RED BLOOD CELL DISTRIBUTION WIDTH IS A PREDICTOR OF CHRONIC KIDNEY DISEASE PROGRESSION AND ALL-CAUSE MORTALITY

Yilmaz F1, Sozel H2

Department of Nephrology, Antalya Ataturk State Hospital, Antalya, Turkey. fthylm79@gmail.com

ABSTRACT

OBJECTIVES: The aim of this study was to investigate the association of RDW with all-cause mortality and disease progression in patients with CKD in stage 3–4.

METHODS: This longitudinal observational cohort study of patients with CKD was conducted at a single center. We categorized baseline RDW into two groups by its median (14.9%). The associations between baseline RDW values and all-cause mortality over 56 months were examined in unadjusted and adjusted models. The effect of RDW value on renal outcomes and mortality was evaluated by using Cox regression analysis.

RESULTS: A total of 261 patients were enrolled in the study. During an average follow-up of 56 months, 19.8% of patients died. The area under the ROC curve for RDW for all-cause mortality was 0.746, with sensitivity of 0.74 and specificity of 0.69 for a cut-off point of 14.3%. The incidence of all-cause mortality in the group with increased RDW was significantly higher than in the normal RDW group (p < 0.001). The Cox proportional hazard model showed that the elevated RDW level was an independent risk factor for all-cause mortality in patients with CKD in stage 3–4.

CONCLUSION: RDW is a powerful and independent prognostic marker for predicting all-cause mortality and disease progression in stage 3–4 of CKD (Tab. 4, Fig. 4, Ref. 29). Text in PDF www.elis.sk

KEY WORDS: chronic kidney disease, red blood cell distribution width, mortality, progression.

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem because of long life expectancy, increased frequency of diabetes and hypertension (1). Regardless of etiology, it is a progressive disease and the rate of progression is unpredictable (1). CKD is characterized by an increase in cardiovascular mortality as compared to general population. Cardiovascular disease (CVD) is the leading cause of death among patients with CKD (2). Anemia is highly prevalent among CKD patients and is associated with an increased risk of CVD and mortality (3).

Red blood cell distribution width (RDW) is an indicator of variability in the size of circulating red blood cells. It is a numerical index used for classification of anemia (4). It is automatically evaluated in measurements of complete blood count and is expressed as a percentage (5). According to results of many studies, RDW has been associated with unfavorable outcomes in several acute and chronic illnesses. Recently, an increase in the level of RDW was reported to indicate a poor prognosis in patients with diabetes, coronary artery disease, heart failure, stroke, peripheral artery disease, and pulmonary hypertension (6–10). A 1 % increase in RDW in an elderly population was associated with a 14 % mortality increase (11).

RDW is often used to classify anemia, but has also been associated with factors such as renin-angiotensin aldosterone system (RAAS) activation, malnutrition, inflammation, endothelial dysfunction, diastolic dysfunction, carotid intima-media thickness, and microalbuminuria (4, 5, 12–14). These factors together with anemia cause disease progression in patients with CKD and are associated with poor renal outcomes. The RDW value increases alongside the progression of the CKD phase. Previous studies have shown that high RDW levels in CKD patients are related to the increase in their mortality (14, 15). In addition, elevated RDW values may be used as cardiovascular and all-cause mortality predictors in patients receiving renal transplantation (16), peritoneal dialysis (17), hemodialysis (18) and continuous renal replacement therapy due to acute kidney injury (19). RDW may be used as a chronic inflammatory marker (20). This is a reliable risk factor with regard to mortality at all stages of CKD. In the effort to facilitate the prognosis of CKD, diverse biomarkers have been evaluated in many studies. However, the relationship of mortality with RDW is not illuminated in all aspects. Little is known about the relationship between RDW and progression of CKD and mortality.

The aim of this study was to evaluate the association of RDW with disease progression and risk of all-cause mortality in patients with mild or moderate CKD.
Material and method

Study population

This single-center, retrospective longitudinal observational cohort study was conducted by analyzing patients with CKD in stage 3–4 who were admitted to the Polyclinic of Nephrology. The study was performed according to the ethical principles of the Declaration of Helsinki. The study was approved by the local ethics committee. For this type of study (retrospective), the formal consent is not required.

