Hematological Parameters and Clinical Features in Patients with Advanced Chronic Kidney Disease

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ABSTRACT

Background Hematological parameters like red cell distribution width (RDW) and mean platelet volume (MPV) were reported to be associated with inflammation, atherosclerosis, and chronic kidney disease (CKD) progression. In this study, we evaluated RDW and MPV along with clinical features in patients with advanced CKD. We also aimed to detect clues for causative relations concerning these parameters, renal function and comorbidities.

Methods Stage 3-5 CKD patients (627 total) were included (mean age 63.1 years, 48.3% male). Patients with malignancies, cirrhosis, infections, severe anemia, and systemic inflammation were excluded. Patients were evaluated for clinical features and grouped for comparison using median RDW and MPV. Linear regression models were generated to predict potential influences on RDW and MPV.

Results Mean estimated glomerular filtration rate (eGFR) was 27.3 mL/min/1.73m². Mean Charlson Comorbidity Index (CCI) score was 5.83 ± 2.06. Patients with high RDW (n = 303) were older with higher CRP and CCI, they also had lower eGFR, hemoglobin, and albumin (P < 0.001 for all). Patients with low MPV (n = 311) had lower eGFR, and platelet counts (P = 0.015 and 0.017). eGFR was negatively correlated with RDW after adjusting for age, gender and comorbidities. In a further adjusted model RDW was associated with CRP, CCI, hemoglobin and albumin (P < 0.05 for all), not with eGFR. MPV was positively correlated with eGFR in our adjusted, and fully adjusted regression models (P = 0.003).

Conclusion In this study, we found that high RDW is associated with comorbidity burden, anemia, and inflammatory status in patients with advanced CKD. Meanwhile, low MPV seems to be associated with worse renal function.

Key words blood platelets; chronic kidney failure; erythrocyte indices; mean platelet volume; red cell distribution width

Chronic kidney disease (CKD) is considered as an inflammatory state leading to atherosclerosis, metabolic abnormalities, and accelerated aging. Hematological parameters like red cell distribution width (RDW), and mean platelet volume (MPV) have been reported as measures of chronic inflammation, cardiovascular disease (CVD), anemia, and worse renal outcome, in CKD patients.1, 2 Therefore, it could be wise to use them as follow-up markers for some of our patients with CKD.

RDW measures the size variation of the circulating erythrocytes. Increased size variability of the erythrocytes is defined as anisocytosis, and demonstrated as high RDW values on blood count readings.3 High RDW was found to be associated with adverse renal outcome, CVD, and mortality in patients with CKD.1, 3, 4

MPV is a test that measures the size of the circulating platelets. Large platelets are generally younger with more reactive granules to induce adhesion and aggregation. Therefore, increased MPV was introduced as an indicator of platelet reactivity, atherosclerosis, and inflammatory status.2, 5 On the other hand, patients with severe inflammation and some patients with advanced CKD have been reported to have low MPV levels.6, 7

In the routine follow-up of patients with advanced CKD, we monitor them for complications like anemia, phosphorus retention, metabolic acidosis and loss of glomerular filtration. On the other hand, we do not have numeric follow-up markers that provide information about their inflammatory status and susceptibility to these disease related complications. Using markers of everyday clinical practice like RDW and MPV for this purpose could be quite advantageous. Yet, it is not clear which clinical outcomes are predominantly associated with hematological parameters in CKD patients. New studies could make it possible to integrate RDW and MPV.
MPV in the follow-up of CKD patients.

In this study, we evaluated these hematological parameters along with clinical features in patients with advanced CKD. We also aimed to detect some clues for causative relations concerning these hematological parameters, renal function and comorbidity.

