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ORIGINAL PAPERS

Correlation Between Red Cell Distribution Width (RDW) and Chronic Kidney Disease Patients in Semarang, Indonesia

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Abstract

Background: Chronic Kidney Disease (CKD) describes abnormal structural and functional kidney conditions that mark a decrease in GFR. Erythropoietin producing peritubular cells are partially or completely damaged by the severity of kidney disease, causing inadequate erythropoiesis and anemia. Anemia is one of the factors causing erythrocyte size variations assessed by the red cell distribution width (RDW). The relationship between GFR kidney function and RDW is currently little studied, this encourages researchers to conduct a study of the correlation between GFR and RDW in patients with chronic kidney disease.
Methods: Retrospective observational analytic study with cross sectional approach was conducted in 45 chronic kidney disease patients in RSUP dr. Kariadi Semarang in December 2018-January 2019. Data include age, weight, urea and creatinine serum, and RDW. Calculation of GFR values using the Cockroft Gault formula. Statistical tests using Spearman's correlation, $p<0.05$ were considered significant.
Results: The median (minimum-maximum) GFR and RDW are respectively 20 (6-35) mL/min /1.73 m^2; 15.7 (12.8-20.6)%. The correlation test of GFR with RDW is $r = -0.468$ with $p=0.001$. Ureum, creatinine and RDW have significant different in chronic kidney disease between stadium 3, 4, and 5 ($p=0.001$).
Conclusion: There is a moderate negative correlation between GFR and RDW in patients with chronic kidney disease. Red cell Distribution Width (RDW) can be used as a alternative parameter to evaluate declining of kidney function in patients with chronic kidney disease stage 3-5.

Keywords: Glomerular Filtration Rate; Red Cell Distribution Width; Chronic Kidney Disease

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INTRODUCTION

The prevalence of chronic kidney disease is increasing and becoming one of the health problems with highest healthcare cost in Indonesia after heart disease[1]. World Health Organization (WHO) data showed that kidney failure patients has increased 50% from prior year in 2013. Data from *Riset Kesehatan Dasar* (Riskesdas) in 2013 indicated that prevalence of kidney failure patients in Indonesia was 0.2% or 2 in 1000 population[2]. Global Burden of Diseases data in 2010 showed that chronic kidney disease was the 27th cause of death globally in 1990 and 18th in 2010[1]. The National Basic Health Research (Riset Kesehatan Dasar, Riskesdas), reported that the prevalence CKD in 2018 is 3.8 permil (%) increased from 2.0 (%) in 2013[2]. However, these data may underestimate the real number of CKD patients as screening for CKD is notoriously challenging. Prodjosudjadi *et al* in their study found the prevalence of CKD was 12.5% of subjects with either hypertension, proteinuria, and/or diabetes mellitus (DM)[3]. This data fits well with international studies on CKD prevalence and burden of the disease

Chronic kidney disease (CKD) presented an abnormal kidney structure and function, occurring progressively and usually irreversible[4]. Prevalence Chronic Kidney Disease was increased along with an increasing prevalence of diabetes and hypertension. Diabetes Mellitus and Hypertension becoming two major health problem that causes a decrease in kidney function[5]. The degree of abnormal kidney function is scored using Glomerular Filtration Rate (GFR). GFR (glomerular filtration rate) is total filtration rates of the functioning nephrons in the kidney. GFR will decrease along with progressivity of kidney damage[6]. CKD divided into five stages based on GFR level. Staging of CKD based on GFR is classified as Stage 1 (GFR ≥90 mL/min/1.73 m^2), Stage 2 (GFR 60–89 mL/min/1.73 m^2), Stage 3a (45–59 mL/min/1.73 m^2), Stage 3b (30–44 mL/min/1.73 m^2), Stage 4 (15–29 mL/min/1.73 m^2), and Stage 5 (<15 mL/min/1.73 m^2). GFR can be assessed using Cockroft-Gault formula, based on age, weight, and sex[7].