This study included 261 patients who were treated between January 2012 and December 2012 and whose follow-up ended in December 2017. The study population consisted of patients with CKD in stage 3–4 who were not receiving renal replacement therapy. All patients were diagnosed with CKD based on the National Kidney Foundation K/DOQI guidelines. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (21). Demographic, clinical and biochemical data were collected for all the patients enrolled in the study. All data to be analyzed retrospectively were retrieved from the hospital medical files. The exclusion criteria in this study were age < 18 years old (1), lack of biochemical data (2), history of biopsy or chemotherapy (3), history of blood transfusion within 3 months (4), previous renal replacement therapy (5), liver disease, viral hepatitis, cirrhosis (6), autoimmune disease and treatment with immunosuppressive drugs (7), active gastrointestinal disorders (8), systemic inflammatory diseases and acute infection (9), current hospitalization (10).

Sociodemographic variables

The etiology of chronic kidney disease is shown in Table 1. The heights and weights were measured. The BMI was calculated as weight/height$^2$ (kg/m$^2$). Diabetes, hypertension and hyperlipidemia were defined in current guidelines. Anemia was defined as hemoglobin concentration < 12 mg/dl in women, and < 13 mg/dl in men (National Kidney Foundation). The history of medication in use included angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers, antihyperlipidemic agent (statin, fenofibrate), anti-anemic agents (iron preparation, folic acid, and vitamin B12), erythropoiesis stimulating agents, vitamin D and acetylsalicylic acid.

Data collection

At the first and last visits, clinical, biochemical data and GFR were collected for all the patients. The formula ‘initial eGFR –
last eGFR) ×12/time was used to calculate the annual GFR loss. The progression in patients with an annual loss of GFR ≥ 5 ml/min/1.73 m² was evaluated as being rapid and in those with < 5 ml/min/1.73 m² as slow. RDW was reported as percentage in the complete blood cell count. RDW is calculated by the following equation: (standard deviation of MCV ÷ mean MCV) × 100 (26). Normal RDW was defined as a level of 11.3–14.9 %. The upper normal limit of RDW at our laboratory is 14.9 %. The patients were separated into two groups based on their RDW values; normal RDW (RDW ≤ 14.9 %) or high RDW (RDW > 15.0 %) group.

Laboratory measurement

Venous blood samples were collected from all the patients after 12 h of fasting. The tubes with EDTA were used for automatic blood count according to the protocol of our hospital. All laboratory tests were performed by the central laboratory of hospital. Biochemical factors were analyzed with a Cobas Integra 800 system (Roche) measured by standard laboratory methods. Complete blood counts were made with the Beckman Coulter LH 750 (Fullerton, CA, USA) automated blood counting device. The intact parathyroid hormone level was measured by the electrochemiluminescence immunoassay (Roche PTH (Intact PTH)). Serum c-reactive protein (CRP) level was detected by rate nephelometry (normal range: 0–0.5 mg/dL).

Follow up

The median follow-up period was 56 months (IQR: 22–69 months). In this study, the initiation of renal replacement therapy or reaching the stage 5 of CKD was determined as primary outcome. The secondary outcome variable was all-cause mortality.

Statistical analysis

All statistical analyses were carried out using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp. Armonk, NY). Continuous data are presented as mean ± standard deviation, while categorical data are expressed as percentage. The distribution of variables was analyzed using the Kolmogorov-Smirnov test. The statistical analysis was performed by the Student’s t-test for parametric variables, Mann-Whitney U test for nonparametric variables, and χ²-test for qualitative variables between two groups. Pearson’s correlation coefficients were calculated to determine the strength of associations between RDW and other laboratory parameters. The relationship between study endpoint and RDW values was analyzed using univariate/multivariate regression models. In order to determine whether the RDW value was independently associated with mortality, six multivariable analysis models were established on the basis of RDW groups. The following models were used: unadjusted model (1), model adjusted for age and gender (2), model further adjusted for diabetes mellitus and hyperlipidemia (3), model further adjusted for ferritin, albumin, CRP and iPTH (4), model further adjusted for hemoglobin and proteinuria (5), and model further adjusted for glomerular filtration rate (6). The cumulative survival curves for major composite all-cause during the 56-month follow-up period were generated using the Kaplan-Meier method. The difference between the two groups was evaluated using a log-rank test. Hazard ratios and 95 % confidence intervals for the adjusted and unadjusted models were estimated using Cox proportional hazard models. All p values were planned two-sided, and the value of < 0.05 was considered statistically significant. The receiver-operating characteristic (ROC) curve was applied for predicting all-cause mortality, and the glomerular filtration rate loss area under the curve was calculated for RDW.