MATERIALS AND METHODS

Recruitment and data collection

Our retrospective, cross-sectional study included 627 patients with stage 3-5 CKD who admitted to our hospital in the last 2 years (366 male, 261 female; mean age: 63.18 ± 14.94 years). Exclusion criteria were: patients younger than 18 years of age, patients with missing data, patients with a diagnosis of malignant disease, liver cirrhosis, congestive heart failure, thyroid dysfunction, those with active infection, having the diagnosis of hematologic diseases, and/or severe anemia (hemoglobin < 8 gr/dL), active systemic inflammatory conditions, and having corticosteroid therapy.

Laboratory values were obtained from the data bank. Patients were divided into CKD stages using their estimated glomerular filtration rates (eGFR) calculated by MDRD (Modification of Diet in Renal Disease) formulation. For HD patients we selected the laboratory data of their mid-week pre-dialytic values. Accordingly, 280 patients were in stage 3, 172 in stage 4, and 175 were in stage 5 (86 in maintenance hemodialysis, 18 in chronic peritoneal dialysis) CKD. The comorbidity scores of our CKD patients were calculated using the Charlson Comorbidity Index (CCI). CVD was defined as the history of cardiac and/or peripheral vascular disease, and hypertension was defined as the use of one or more anti-hypertensive drugs. The reference range values for RDW and MPV in our laboratory were 11.5-14.5%, and 7-11 fl respectively. CKD patients were also grouped for comparison using the median values for RDW, and MPV. The study was approved by the institutional ethics review board (IRB number: 2019/18-10), and conducted between October and December of 2019.

Statistical analysis

We analyzed the data using SPSS software, version 19.0 (IBM Corp., Armonk, NY). Values were expressed as mean ± standard deviation or percentages. Any P value less than 0.05 were accepted as statistically significant. Categorical data were compared using chi-square test or Fisher’s exact test. Shapiro-Wilk test was used to check the normality of distribution for continuous variables. Differences between continuous variables were compared by the Student’s t-test and the Mann Whitney-U test. Pearson’s and Spearman’s tests were used for correlation analysis. Multiple comparisons of RDW and MPV were conducted by Tukey’s test. We generated linear regression models with Enter method to predict the potential influences on RDW and MPV. The first model was used to show the effect of eGFR on RDW and MPV. The second model included adjustments for demographics and comorbid conditions, and the final model was designed to reveal the influences of various confounders on hematological parameters.

RESULTS

Hematological parameters and clinical data

The mean RDW was 14.79 ± 1.99, and the mean MPV was 9.73 ± 1.55 in our patients with stage 3-5 CKD. The number of patients with the diagnosis of diabetes mellitus (DM) and coronary artery disease (CAD) were 291 (46.4%) and 242 (38.6%), respectively. The mean CCI score was 5.83 ± 2.06. The mean hemoglobin and platelet values were 12.02 ± 2.21 g/dL, and 238.49 ± 79.20 x10³/mm³, respectively. Demographics, clinical features, and laboratory values within the study population is presented in Table 1.

Comparison of hematological parameters and clinical data

In our study stage 3-5 CKD patients with RDW above the median value (14.5%) were older with increased frequencies for DM and CVD. They had lesser male gender predominancy, lower mean eGFR, albumin, and hemoglobin values, but higher mean CCI scores and CRP values. On the contrary, patients with MPV below the median value (9.9 fl) had lower mean eGFR, higher serum creatinine levels, and higher platelet counts (P < 0.05 for all, Table 2).

RDW was negatively correlated with eGFR, albumin, and hemoglobin levels, it was also positively correlated with patient age, CCI score, and CRP levels in our patients with advanced CKD. On the other hand, MPV was positively correlated with eGFR, albumin, and hemoglobin levels, it was also negatively correlated with CRP levels and platelet count (P < 0.05 for all, Table 3).