Erythropoiesis is one of the kidney functions in human body. Decreased kidney function can causes abnormalities synthesis of red blood cells because kidney produce erythropoietin hormone that have major role for red blood cell production in bone marrow[8]. Normochromic normocytic anemia is particularly frequent among patients with progressive chronic kidney disease (CKD). Anemia in CKD causes by inadequate production of erythropoietin, erythropoiesis inhibition due to the accumulation of uremic toxins, reduced red blood cell survival, iron deficiency, malnutrition, inflammation, folate and/or vitamin B12 deficiency, dysregulated iron metabolism, oxidative stress, chronic gastrointestinal blood loss, secondary renal hyperparathyroidism, and blood losses during hemodialysis sessions in patients with end-stage renal disease requiring replacement therapy[9,10].

Red Cell Distribution Width (RDW) is a measurement of erythrocyte sizes in circulation and routinely reported as a part of complete blood count without any additional cost[11,12]. This parameter commonly used together with Mean Corpuscular Volume (MCV) as one of the indexes to narrow differential diagnosis of anemia. High RDW means heterogeneity in RBC sizes (anisocytosis)[10]. Increasing RDW may indicated changes in erythrocytes ages caused by production problem or increasing erythrocyte destruction. Several studies showed that RDW has a correlation with mortality in many disease populations, including chronic kidney disease. In dialysis patients, high RDW is associated with mortality and is a stronger mortality predictor than anemia marker, such as transferrin and ferritin saturation[13].

In chronic kidney disease, peritubular cells which producing erythropoietin was partially or fully damaged along with severity of kidney disease. Uremia also inactivates erythropoietin or suppress bone marrow response toward erythropoietin, thus causing inadequate erythropoietin and anemia[14]. Anemia is one of the important cause factors for variation of erythrocyte sizes shown by RDW. As kidney function decreases indicated by GFR, anemia may be more severe, indicated by high RDW[15].

Previous research that was almost similar to this study regarding the correlation of RDW with kidney function in Indonesia was carried out in 2020. Soraya et al from their study that include 20 patients chronic kidney disease with hemodialysis showing that there are significant positive correlation between RDW and creatinine[16]. Other result from this study also showing that there are no significant correlation between RDW with ureum and eGFR[17]. The results of this study are different from previous studies conducted in Japan in 2018 where the results showed that there was a significant negative correlation between RDW and eGFR in patients with chronic kidney disease without hemodialysis[13]. Lippi et al from their cross-sectional study that conduct in 2008 also indicate that there is negative significant correlation between RDW and GFR in outpatient's chronic kidney disease[17].

This study aimed to prove the correlation between GFR and RDW in chronic kidney disease patients.The difference in results regarding the correlation between RDW and GFR makes researchers interested in conducting research related to this topic. Besides that, this topic was chosen by researchers because researchers feel that research on analyzing the correlation between GFR and RDW in Indonesia is still very limited although quite a lot of research related to this topic has been carried out in countries other than Indonesia. the existence of differences in environmental and physiological characteristics that are different in each country is one of the variables that can cause differences in research results.

METHOD

Research design

This study was approved by the Ethical Committee of Medicine Faculty and Dr. Kariadi Hospital Semarang (078/EC/KEPK-RSDK-2019). This was a cross-sectional study using medical record data conducted in December 2018-January 2019 at Dr. Kariadi Hospital Semarang.

Research subjects

Total subject in this study was 45 patients with inclusion criteria in this study were men and women, aged above 40 years old, normal body temperature and leukocyte count. Exclusion criteria such as post-transfusion patients, history of bleeding or occurring bleeding, treated with iron supplementation, folic acid, and vitamin B12, had a liver disease, and diabetes mellitus. Subject divided into 3 groups based on GFR. GFR 30-50 ml/min/1.73 m^2 is CKD stage 3, GFR 15-29 ml/min/1.73 m^2 is CKD stage 4, and GFR <15 ml/min/1.73 m^2 is CKD stage 5.

