5	5	15.2	1.000***
Heart failures (n, %)	7 (11.9)	4	15.4	3	9.1	0.688***
Cardiovascular diseases (n, %)	4 (6.8)	1	3.8	3	9.1	0.623***
Sepsis (n, %)	6 (10.2)	2	7.7	4	12.1	0.685***
Decubitus ulcer (n, %)	4 (6.8)	2	7.7	2	6.1	1.000***
Hemodialysis						1.000***
Yes (n, %)	55 (92.2)	24	92.3	31	93.9	
No (n, %)	4 (6.8)	2	7.7	2	6.1	

*Uji T Independent (p<0.05), **Uji Mann Whitney (p<0.05), ***Uji Chi Square

in MCV, leukocytes, TLC, albumin, creatinine, BUN, potassium, ferin, TIBC, and ferritin (Table 2).

Analyzes of nutritional status, LOS, and clinical outcomes are summarized in Table 3. In nutritional status, there were 42 patients with moderate malnutrition, including 23 patients (88.5%) with normal RDW and 19 patients (57.6%) with high RDW. Meanwhile, there were 17 patients with severe malnutrition, including 3 patients (11.5%) with normal RDW and 14 patients (42.4%) with high RDW. There was a significant relationship (p = 0.021) < 0.05 between nutritional status and RDW. Whereas in the LOS and clinical outcome, there was no significant difference between both groups with p-values 0.890 and 0.968, respectively (Table 3).

Kaplan–Meier survival curve is one of statistical analysis to compare LOS between the normal and high RDW groups. This analysis was limited to patients with good clinical outcomes. This curve shows that the high RDW group was treated longer than the normal RDW group and the survival percentage was higher in the normal RDW group than the high RDW group but statistically not significant (Log-rank test, p = 0.7138) (Figure 2).

Discussion

Nutritional status and RDW

Throughout our knowledge, this study was the first study to directly link RDW with SGA to demonstrate malnutrition/PEW conditions in PGK patients. In the

Table 2: The biochemical data of CKD patients based on normal and high RDW groups

Characteristics	n total	RDW				p value
		Normal group (26)		High group (33)		
		n/mean	%/SD	n/mean	%/SD	
Hemoglobin (g/dL) (mean ± SD)	8.12 ± 2.20	9.15	2.01	7.31	2.01	0.001*
MCV (FL) (mean ± SD)	80.39 ± 15.27	80.91	15.78	79.98	15.08	0.636**
Leukocytes						0.078***
Leukopenia (n, %)	2 (3.4)	0	0.0	2	6.1	
Normopenia (n, %)	13 (22.0)	3	11.5	10	30.3	
Leukocytosis (n, %)	44 (74.6)	23	88.5	21	63.6	
TLC (per μL) (mean ± SD)	1201.97 ± 707.83	1382.33	816.40	1059.87	583.21	0.189**
GDS						0.030***
Hypoglycemia (n, %)	5 (8.5)	5	19.2	0	0.0	
Normoglycemia (n, %)	48.(81.4)	19	73.1	29	87.9	
Hyperglycemia (n, %)	6 (10.2)	2	7.7	4	12.1	
Albumin (g/dL) (mean ± SD)	2.89 ± 0.56	2.99	0.52	2.81	0.59	0.400**
BUN (mg/dL) (mean ± SD)	87.06 ± 41.63	89.55	40.59	85.11	42.96	0.688**
Creatinine (mg/dL) (mean ± SD)	10.03 ± 5.98	10.07	5.98	10.00	6.08	0.951**
Natrium						0.010***
Hyponatremia (n, %)	36 (61.0)	21	80.8	15	45.5	
Normal (n, %)	19 (32.2)	3	11.5	16	48.5	
Hypernatremia (n, %)	4 (6.8)	2	7.7	2	6.1	
Kalium						0.696***
Hypokalemia (n, %)	5 (8.5)	2	7.7	3	9.1	
Normal (n, %)	35 (59.3)	17	65.4	18	54.5	
Hyperkalemia (n, %)	19 (32.2)	7	26.9	12	36.4	
Fe (μg/dL) (mean ± SD)	50.00 ± 37.14	56.58	41.09	44.82	33.44	0.299**
TIBC (μg/dL) (mean ± SD)	184.00 ± 286.67	226.27	427.90	150.70	57.50	0.593**
Ferritin (ng/dL) (mean ± SD)	880.50 ± 402.33	876.31	385.94	883.80	420.71	0.947**