Results

Subject characteristics

Initially, in total, 389 patients were included in the study, of whom 128 were dropped out for the following reasons: lost to follow-up (n = 64), follow-up less than six months (n = 24), previous renal transplantation (n = 9), hematologic-oncologic disease (n = 7), acute infection (n = 12), liver disease (n = 7), and autoimmune disease (n = 5). Ultimately, 261 implemented patients were enrolled in the study.

Of the 261 CKD patients, 135 (51.7 %) were women and 126 (48.3 %) were men. Mean age of the patients in the study was 52.6 years (interquartile range: 22–83). Baseline patient characteristics are shown in Table 1. The clinical and biochemical characteristics of the patients in this study are shown in Table 2.

Red cell distribution width

The RDW levels ranged from 11.6 % to 17.8 % (14.4 % ± 1.9 %). The RDW distribution of the patients is shown in Figure 1. According to their RDW values, there were two groups: 184 pa-
Patients were in the normal RDW group (70.4 %; \( \leq 14.9 \% \)) and 77 patients were in the high RDW group (29.6 %; > 14.9 %). RDW levels of the patients with CKD in stage 4 were higher than in those with CKD in stage 3. Between normal and high RDW groups, no statistically significant difference was found in mean age, gender, and BMI (p > 0.05). Likewise, there was no difference in comorbidities and drug usage between the two groups.

Association between RDW and other parameters

We determined the median value for RDW as 14.4 %. The Spearman correlation coefficients showed that RDW was significantly positively correlated with CRP, BUN, serum creatinine and diabetes. Moreover, the baseline RDW value was negatively correlated with hemoglobin levels, eGFR, serum albumin, and ferritin. The levels of albumin were found to be significantly lower while the CRP values were significantly higher in the patients from the higher RDW group. The correlations of clinical and laboratory parameters with RDW are shown in Table 3.

RDW as a predictor of the primary outcome

Over a median follow-up of 56 months, 57 patients (21.8 %) reached the renal endpoint. 39 (14.9 %) of these patients were in the high RDW group and 18 (6.8 %) were in the low RDW group (p < 0.001). Thirty-five patients (13.4 %) initiated hemodialysis, 4 patients (1.5 %) underwent renal transplantation, and 3 patients (1.1 %) initiated peritoneal dialysis. Fifteen patients with CKD in stage 5 had been followed up before their renal replacement therapy started. A significantly higher baseline RDW value was observed in patients who have initiated their renal replacement therapy (16.7 % (14.5–18.2 %) vs 14.5 % (13.3–16.2 %), HR 1.34 (1.16–2.19); p < 0.001). RDW showed a significant positive correlation with GFR loss in the studied groups. Additionally, by ROC curve analysis, a cut-off level of 14.95 was determined for RDW for predicting CKD-progression (area under the curve (AUC): 0.746, 95 % CI: 0.675–0.816; Log rank p < 0.0005 (Fig. 2).

RDW as a predictor of the secondary outcome

After a median follow-up period of 56 months, 47 patients died including 22 (31.1 %) from the higher RDW group and 25 (13.5 %) from the normal RDW group. The higher RDW group (> 14.9 %) was associated with an increased risk of all-cause mortality as compared to the normal RDW group (HR 1.63 (1.24–3.32); p < 0.001). Additionally, in ROC curve analysis, a cut-off level of 14.65 was determined for RDW for predicting all-cause mortality (area under the curve (AUC): 0.714, 95 % CI: 0.646–0.781; Log rank p < 0.0005 (Fig. 3).