Respondent that who are willing to take part in the study and meet all the criteria subjects who are willing to take part in the study and meet all the criteria will sign an informed consent and fill out a questionnaire containing data related to their identity.

Blood sample were collected around 3 ml to examined blood profiles, ureum, and creatinine serum. The complete blood profile examination was checked using a hematology analyzer Sysmex XS 800i.

GFR was measured using Cockroft-Gault formula as below [18]:

$$\mathbf{GFR} = \frac{\mathbf{(140 - age)\ x\ weight}}{\mathbf{72\ x\ serum\ creatinine\ (mg/dL)}}$$

Unit: mL/minute/1.73m^2
*if women, multiply by 0.8

RDW-CV was calculate using formula as below[19]:

$$\mathbf{RDW - CV} = \frac{\mathbf{1}\ \boldsymbol{SD}}{\mathbf{MCV}}\ \boldsymbol{x}\ \mathbf{100}$$

STATISTICAL ANALYSIS

Data was processed using statistical software SPSS version 5. For all blood profile variable normality test was conducted using Saphiro Wilk test because sample size was less than 50. Independent T-Test analysis was performed for variable that have normal data distribution while Kruskal wallis analysis was performed for data that not normally distributed. Correlation analysis in this study was performed by Spearman correlation test was used to understand the correlation between GFR and RDW. P value is statistically significant if $p < 0.05$.

RESULT

Table 1. describe characteristic of total 45 respondent of this study meanwhile Table 2. show the difference characteristic from 3 groups in this study. Kruskall Wallis statistical analysis test show that there was no significant difference among three groups in terms of age, weight, hemoglobin, erythrocyte count, MCV, MCH, MCHC ($p>0.05$). Significant difference in this study based on statistical analysis can be seen in serum urea level, serum creatinine level and RDW in chronic kidney disease patients stage 3, 4, and 5 ($p<0.05$). The results of Spearman correlation analysis showed that there was significant moderate negative correlation ($r = -0.468$) between GFR and RDW (Table 2).

Table 1. Difference Test between Groups

Parameter	All Patients (n=45)	CKD staging			p
		Stage 3 (n=15)	Stage 4 (n=15)	Stage 5 (n=15)	
Age (years)	55.4 ± 6.97	55.67 ± 8.35	55.73 ± 6.04	54.80 ± 6.77	0.923
Weight (kg)	74.4 ± 5.34	75.65 ± 5.00	75±6.04	77±6.00	0.595
Urea (mg/dL)	88.89 ± 51.4	61.13 ± 26.62	76.93 ± 21.77	128.60 ± 66.76	<0.001*
Creatinine (mg/dL)	5.10 ± 3.1	2.60 ± 0.38	3.99 ± 0.94	8.70 ± 2.79	<0.001*
Hemoglobin (g/dL)	9.61 ± 1.36	9.91 ± 1.77	9.71 ± 0.90	9.54 ± 0.91	0.720
RBC count (10^{6}/µL)	3.93±4.01	3.47±0.70	5.19±6.88	3.11±0.51	0.183
MCV (fL)	84.96±5.6	84.98±4.57	84.13±7.78	85.81±3.93	0.808
MCH (pg)	28.41 ± 5.62	28.41 ± 0.93	28.52 ± 2.72	28.76 ± 1.33	0.865
MCHC (g/dL)	33.39 ± 5.62	33.61 ± 1.40	33.94 ± 1,39	33.49 ± 1.25	0.532
RDW (%)	15.86 ± 1.71	15.04 ± 1.26	15.46 ± 1.35	17.12 ± 1.83	0.001*

Note: * $p < 0.05$, statistically significant; Difference test using Kruskall Wallis

Table 2. Correlation between GFR and RDW

Variables	RDW (%)	
	r	P
GFR (mL/min/1.73 m^2)	-0.468	0.001*
Ureum (mg/dL)	0.372	0.012*
Creatinine (mg/dL)	0.477	0.001*