*Uji T Independent (p<0.05), **Uji Mann Whitney (p<0.05), ***Uji Chi Square

previous studies, it is shown nutritional status using laboratory parameters such as serum albumin or
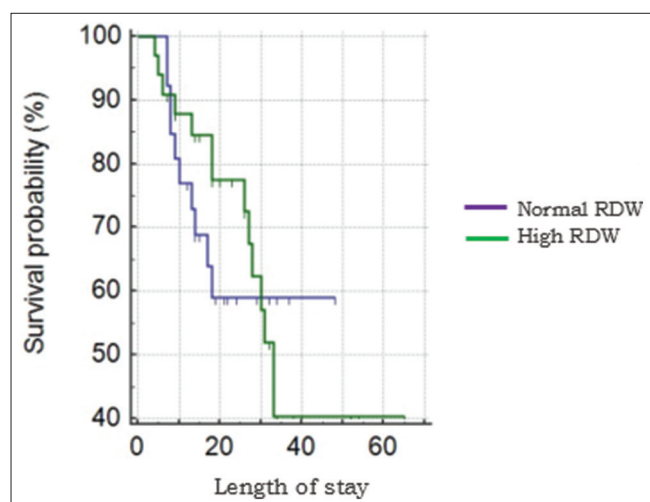

Figure 2: Kaplan–Meier survival probability curve and length of stay based on normal and high RDW groups

cholesterol level [19], [20]. In general, SGA can be assessed several aspects, namely, weight changes, a decrease in food intake, gastrointestinal symptoms, functional status, metabolic stress, and physical examination. In our center used SGA modification by adding serum albumin and TLC parameters.

Table 3: The nutritional status, LOS, and clinical outcomes in CKD patients based on normal and high RDW groups

Variables	n total	RDW				p value
		Normal group		High group		
		n	%	n	%	
Nutritional status						0.021
B	42 (71.2)	23	88.5	19	57.6	
C	17 (28.8)	3	11.5	14	42.4	
LOS						0.890
≤10 days	12 (20.3)	6	23.1	6	18.2	
>10 days	47 (79.7)	20	76.9	27	81.8	
Clinical outcomes						0.968
Good	24 (40.7)	16	61.5	19	57.6	
Bad	35 (59.3)	10	38.5	14	42.4	

Malnutrition is a deficit of energy and/or protein, as well as multivitamin and mineral deficiencies and it is often appearing in hospitalized patients. The energy deficits are common in malnourished patients, which can be associated with anisocytosis conditions [21]. It interferes with the ability of erythrocytes to enter the microcircuits, causing decreased oxygenation of the target organs due to reduced oxygen saturation in the blood (hypoxia). The oxygen is important for mitochondria to produces adenosine triphosphate by oxidative phosphorylation. When there are fewer oxygen to receive electrons from oxidative phosphorylation, reactive oxygen species can accumulate and it is can led to mass productions of radical superoxide, peroxide, and hydroxyl that can damage mitochondria. Therefore, increased RDW can result in limited oxygen supply and inefficient energy productions [11], [22].

Low protein consumption can lead to decrease in erythropoietin, which in later stages will interfere with the process of proliferation and maturation of erythrocytes. At the molecular level, protein deficiency is associated with bone marrow hypoplasia which is histologically evidenced by extracellular matrix changes. To a severe degree, there was also a depletion of megakaryocytic components and inhibition of maturation [23].

Deficiency both of Vitamin B12 and folic acid, disrupting the normal maturation of all modular lineages, especially in the production of erythrocytes, and iron deficiency is a common condition associated with erythropoiesis [11]. Decreased levels of selenium and Vitamin E were associated with increased fragility of erythrocytes thus shortening the age of erythrocytes [23]. It is associated with anisocytosis which consequently contributes to the increase in RDW. Besides, hypoxia itself (due to anemia) accompanied by uremic in PGK patients undergoing HD further increases the death of circulating erythrocytes (eryptosis), the more severe the condition of anemia and the higher heterogeneity of erythrocytes [24].