CKD patients with a diagnosis of CAD had higher RDW levels (15.21 ± 2.17 > 14.52 ± 1.82, P < 0.001). Mean MPV was not different for CKD patients with a diagnosis of CAD compared with those without CAD (9.70 ± 1.71 vs 9.75 ± 1.44, P = 0.732). Multiple comparisons of RDW and MPV according to CKD stages revealed some significant differences. RDW was significantly higher in patients with stage 5 CKD compared to patients with stage 3 CKD (15.14 ± 1.85 vs 14.62 ± 2.00, P = 0.017), but not to those with stage 4 CKD (15.14 ± 1.85 vs...
Table 1. Demographics, clinical features, and laboratory values within the study population

| Variable              | CKD patients (n = 627) |
|-----------------------|------------------------|
| Age, years            | 63.18 ± 14.94          |
| Gender, M/F; n (%)    | 366 (58.4)/261 (41.6)  |
| Body mass index, kg/m²| 26.23 ± 4.48           |
| CKD stage 3/4/5; n (%)| 280 (44.6)/172 (27.4)/175 (28.0) |
| eGFR, mL/min/1.73 m²  | 27.36 ± 1.51           |
| DM; n (%)             | 291 (46.4)             |
| CVD; n (%)            | 242 (38.6)             |
| Hypertension; n (%)   | 505 (80.5)             |
| RDW mean/median, %    | 14.79 ± 1.99/14.50     |
| High RDW; n (%)       | 303 (48.3)             |
| MPV mean/median, fl   | 9.73 ± 1.55/9.90       |
| Low MPV, n (%)        | 311 (49.6)             |
| CCI score             | 5.83 ± 2.6             |
| Haemoglobin, g/dL     | 12.02 ± 2.21           |
| Platelet count, X10⁹/mm³| 238.49 ± 79.20        |
| Creatinine, mg/dL     | 3.23 ± 2.21            |
| CRP, mg/L             | 19.08 ± 27.96          |
| Albumin, g/dL         | 3.89 ± 0.54            |
| Ca × P product, mg²/dL²| 35.82 ± 10.46         |
| SBP, mmHg             | 139.83 ± 27.96         |

Data presentation; mean ± SD. CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; F, female; M, male; MPV, mean platelet volume; P, phosphorus; RDW, red cell distribution width; SBP, systolic blood pressure.

DISCUSSION

Recent studies indicated some relations between routine hematological parameters and adverse clinical outcomes in patients with CKD.²,⁴,¹⁰,¹¹ New studies might help to find the causality of such relations, whether they are predominantly associated with renal anemia, chronic inflammation or residual renal function.

CKD is a condition that leads to anemia, endothelial dysfunction, systemic inflammation, malnutrition, and accelerated atherosclerosis. Altogether, these conditions may affect the maturation of erythroid cell lines due to microvascular hypoxia and chronic cytokine exposure in the bone marrow.¹,¹¹,¹² Therefore, it is probable that patients with advanced CKD would have elevated RDW. Platelets that are larger and more reactive may increase the tendency to vascular thrombosis in patients with CKD who usually have an unhealthy endothelium. MPV is usually increased in chronic inflammatory conditions including CKD, but the opposite is also possible in severe inflammatory status.⁵,⁷,¹⁰

RDW and MPV might become easy to use follow-up markers in patients with CKD, but what kind of risk should we attribute to CKD patients first, when we take these hematological parameters into account? Possible alternatives are; accelerated progression of CKD, increased probability of cardiovascular events, and emerging of a condition called malnutrition-inflammation syndrome. The relations concerning these hematological parameters and adverse outcomes in patients with CKD are thought to be associated with chronic inflammation, oxidative stress, and malnutrition. Yet, the exact causal link or the order of importance is not solved.