| Parameters       | r      | p     |
|------------------|--------|-------|
| Diabetes         | 0.352  | 0.002 |
| BUN              | 0.223  | 0.012 |
| Creatini         | 0.178  | 0.019 |
| eGFR (ml/min/1.73 m2) | –0.302 | 0.042 |
| Serum albumin, g/dL | –0.398 | 0.017 |
| Hemoglobin, g/dL | –0.422 | 0.024 |
| CRP              | 0.651  | 0.023 |
| Ferritin         | –0.288 | 0.021 |

*Spearman’s rank test correlation. iPTH, parathyroid hormone, BMI: body mass index, BUN: blood urea nitrogen, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein
There was a significant difference in the crude mortality rate and in Kaplan-Meier survival curves (log-rank test p < 0.001) for the two groups (p < 0.001) (Fig. 4).

Discussion

In this study, the effect of RDW on mortality and disease progression in stage 3–4 of CKD was evaluated. Higher level of RDW was associated with an increased risk of all-cause mortality in CKD in stage 3–4 (Tab. 4). Also, RDW increased alongside the increase in kidney function loss and risk of death. When the cut-off value was determined as 14.95 for RDW, the specificity in determining the stage 5 of CKD was 78.8 % and its sensitivity was 61.5 %. Similarly, when the RDW value was determined as 14.65, the sensitivity for all-cause mortality was 66 % and the specificity was 66.8 %. There was a statistically significant correlation between low levels of albumin, eGFR, hemoglobin, ferritin, high levels of BUN, creatinine, and CRP, and high RDW levels. In univariate logistic regression analysis, it was determined that diabetes, albumin, CRP, hemoglobin, eGFR and RDW were statistically significant in determining the progression to stage 5 of CKD. By multivariate logistic regression analysis, it was determined that diabetes, albumin, CRP, hemoglobin and RDW were statistically significant in determining the progression to stage 5 of CKD. Lippi et al. have shown that increased RDW levels are independently associated with impaired renal function (22). This is due to decreased erythropoietin with worsening renal function and infectious erythropoiesis due to increased uremic toxins. An increase in RDW values can be a novel marker for showing progression in CKD.

CKD is associated with a high mortality rate, which increases inversely with the glomerular filtration rate. The relationship between basal RDW value and increased cardiovascular and all-cause mortality in patients with CKD has also been shown in previous studies (3, 14, 16, 17, 19). Anemia is a possible cause of the ability of RDW to predict the renal outcome, and all-cause or cardiovascular mortality. In HD patients, RDW is a stronger predictor of mortality than traditional anemia markers (18).

The exact cause of RDW’s association with poor outcome in CKD patients is unclear, but several hypotheses have been proposed to explain this. Anemia is a possible cause of the ability of RDW to predict renal outcome, and all-cause or cardiovascular mortality. RDW was reported as an emerging novel biomarker for systemic inflammation (23). RDW levels have been shown to be associated with common inflammatory markers such as CRP (24), interleukin-6 (9) and soluble tumor necrosis factor (25). The chronic inflammation feature of CKD can increase the RDW values by suppressing the bone marrow and altering iron metabolism. It is thought that inflammation damages the erythrocyte membranes, disrupts its maturation and shortens the life span, thereby increasing RDW. Increased RDW may also be a symptom of impaired iron metabolism (intestinal iron absorption, iron transition to erythropoietic precursor cells, or iron mobilization). These results show that RDW is correlated with anemia and iron metabolism, as well as nutritional and inflammatory parameters.

CKD is characterized by increased oxidative stress which may be a potential mechanism for increased RDW levels (5, 26). Oxidative stress increases the fragility of red blood cells (27). It also decreases the rate of erythroid maturation and erythrocyte lifespan (26). These factors play an important role in CKD progression. Additionally, a subsequent study showed that higher RDW values are associated with microalbuminuria (13). In this study, there was

Tab. 4. Binary logistic regression analysis to identify predictors of stage 5 CKD.