The previous research showed a significantly higher increase in RDW in the group with malnutrition and higher within the inflammatory-malnutrition group, where malnutrition was shown with albumin values ≤ 3.5 mg/dL and inflammation shown with CRP values >5 mg/L [25]. Förhécz _et al._ reported that increased RDW was correlated significantly with both inflammatory and erythropoiesis markers, also, nutritional markers such as serum albumin and cholesterol level [19].

Length of stay and RDW

There have been no previous studies regarding LOS associated with RDW in CKD patients but it was reported in other diseases such as reported by Lee _et al._, a retrospective study involving 744 pneumonia patients with secondary outcomes to assess LOS where RDW level was grouped into four quartiles: Quartile 1 (RDW < 13.3%, n = 196) which were 10 (6−15) d; Quartile 2 (RDW 13.3%−< 14.1%, n = 172) which were 11 (8−17.5) d; Quartile 3 (RDW ≤ 14.1%−< 15.2%, n = 190) which were 11.5 (8−21) d; and Quartile 4 (RDW ≥ 15.2%, n = 186) which were 12 (8−20) d, where there is a significant difference in LOS with p = 0.004 [26]. In critically ill patients admitted to the ICU, it also showed a significant association between increased RDW and LOS both in hospital and ICU [27], [28], [29].

Many factors affect the LOS in the hospital for CKD patients, including the severity of anemia [9], infection [30], whether or not they are undergoing dialysis [12], the treating experts [31], and complications during the treatment [32]. The LOS is also related to the use of antibiotics, electrolyte disturbances, and hospital service conditions/procedures [7].

In our study, the biochemical analysis was significant differences in hemoglobin, RBG, and serum sodium levels between the normal RDW and high RDW

groups. However, the normal RDW subgroup analysis showed that those with LOS ≤ 10 d had lower sodium levels and more severe anemia when compared with LOS > 10 d. However, in the high RDW subgroup analysis, there were no significant differences in the levels of GDS, serum sodium, and hemoglobin levels (Table 4). This might be the reason, there were no significantly differences between LOS and RDW in this study.

Table 4: Relationship of RBG, serum sodium, and hemoglobin levels to nutritional status, LOS, and clinical outcomes in CKD patients based on normal and high RDW groups

Variables	Normal RDW Group			High RDW Group		
	RBG	Na	Hemoglobin	RBG	Na	Hemoglobin
Nutritional status						
B						
Mean	125.35	126.74	9.19	117.53	135.58	7.34
SD	93.93	12.29	2.04	32.34	7.06	2.03
C						
Mean	94.33	130.00	8.87	143.57	134.93	7.27
SD	38.00	11.53	2.15	71.71	6.86	2.06
p values	0.748**	0.668*	0.936**	0.585**	0.441**	0.922*
LOS						
≤10 days						
Mean	121.50	118.00	7.70	137.50	133.67	6.22
SD	33.95	13.16	1.31	82.95	9.56	2.57
>10 days						
Mean	121.85	129.85	9.59	126.59	135.67	7.56
SD	100.99	10.52	2.00	46.47	6.31	1.84
p values	0.223**	0.031*	0.041**	0.657**	0.833**	0.143*
Clinical outcomes						
Good						
Mean	109.13	129.63	9.75	129.37	135.63	7.09
SD	66.40	9.79	2.08	44.39	7.37	1.91
Bad						
Mean	142.00	123.10	8.20	127.50	134.86	7.61
SD	118.69	14.60	1.52	65.43	6.37	2.18
p values	0.510**	0.184*	0.040**	0.215**	0.634**	0.478*

*Uji T Independent (p<0.05), **Uji Mann Whitney (p<0.05), ***Uji Chi Square

The results of another study, conducted by Zhang *et al.* [33] in an ICU setting compared hospital mortality in all critical patients as the primary outcome. The study also found data on LOS of patients (limited to patients who survive) associated with RDW. The results obtained showed that patients with RDW > 14.8% experienced significantly longer LOS (log-rank test, p < 0.001) [33]. Similar results were shown in the study of Silva NC da *et al.*, where the survival rate of patients with an RDW value of ≥ 13.6% was significantly lower for all causes of death as shown by the log-rank test <0.001 [13].