In the absence of systemic inflammation, RDW could be a marker for the differential diagnosis of microcytic anemia. However, in patients with advanced CKD, there is more to it than that because RDW seems to be a marker of inflammatory and nutritional status in this population.¹³,¹⁴ High RDW was found to be associated with all-cause and cardiovascular mortality in CKD patients after adjusting for hemoglobin levels.¹,¹²,¹⁴

A study by Lu et al. revealed a result that the effect of RDW on CVD was independent of hemoglobin and also creatinine levels in stage 1-5 CKD patients.⁴ Interestingly, in the fully adjusted model of our study, RDW was not associated with CVD along with eGFR, but it was associated with the comorbidity score, CRP, albumin, and hemoglobin values. As in our patients, when CKD has already progressed to advanced stages, adverse conditions such as systemic inflammation, comorbidity burden and renal anemia increase the risk for CVD and all-cause mortality.¹⁵,¹⁶ We think that high RDW could be the reflection of this cumulative trend.

mpv was significantly lower in patients with stage 5 CKD compared to patients with stage 3 and stage 4 CKD (9.34 ± 1.53 vs 9.88 ± 1.39, P = 0.001), (9.34 ± 1.53 vs 9.88 ± 1.74, P = 0.003), respectively (Fig. 1).

We used a stepwise linear regression analysis model for eGFR and other potential influences on RDW and MPV. In the first adjusted model (controlled for age, gender, DM, CVD, and HT), both RDW and MPV were still associated with eGFR. In a further adjusted model controlled for multiple possible confounders, RDW was not associated with eGFR, but it was associated with CCI score, CRP, albumin, and hemoglobin values. On the other hand, MPV was associated with eGFR and the platelet count in the fully adjusted regression model (P < 0.05 for all, Table 4).
encircled around inflammatory stress in patients with advanced CKD. In another study by Yonemoto et al. CKD patients with high RDW were older with higher prevalence of prior CVD, higher CRP levels, lower eGFR, albumin and hemoglobin levels. 3 In addition to their results, our CKD patients with high RDW had higher prevalence of DM along with higher comorbidity scores, and male gender predominancy.

Studies comparing CKD patients with healthy individuals have revealed larger platelet volumes in patients with CKD. 5, 10 Thus, large and reactive platelets might contribute to the increased incidence of vascular disease. In fact, some studies have demonstrated a relation between increased platelet size and CVD in CKD patients. 10, 17 On the other hand, as CKD progresses to end stage renal disease (ESRD), the presence of uremic toxins may lead to a qualitative decrease in platelet functions. 2 Therefore, we might assume that the size

| Variable | RDW \(\leq 14.50\%\) \((n = 324)\) | RDW > 14.50\% \((n = 303)\) | \(P\) value | MPV \(\geq 9.90\) fl \((n = 316)\) | MPV < 9.90 fl \((n = 311)\) | \(P\) value |
|----------|-------------------------------|-------------------------------|--------------|-------------------------------|-------------------------------|--------------|
| Age, years | 61.13 ± 14.94 | 65.38 ± 14.64 | < 0.001 | 62.02 ± 14.64 | 64.36 ± 15.19 | 0.050 |
| Male, n(\%) | 210 (64.8) | 156 (51.4) | 0.001 | 177 (56.0) | 189 (60.7) | 0.227 |
| eGFR, mL/min | 29.95 ± 15.79 | 24.59 ± 14.74 | < 0.001 | 28.85 ± 15.33 | 25.85 ± 15.58 | 0.015 |
| DM, n(\%) | 129 (39.8) | 162 (53.4) | 0.001 | 154 (48.7) | 137 (44.0) | 0.240 |
| CVD, n(\%) | 97 (29.9) | 145 (47.8) | < 0.001 | 127 (40.1) | 115 (36.9) | 0.409 |
| HT, n(\%) | 254 (78.4) | 251 (82.8) | 0.160 | 253 (80.0) | 252 (81.0) | 0.760 |
| CCI | 5.43 ± 2.03 | 6.26 ± 1.99 | < 0.001 | 5.76 ± 2.01 | 5.90 ± 2.10 | 0.414 |
| Hemoglobin | 12.6 ± 2.14 | 11.30 ± 2.06 | < 0.001 | 12.19 ± 2.20 | 11.85 ± 2.21 | 0.61 |
| Platelets | 241.53 ± 68.36 | 235.25 ± 89.34 | 0.326 | 231.00 ± 78.16 | 246.10 ± 79.64 | 0.017 |
| Creatinine | 3.01 ± 2.16 | 3.47 ± 2.25 | 0.009 | 2.98 ± 2.01 | 3.49 ± 2.38 | 0.004 |
| CRP | 14.47 ± 24.40 | 24.02 ± 30.59 | < 0.001 | 17.72 ± 28.04 | 20.47 ± 27.85 | 0.218 |
| Albumin | 4.01 ± 0.46 | 3.76 ± 0.57 | < 0.001 | 3.92 ± 0.52 | 3.86 ± 0.54 | 0.165 |
| Ca × P | 35.17 ± 10.19 | 36.52 ± 10.72 | 0.108 | 35.43 ± 9.99 | 36.22 ± 10.93 | 0.344 |
| SBP, mmHg | 139.15 ± 27.04 | 140.56 ± 27.50 | 0.545 | 138.07 ± 25.91 | 141.71 ± 28.54 | 0.118 |