Note: $p < 0.05$, statistically significant; *Statistical test using Spearman's

DISCUSSION

Total respondent in this study was 45 CKD patients that divided into three groups based on their GFR level that is Stage 3, Stage 4 and Stage 5 group. Respondent in this study consist of 57.8% male and 42,2% female patients. This result indicated that in this study, CKD was found more in male than female. This result was in line with Riset Kesehatan Dasar report in 2018 which showed that prevalence of CKD in male (4.17%) is higher than female (3.52%). Male subjects were vulnerable to systemic diseases, such as hypertension, diabetes mellitus, glomerulonephritis, and polycystic kidney because of hormonal effect, physical condition, and activity intensities. Narrow urinary tract in male patients make them susceptible to blockage and kidney stone. Men tend to have an unhealthy lifestyle such as smoking and alcohol consumption that can increase the risk of CKD[18].

Among three groups in this study, there was no significant age difference. The age range of respondents in this study was 41-69 years old with average age 55 years old. Kidney disease has the potential occurs in all ages but is principally prevalent in older individuals Kidney function will decrease with aging. Basic Health Research Indonesia in 2018 also show that the highest prevalence of CKD occurs in age range above 65 years old. Aging is major risk factor that can led to deleterious changes of kidney parenchyma secondary to cellular senescence as well as to cumulative effects of nephrotoxic agents prescribed during the patient's life. Chronic kidney disease in age below 65 years old commonly caused by unhealthy lifestyle, high stress level, fatigue, over supplement drink consumption, and drinking less water[19]. High work demand needs more energy instantly; thus patients may consume energy supplement. High frequency of consuming energy drink may increase the risk of kidney disease[20].

Urea and creatinine are blood parameters that reliable and sensitive for detection of kidney failure[21]. Progression of kidney damage is detected with the rise of these two chemical substances in the blood, which assess the renal function. Creatinine is a waste product of the breakdown of creatine phosphate happens in the muscles[22]. Creatine phosphate is the first source of energy to supply additional ATP. If the kidney is damaged, it will be more and more ATP is used for the formation of energy, the more There are many metabolic wastes, creatine clearance will decrease and creatinine concentration will increase. Urea is an organic compound and has an important role in the metabolism of nitrogen-containing compounds[22]. Urea is the metabolized product of dietary proteins, the waste product filtered through the kidney into the urine. Statistical analysis about urea and creatinine serum in this study show that there are significant difference among three groups ($p<0.005$). Stage 5 group have the biggest urea and creatinine serum among two others group. This result in line with previous study that explained that an increase in serum urea and creatinine values indicated a decrease in kidney function. Statistical analysis using SPSS in this study indicate that there is a positive correlation between red distribution width (RDW) with ureum and creatinine serum. Result from Spearman test show that RDW and serum creatinine have significant positive correlation ($p< 0.05$) with medium strength of association ($r = 0.477$). Result from this study in line with previous study that conduct by Hutasuhut *et al*, 2020. Positive correlation between those two variable explained that the increase in rdw value is directly proportional to the increase in creatinine value. An increase in the RDW value indicates a progressive kidney glomerular damage. Damage to the kidney glomerulus will cause the amount of creatinine that passes into the blood serum to increase. Positive correlation was also found between red distribution width and serum urea in patient CKD stage 3-5 ($p<0.05$, $r=0.372$). Just like creatinine, the higher the amount of urea in the blood serum, this is also one of the results of a decrease in glomerular function in the kidneys to carry out the the filtering function.