Clinical outcomes and RDW

Clinical outcomes referred to the patient's condition when discharged from the hospital and were categorized into two: (1) The presence of clinical improvement and (2) clinical deterioration/patient death. Based on the biochemical analysis, there were a significant differences in hemoglobin, RBG, and serum sodium levels between the normal and high RDW groups. However, in clinical outcome subgroup analysis, the normal RDW group showed a significant difference that the poor clinical outcome had a heavier degree of anemia was compared to the good clinical outcomes but no differences in serum sodium levels and RBG. Whereas in the high RDW subgroup analysis, there were no significant differences between serum sodium, RBG, and hemoglobin levels between good

clinical outcomes and worse clinical outcomes. This why there is no significant difference between clinical outcome and RDW in this study.

Several factors that cause death in CKD patients include cancer, infection, cardiovascular diseases such as IDH, HF, CVS, arrhythmias, and heart valve disease, and others such as chronic lung disease, diabetes, dementia, and suicide [34].

A previous retrospective and cohort study design in critically ill patients admitted to the intensive care unit showed that RDW and albumin were significantly associated with hospital mortality. While RDW remained, adjusted with gender, age, Charlton albumin index, and CRP significantly associated with mortality an odds ratio of 1.1 (95% CI: 1.03−1.16) [27]. Likewise, another study to assess 30 d mortality in pneumonia patients showed higher mortality in patients with higher RDW [26]. A retrospective and observational study with a population of CKD who underwent HD with 109,675 participants showed that increased RDW was a strong predictor of mortality compared to other markers of anemia such as hemoglobin, ferritin, and transferrin saturation [15]. The latest study of high RDW is associated with short-term risk of death in post-operative patients. Red cell distribution width was associated with adjusted for all risk causes of death in hospital in surgical patients (HR 1.17, IC 95% 1.02−1.32) but not in non-surgical patients. Each 1% step-up in RDW increased 17% all-cause mortality in surgical patients and an RDW ≥13.6% increased the short-term post-operative risk of death [11].

The results of a systematic review and meta-analysis published in 2017 involving nine's studies with 117,047 CKD patients showed that every 1% step-up in RDW would increase the risk of mortality (all causes of death) by 47% (HR 1.47, 95% CI 1.35−1.61) regardless of heterogeneity between studies (I2 = 44.5%, p = 0.094). When RDW was in the categorical variables, the risk mortality was significantly increased (HR 1.84, 95% CI 1.21−2.81). Even when heterogeneity into account (I2 = 82.3%, p = 0.001) and subgroup tests in the population, there was shown that every 1% increase in RDW would increase the risk of mortality by 36% (HR 1.36, 95% CI 1.20−1.53) in undergoing HD [16].

This study has several limitations, first, this study was a retrospective cohort design so that it could not provide a causal relationship between RDW and nutritional status, LOS, and clinical outcomes, besides, the patients that we studied were small in number and the same population, so that the results obtained are difficult to generalize to other populations. Second, there were no comprehensive data related to RDW, such as a history of blood transfusion before admission, a diagnosis of sepsis that no recorded, duration of dialysis, and treatment given by other divisions in one team led to bias interpretations. Third, in terms of LOS, we did not assess other aspects beyond the medical condition, such as the health insurance and hospital

regulations. Fourth, clinical outcomes, we did not have information on the discharged patients who were improving. In patients with poor clinical outcomes/death, due to short observation and we did not verify the cause of death, this would allow for bias in interpretations.

Conclusion

There was a significant relationship between nutritional assessment and RDW, but not significant relationships between LOS and clinical outcomes with RDW in CKD patients. However, the RDW is an inexpensive marker that can apply at all levels of health care, so we suggest a prospective study comparing other definitive markers of inflammation with RDW in CKD patients, with a larger sample size for more accurate results.

Acknowledgment

The authors express their sincere appreciation to the that ensure the extensive data collection on which this work is based.

References

1. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Diasease. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. J Int Soc Nephrol KDIGO. 2013;3:1-163.