Data presentation; mean ± SD. CCI, Charlson Comorbidity Index; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HT, hypertension; MPV, mean platelet volume; P, phosphorus; RDW, red cell distribution width; SBP, systolic blood pressure.

| Variable | \(r\) | \(P\) | \(r\) | \(P\) |
|----------|------|------|------|------|
| Age | 0.172 | < 0.001 | -0.035 | 0.386 |
| eGFR | -0.171 | < 0.001 | 0.147 | < 0.001 |
| CCI | 0.230 | < 0.001 | -0.024 | 0.552 |
| Hemoglobin | -0.329 | < 0.001 | 0.102 | 0.010 |
| Platelet count | -0.077 | 0.054 | -0.127 | 0.001 |
| Creatinine | 0.122 | 0.002 | -0.144 | < 0.001 |
| CRP | 0.359 | < 0.001 | -0.116 | 0.004 |
| Albumin | -0.308 | < 0.001 | 0.080 | 0.046 |
| Ca × P product | 0.054 | 0.180 | -0.044 | 0.271 |
| SBP | 0.042 | 0.321 | -0.050 | 0.243 |

CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MPV, mean platelet volume; P, phosphorus; RDW, red cell distribution width; SBP, systolic blood pressure.
and reactivity of the platelets in patients with CKD might differ according to the CKD stage and inflammatory status.

High MPV was also found to be associated with worse renal function in patients with pre-dialytic stages of CKD, and higher extent of coronary disease in patients with ESRD.², 5, 18 However, some studies have reported decreased MPV values, particularly in patients with ESRD.², 19 In our study, stage 3-5 CKD patients with lower MPV had lower mean eGFR and, MPV was inversely correlated with serum CRP levels. On top of that, our fully-adjusted regression model supported the positive correlation between MPV and eGFR. We would like to interpret our results as the reflection of systemic inflammation and uremic state in our patients with advanced CKD.

This study reached a satisfactory sample size even though we used extensive exclusion criteria. Nevertheless, there were some limitations to it. The cross-sectional design of our study seems to be its’ main limitation. DM is a condition that may affect RDW values, but it is the most common etiology for CKD. Therefore, instead of excluding CKD patients with DM we tried to determine its’ effects in a regression model along with other comorbidities. The presence of other possible confounders that we were not able to take into account, such as vitamin B12 and folic acid levels of the patients and the use of the medications like ticlopidine and clopidogrel could be another limitation. The use of erythrocyte stimulating agents is also a limitation that may affect the RDW results, but most of the patients with advanced CKD receive these medications at anemic intervals.

In conclusion, high RDW was associated with many clinical features including worse renal function, older age, male gender, DM, CVD, comorbidity score, anemia, and increased CRP levels in patients with advanced CKD in this study. However, after controlling for multiple confounders, our regression model revealed that higher RDW levels could more likely be the reflection of comorbidity burden, anemia, and inflammatory status of the CKD patients. Meanwhile, CKD patients with low MPV had a worse renal function, and higher platelet counts. Low MPV was still associated with low eGFR after controlling for multiple confounders. We think that patients with advanced CKD, especially those who have ESRD along with high comorbidity burden and chronic inflammation might have low instead of normal or high MPV values. MPV also showed correlations with CRP and albumin levels, but our data was not enough to deduce an important relation.