Anemia is one of the complications that is often experienced by patients with chronic kidney failure. Anemia in CKD patient associated with a reduced quality of life, and an increased morbidity and mortality. A cross-sectional study from the National Health and Nutrition Examination Survey (NHANES) in 2007–2008 and 2009–2010 revealed that anemia was twice as prevalent in patients with CKD as in the general population (15.4% vs 7.6)[23]. WHO defines anemia as hemoglobin (Hb) concentration lower than 13 g/dl in men and postmenopausal women and lower than 12 g/dl in younger women[24]. Mild anemia was defined as Hb > 11 g/dL, whereas moderate and severe anemia were defined as Hb 9-11 g/dL and < 9 g/dL, respectively[24]. All groups in this study had hemoglobin values below normal with average hemoglobin level (9.61 ± 1.36) mg/dL that include in severe anemia. Other blood count about red blood indices like Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and MCH concentration (MCHC), and RBC count are also calculated. This study shows that mean MCV, MCH, MCHC, and RBC count value of all respondent are in normal range. Normal range of MCV, MCH, and MCHC are define as Normochromic and normocytic anemia that common in chronic disease patients such as CKD[25]. Normochromic normocytic anemia is anemia with normal red blood cell size and hemoglobin content in each red blood cell. This is due to severe blood loss, excessively increased plasma volume, hemolytic diseases, endocrine, renal, and hepatic disorders[8].

This study results also showing significant correlation Red Cell Distribution Width (RDW) among three groups ($p<0.05$). The highest mean of RDW value is in Stage 5 groups (17.12 ± 1.83) % meanwhile RDW value from Stage 3 and Stage 4 group respectively are (15.04 ± 1.26) % and (15.46 ± 1.35) %. It can be inferred that only respondent in Stage 5 group that have high RDW value and respondent in the two others group have normal RDW value. A red cell distribution width (RDW) test measures the differences in the volume and size of your red blood cells (erythrocytes)[11]. Red blood cells have function to carry oxygen from your lungs to every cell in your body because all cells in your body need oxygen to grow, make new cells, and make your body in healthy condition. Normally, your red blood cells are all about the same size with the same capability to carried oxygen. High RDW value means that there is a major difference between the size of your smallest and largest red blood cells that affect their ability to carried oxygen. This may be a sign of a medical condition like CKD[14].

High Red Cell Distribution Width (RDW) conclude that there is heterogeneity in erythrocyte sizes (anisocytosis)[13]. Increasing RDW also may indicate changes in erythrocyte ages caused by production problem or increasing erythrocyte destruction[13]. Kidney is one of the important organs in human body that play role in red blood cell production. Impaired kidney function can affect Erythropoietin (EPO) production. Erythropoietin (EPO) is a hormone produced by the kidneys that promotes the formation of red blood cells by the bone marrow[26].

Patient with impaired kidney function having only half of erythrocyte life span than the normal erythrocyte. Changes in erythrocyte ages is caused by decreasing erythropoietin level showed by increasing RDW[27]. Chronic Kidney Disease is degenerative disease which can cause inflammation and increased oxidative stress in the body. Result from previous studies also found that association of RDW with oxidative stress and reported that increased disruption of erythropoiesis, blood cell membrane deformity, and alteration in circulating erythrocyte half life under oxidative stress, ultimately leading to increased RDW.

Result from this study that show highest RDW values are found in Stage 5 CKD patients in line with other previous study that conclude anemia is more prevalent and severe as the estimated glomerular filtration rate (eGFR) declines. The prevalence of anemia raised with the progression of CKD was 8.4% at stage 1 to 53.4% at stage 5 showing from RDW value.

This study also perform statistical analysis related with correlation between RDW values and GFR using Spearman Rank Test. Result from Spearman test indicated that there was a significant moderate negative correlation between GFR and RDW in chronic kidney disease patient ($p<0.05$, $r=-0.468$). It shows that RDW value will increase in value according to the prognosis of kidney damage. This results in line with previous cohort study from Sayoko et al. (2018) and Yao Pen et al. (2016) in Japan also stated that high RDW was correlated with poor renal outcome and increasing risk of mortality in CKD patients[28,29].

Previous studies discussed more about RDW as a risk factor that can increase mortality in patients with CKD, while this study analyzes the correlation between RDW values and the level of kidney damage as an alter native indicator of laboratory tests in predicting the level of kidney damage. Damaged glomerulus caused disruption in kidney function, showed by decreasing GFR comparable with the degree of severity. Damage in peritubular kidney cells may cause erythropoietin deficiency, in which it affects erythrocyte production by inducing proliferation, differentiation, and maturation of erythrocyte precursor.