2. Bikbov B, Perico N, Remuzzi G. Disparities in chronic kidney disease prevalence among males and females in 195 countries: Analysis of the global burden of disease 2016 study. Nephron. 2018;139(4):313-8. http://doi.org/10.1159/000489897
   PMid:29791905

3. Bikbov B. Global, regional, and national burden of chronic kidney disease, 1990-2017: A systematic analysis for the global burden of disease study 2017. Lancet 2020;395(10225):709-33. http://doi.org/10.1016/S0140-6736(20)30045-3
   PMid:32061315

4. Ministry of Health. 2018. Hasil Utama Riskesdas. India: Ministry of Health; 2018.

5. Iorember FM. Malnutrition in chronic kidney disease. Front Pediatr. 2018;6:161. http://doi.org/10.3389/fped.2018.00161
   PMid:29974043

6. Gluba-Brzózka A, Franczyk B, Olszewski R, Rysz J. The influence of inflammation on anemia in CKD patients. Int J Mol Sci. 2020;21(3):725. http://doi.org/10.3390/ijms21030725
   PMid:31979104

7. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, *et al.* Persistent systemic inflammation is associated with poor clinical outcomes in copd: A novel phenotype. PLoS One. 2012;7(5):e37483. http://doi.org/10.1371/journal.pone.0037483
   PMid:22624038

8. Karahan I. Effects of comorbidities, inflammation and glycaemic control on length of hospital stay/potentially avoidable readmission risk in type 2 diabetic patients-a retrospective analysis. J Evol Med Dent Sci. 2019;8(40):2991-95.

9. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, *et al.* Etiology of the protein-energy wasting syndrome in chronic kidney disease: A consensus statement from the international society of renal nutrition and metabolism (ISRNM). J Renal Nutr. 2013;23(2):77-90. http://doi.org/10.1053/j.jrn.2013.01.001
   PMid:23428357

10. Fauzan MR, Dahlana CK, Taslim NA, Syam A. The effect of giving fish extract (pujimin plus) on intake of protein and hemoglobin hypoalbuminemic patients. Enferm Clin. 2020;30(4):452-55. https://doi.org/10.1016/j.enfcli.2020.03.009

11. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width : A simple parameter with multiple clinical applications red blood cell distribution width : A simple parameter with multiple clinical applications. Crit Rev Clin Lab Sci. 2015;52(2):86-105. http://doi.org/10.3109/10408363.2014.992064
    PMid:25535770

12. Horta-Baas G, del Socorro Romero-Figueroa M. Clinical utility of red blood cell distribution width in inflammatory and non-inflammatory joint diseases. Int J Rheumat Dis. 2019;22(1):47-54. http://doi.org/10.1111/1756-185X.13332
    PMid:30168259

13. Tam-Tham H, Ravani P, Zhang J, Weaver RG, Quinn RR, James MT, *et al.* Association of initiation of dialysis with hospital length of stay and intensity of care in older adults with kidney failure. JAMA Network Open. 2020;3(2):e200222. http://doi.org/10.1001/jamanetworkopen.2020.0222
    PMid:32108896

14. Schepens T, De Dooy JJ, Verbrugghe W, Jorens PG. Red cell distribution width (RDW) as a biomarker for respiratory failure in a pediatric ICU. J Inflamm (United Kingdom) 2017;14(1):1-7. http://doi.org/10.1186/s12950-017-0160-9
    PMid:28596707

15. da Silva NC, Prestes IV, Gontijo WA, das Graças Pena G. High red blood cell distribution width is associated with a risk of short-term mortality in hospitalized surgical, but not clinical patients. Clin Nutr ESPEN. 2020;39:150-6. http://doi.org/10.1016/j.clnesp.2020.06.023
    PMid:32859310

16. Vashistha T, Streja E, Molnar MZ, Rhee CM, Moradi H, Soohoo M, *et al.* Red cell distribution width and mortality in hemodialysis patients. Am J Kidney Dis. 2016;68(1):110-21. http://doi.org/10.1053/j.ajkd.2015.11.020
    PMid:26786297

17. Zhang T, Li J, Lin Y, Yang H, Cao S. Association between red blood cell distribution width and all-cause mortality in chronic kidney disease patients: A systematic review and meta-analysis. Arch Med Res. 2017;48(4):378-85. http://doi.org/10.1016/j.arcmed.2017.06.009
    PMid:28916240

18. Tonelli M, Wiebe N, James MT, Naugler C, Manns BJ, Klarenbach SW, *et al.* Red cell distribution width associations with clinical outcomes: A population-based cohort study. PLoS One. 2019;14(3):95-9. http://doi.org/10.1371/journal.pone.0212374
    PMid:30865651

19. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, *et al.* Global prevalence of chronic kidney disease-a systematic review and meta-analysis. PLoS One. 2016;11(7):e0158765. http://doi.org/10.1371/journal.pone.0158765
    PMid:27383068