Patients with advanced CKD are in an inflammatory state due to increased cytokine production, oxidative stress, vitamin D deficiency, malnutrition, and susceptibility to infections. This inflammatory state contributes to problems like atherosclerosis, vascular calcification, anemia, sarcopenia, and progression of CKD itself. Hematological parameters like RDW and MPV seem to be affected by not one, but a combination of some of these unappealing conditions. Therefore, RDW and MPV could be promising parameters to indicate CKD patients with a higher probability to reach the adverse outcomes that are related to systemic inflammation.

The authors declare no conflict of interest.
## Table 4. Multiple linear regression models in CKD patients generated for potential influences on RDW and MPV

| Variable | Unadjusted | Adjusted | Further adjusted |
|----------|------------|----------|------------------|
|          | P  | 95% CI | P  | 95% CI | P  | 95% CI |
| eGFR     | 0.002 | –0.026 ~ –0.006 | 0.001 | –0.027 ~ –0.006 | 0.796 | –0.010 ~ 0.013 |
| Age      | –   | –       | 0.002 | 0.007 ~ 0.029 | 0.649 | –0.017 ~ 0.011 |
| Gender   | –   | –       | 0.011 | 0.101 ~ 0.760 | 0.066 | –0.020 ~ 0.630 |
| DM       | –   | –       | 0.217 | –0.120 ~ –0.530 | 0.572 | –0.423 ~ 0.234 |
| CVD      | –   | –       | 0.002 | 0.209 ~ 0.909 | 0.204 | –0.121 ~ 0.566 |
| HT       | –   | –       | 0.998 | –0.401 ~ 0.402 | 0.541 | –0.261 ~ 0.497 |
| CCI      | –   | –       | –    | –       | 0.003 | 0.058 ~ 0.278  |
| Hb       | –   | –       | –    | –       | 0.002 | –0.221 ~ –0.049 |
| CRP      | –   | –       | –    | –       | <0.001 | 0.005 ~ 0.016 |
| Albumin  | –   | –       | –    | –       | <0.001 | –0.964 ~ –0.332 |

| Variable | Unadjusted | Adjusted | Further adjusted |
|----------|------------|----------|------------------|
|          | P  | 95% CI | P  | 95% CI | P  | 95% CI |
| eGFR     | 0.002 | 0.004 ~ 0.020 | <0.001 | 0.009 ~ 0.025 | 0.003 | –0.05 ~ 0.024 |
| Age      | –   | –       | 0.200 | –0.015 ~ 0.003 | 0.179 | –0.015 ~ 0.003 |
| Gender   | –   | –       | 0.024 | 0.040 ~ 0.567 | 0.008 | 0.094 ~ 0.641 |
| DM       | –   | –       | 0.644 | –0.321 ~ 0.199 | 0.783 | –0.226 ~ 0.299 |
| CVD      | –   | –       | 0.909 | –0.296 ~ 0.263 | 0.894 | –0.301 ~ 0.263 |
| HT       | –   | –       | 0.134 | –0.076 ~ 0.566 | 0.124 | –0.069 ~ 0.570 |
| Hb       | –   | –       | –    | –       | 0.470 | –0.046 ~ 0.099 |
| Plt      | –   | –       | –    | –       | 0.001 | –0.004 ~ –0.001 |
| CRP      | –   | –       | –    | –       | 0.178 | –0.008 ~ 0.001 |
| Albumin  | –   | –       | –    | –       | 0.402 | –0.153 ~ 0.382 |

CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HT, hypertension; MPV, mean platelet volume; Plt, platelet count; RDW, red cell distribution width.

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