Linkage between erythropoietin and its receptor in bone marrow may induce proliferation and maturation of the stem cells to produce new mature erythrocyte. In normal condition, 90% of erythropoietin is produced in kidney and only 10% is produced in liver. The higher kidney damage in CKD may decrease erythropoietin and causing anemia in CKD. Uremia also may inactivate erythropoietin and suppress the bone marrow responsiveness toward erythropoietin, thus causing inadequate erythropoiesis[30.]

Erythropoietin deficiency is the main cause of anemia in chronic kidney disease. Anemia is one of the important factors which causing variety of erythrocyte sizes. Anemia mechanism may influence RDW in earlier stage before hemoglobin drops into anemia range. DW was considered as physiological reserve of the patients, when physiological reserve was disrupted or decreased, then immature erythrocytes with different sizes will be found in peripheral circulation. Thus, little changes in RDW may indicate abnormalities that may cause poorer outcome[31].

RDW value widely used as mortality risk predictor in CKD patient. High RDW in CKD patient can may also be a risk factor for incident myocardial infarction, stroke, thromboembolic disease, metabolic syndrome, and albuminuria. The exact underlying pathogenic mechanism remains unclear, most studies have suggested a relationship of RDW with chronic inflammation, nutritional insufficiency, and impaired microcirculation. The aforementioned observations can also be indicative of the lethal triad, the malnutrition - inflammation - atherosclerosis (MIA) syndrome, in patients with end stage renal disease (ESRD)[32].

This study concludes that RDW significantly correlate with urea and creatinine serum and also GFR in patient with CKD Stage 3-5. RDW. Red Distribution Width (RDW) can be an alternative parameter used to measure the progression of kidney damage in patients with chronic kidney disease because it has a significant correlation with laboratory measurement parameters which commonly have been used as predictors such as serum urea, serum creatinine, and GFR. High RDW value can indirectly indicate the progression of kidney glomerular damage that occurs in patients with chronic renal failure. A high RDW value indicates a decrease in the ability of kidney function seen from the GFR value and later will also be indicated by an increase in serum urea and creatinine levels. As an alternative parameter to see the progress of kidney disease, the advantage of the RDW is that this measurement is relatively simpler compared to others, the RDW measurement is also relatively cheaper compared to other measurements RDW. In the future, it is hoped that RDW can be used not only as an indicator of the occurrence of anemia in patients with chronic kidney failure but also as an easy, cheap, and efficient predictor of kidney disease progression.

This study did not analyze total hemodialysis in chronic kidney disease patients which may affect RDW parameter. Hemodialysis factor is not discussed in this study because the main purpose was to look at RDW as an indicator that can be used to predict the level of kidney damage regardless of other factors. This study also did not take risk factors of chronic kidney disease into account which may affect RDW level. Another study with larger sample size, taking hemodialysis into account, and also other risk factors of chronic kidney disease which may affect study variables should be performed. Greater number of research samples will increasing validity of the research results.

CONCLUSION

This study showed that all CKD patient among three groups in this study are in normochromic normocytic anemia condition that seen from their blood count analysis that consist of lower hemoglobin value, normal Mean Corpuscural Volume (MCV), and normal Mean Corpuscural Hemoglobin (MCH). RDW. Highest RDW value was found in stage 5 Chronic Kidney Disease Patient. Statistical correlation also shows that there was a significant moderate negative correlation between GFR and RDW in chronic kidney disease patients and moderate positive correlation between RDW and urea and creatinine serum. RDW may be used as a parameter to evaluate declining kidney function in chronic kidney disease stage 3-5.

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Conflict of interest
The authors declare that there is no conflict of interests regarding the publication of this paper among the writers.

Contributors
In this study, Anita Tri Hastuti contributed for designing the study process and data retrival. Devi Elvina contributed to processing data and writing the article. Edward Kurnia Setiawan was contributed for design study, interpretating data processing, and writing the article.
The author declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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