20. Yonemoto S, Hamano T, Fujii N, Shimada K, Yamaguchi S, Matsumoto A, *et al.* Red cell distribution width and renal outcome in patients with non-dialysis-dependent chronic kidney disease. PLoS One. 2018;13(6):1-13. http://doi.org/10.1371/journal.pone.0198825
    PMid:29889895

21. Taslim NA, Virani D, Sumartini NK, Karmila M, Bukhari A, Aminuddin A, *et al.* Energy regulation in newly diagnosed TB with chronic energy deficiency: Free fatty acids and RBP4. Asia Pac J Clin Nutr. 2017;26(1):S73-8. https://doi.org/10.6133/apjcn.062017.s9
    PMid:28625041

22. Malekmakan L, Khajehdehi P, Pakfetrat M, Malekmakan A, Mahdaviazad H, Roozbeh J, *et al.* Prevalence of chronic kidney disease and its related risk factors in elderly of Southern Iran: A population-based study. ISRN Nephrol 2013;2013:427230. https://doi.org/10.5402/2013/427230
    PMid:24967234

23. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017;389(10075):1238-52. http://doi.org/10.1016/S0140-6736(16)32064-5
    PMid:27887750

24. Jadeja YP, Kher V. Protein energy wasting in chronic kidney disease: An update with focus on nutritional interventions to improve outcomes. Indian J Endocrinol Metab. 2012;16(2):246. http://doi.org/10.4103/2230-8210.93743
    PMid:22470862

25. Pérez-Torres A, Garcia ME, José-Valiente BS, Rubio MA, Diez OC, López-Sobaler AM, *et al.* Protein-energy wasting syndrome in advanced chronic kidney disease: Prevalence and specific clinical characteristics. Nefrologia. 2018;38(2):141-51. http://doi.org/10.1016/j.nefroe.2017.11.018
    PMid:28755901

26. De Mutsert R, Grootendorst DC, Boeschoten EW, Brandts H, van Manen JG, Krediet RT, *et al.* Subjective global assessment of nutritional status is strongly associated with mortality in chronic dialysis patients. Am J Clin Nutr. 2009;89(3):787-93. http://doi.org/10.3945/ajcn.2008.26970
    PMid:19144733

27. Furusho M, Weng J, Mori T, Wang T. Impact of hydration and nutrition status on the watson formula in peritoneal dialysis patients. Adv Perit Dial. 2014;30:110-4.
    PMid:25338431

28. Guan JC, Bian W, Zhang XH, Shou ZF, Chen JH. Influence of peritoneal transport characteristics on nutritional status and clinical outcome in chinese diabetic nephropathy patients on peritoneal dialysis. Chin Med J. 2015;128(7):859-64. http://doi.org/10.4103/0366-6999.154275
    PMid:25836603

29. Vegine PM, Fernandes AC, Torres MR, Silva MI, Avesani CM. Assessment of methods to identify protein-energy wasting in patients on hemodialysis. J Bras Nefrol. 2011;33(1):55-61.
    PMid:21541464

30. Obi Y, Qader H, Kovesdy CP, Kalantar-Zadeh K. Latest consensus and update on protein-energy wasting in chronic kidney disease. Curr Opin Clin Nutr Metab Care 2015;18(3):254-62. http://doi.org/10.1097/MCO.0000000000000171
    PMid:25807354

31. Hanna RM, Ghobry L, Wassef O, Rhee CM, Kalantar-Zadeh K. A practical approach to nutrition, protein-energy wasting, sarcopenia, and cachexia in patients with chronic kidney disease. Blood Purification. 2020;49(1-2):202-11. https://doi.org/10.1159/000504240
    PMid:31851983

32. Zivot A, Lipton JM, Narla A, Blanc L. Erythropoiesis : Insights into pathophysiology and treatments in 2017. Mol Med. 2018;24(11):1-15. https://doi.org 10.1186/s10020-018-0011-z
    PMid:30134792

33. Zhang Z, Xu X, Ni H, Deng H. Red cell distribution width is associated with hospital mortality in unselected critically ill patients. J Thoracic Dis. 2013;5(6):730-36. https://doi.org/10.3978/j.issn.2072-1439.2013.11.14
    PMid:24409348

34. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, *et al.* Cause of death in patients with reduced kidney function. J Am Soc Nephrol. 2015;26(10):2504-11.