| Characteristics | Unadjusted model | Adjusted model |
|----------------|-----------------|---------------|
|                | Hazard ratio (CI) | p | Hazard ratio (CI) | p |
| Age (years)    | 0.92 (0.61–1.18) | 0.341 | 0.89 (0.67–1.25) | 0.279 |
| Gender (female) | 0.93 (0.88–1.04) | 0.456 | 0.91 (0.99–1.13) | 0.337 |
| BMI (kg/m²)    | 1.03 (0.94–1.05) | 0.642 | 1.07 (0.98–1.27) | 0.561 |
| Diabetes       | 1.23 (1.14–1.66) | 0.003 | 1.29 (1.12–1.91) | 0.002 |
| Hemoglobin (g/dL) | 1.24 (1.09–1.56) | 0.003 | 1.33 (1.05–1.74) | 0.002 |
| Albumin (g/dL) | 1.43 (1.24–1.81) | 0.001 | 1.24 (1.16–1.57) | 0.001 |
| CRP (mg/dL)    | 1.25 (1.14–1.53) | 0.001 | 1.32 (1.22–1.76) | 0.001 |
| PTH            | 1.11 (1.02–1.24) | 0.114 |
| Ferritin       | 1.04 (0.94–1.16) | 0.271 |
| eGFR (ml/dk/1.73m²) | 1.18 (1.09–1.31) | 0.003 | 1.12 (1.06–1.26) | 0.128 |
| Proteinuria (mg/d) | 1.08 (0.97–1.16) | 0.123 | 1.04 (0.95–1.21) | 0.231 |
| RDW            | 1.33 (1.190–1.73) | 0.002 | 1.36 (1.24–1.72) | 0.0001 |

a: The crude effect of the variables on the outcome measure, b: The effect obtained when all variables participate in the regression equation, CI 95% confidence interval, BMI: body mass index, CRP: c-reactive protein, eGFR: estimated glomerular filtration rate, RDW: red blood cell distribution width.

Fig. 4. Kaplan–Meier curve of overall patient survival according to the RDW groups (log-rank test, p < 0.001).
no significant difference in proteinuria between normal and high RDW groups.

Another explanation is that a high RDW level might be directly harmful to the kidneys. An increased RDW is associated with decreased erythrocyte deformability, which can result in an impairment of microcirculation and hypoxia (15). Developing hypoxia increases the existing renal injury by increasing the glomerulosclerosis and tubular atrophy.

Solak et al. showed that RDW increases as CKD stage progresses while RDW is associated with endothelial dysfunction independent of inflammation, diabetes or anemia (12). In this study, RDW showed to be in a significant negative correlation with eGFR.

In pre-dialysis CKD patients, an increase in RDW level is strongly associated with low cholesterol level, while the latter has also been shown to be associated with increased mortality rates. (28). We detected no association between RDW and low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride values in CKD patients.

Vashistha et al. stated that RDW predicts mortality better than anemia parameters such as hemoglobin, ferritin, and transferrin saturation. (3). Patients with high RDW levels have lower albumin values, higher CRP values, but lower initial GFR values. In our study, the frequency of dialysis initiation was increased in the higher RDW group. Also, the baseline RDW at the beginning of follow-up of the patients who reached the primary or secondary endpoints were higher. In their 13-year study, where Yeh et al. followed patients with CKD, RDW was associated with all-cause mortality. (29). It has been reported that the underlying mechanisms for mortality are malnutrition, inflammation and atherosclerosis (29).

There are several potential limitations to this study. Firstly, this study was performed with a single-center, cross-sectional, retrospective analysis and with a relatively small number of patients, possibly affected by a selection bias. Secondly, the objective markers of inflammation have not been studied. Thirdly, the observational nature of the study does not explain the relationship between RDW and kidney outcomes. Despite these limitations, RDW can be useful for distinguishing patients with rapid progression from CKD patients with progressive GFR loss and high mortality rates, as well as for closer clinical follow-up because inflammation and oxidative stress parameters (IL-6, IFN-gamma) cannot be easily reached in daily practice.

In conclusion, there was a significant association between high RDW level and poor renal outcome. RDW values may predict the progression of CKD and the initiation time of dialysis. Also, RDW is a powerful and an independent prognostic marker for predicting all-cause mortality in patients with CKD in stage 3-4. The monitoring of RDW and monitoring of patients with high RDW levels may be beneficial for patients at high mortality risk. However, RDW is not specific for a particular disease. Therefore, the feasibility of its use in clinical applications is unclear.

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