Red cell distribution width and renal outcome in patients with non-dialysis-dependent chronic kidney disease

Sayoko Yonemoto[1,2], Takayuki Hamano[3]*, Naohiko Fujii[2], Karin Shimada[1], Satoshi Yamaguchi[1], Ayumi Matsumoto[1], Keiichi Kubota[1], Nobuhiro Hashimoto[1], Tatsufumi Oka[1], Masamitsu Senda[1], Yusuke Sakaguchi[3], Isao Matsui[1], Yoshitaka Isaka[1]

1 Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan,
2 Department of Internal Medicine, Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Hyogo, Japan,
3 Department of Inter-Organ Communication Research in Kidney Disease, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

* hamatea@kid.med.osaka-u.ac.jp

Abstract

Higher red cell distribution width (RDW) has been reported to predict mortality among patients with various diseases, including chronic kidney disease (CKD). However, whether RDW is associated with renal outcome remains unclear. We investigated the relationship between RDW and renal outcome in patients with non-dialysis-dependent CKD (NDD-CKD). This prospective, observational study of patients with CKD was conducted at a single nephrology department. First, we performed regression analyses for the decline in estimated glomerular filtration rate (eGFR) during the first 3 months of observation to determine its short-term association with RDW. Next, we categorized baseline RDW into two groups by its median (13.5%) and performed Cox regression analyses to investigate whether higher RDW was an independent predictor of renal outcomes defined as a composite of the initiation of dialysis and doubling of the serum creatinine concentration. Furthermore, we repeated the analyses to confirm whether the transition of the RDW category during the first 3 months would also predict renal outcomes. We enrolled 703 patients. Baseline RDW showed a non-linear association with the eGFR decline during the first 3 months, with a greater negative correlation at the lower end of the RDW distribution. Over a median follow-up of 1.8 years, 178 patients (25.3%) reached the renal endpoint. Multivariable Cox regression analyses showed that patients with higher RDW had a higher risk of developing renal outcomes (adjusted hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 1.05–2.07) than did those with lower RDW. Furthermore, patients with sustained, higher RDW demonstrated a significantly higher risk than did those with consistently lower RDW (adjusted HR: 1.65, 95% CI: 1.02–2.67). In conclusion, higher RDW was independently associated with worse renal outcome in patients with NDD-CKD. RDW could be an additional prognostic marker of the progression of CKD.

Introduction

Red cell distribution width (RDW) is a measure of the range of variation in the red cell volume, and it is routinely reported as a part of the standard complete blood count. RDW has traditionally been used to diagnose different types of anemia, and elevated RDW is considered a marker of malnutrition (iron, vitamin B_{12}, and folate deficiencies), inflammation, and other disturbances in hematopoiesis [1].

According to recent studies [2–7], RDW may be associated with mortality in various populations, including patients with kidney disease, and could be a new, independent predictor in such patients. In dialysis patients, higher RDW was associated with mortality, and was a stronger predictor of death than were traditional laboratory markers of anemia, such as transferrin saturation (TSAT) and ferritin levels [8, 9]. In a study from Taiwan on patients with chronic kidney disease (CKD) stages 3–5, higher RDW was associated with death from all-causes, cardiovascular disease (CVD), and infections [10]. However, little is known about the relationship between RDW and renal outcome, including the progression of CKD.

Several studies have already demonstrated that anemia is a strong predictor of the progression of CKD [11, 12]. Since RDW is a marker of erythropoiesis, we hypothesized that RDW would predict not only mortality, but also renal outcome. To test this hypothesis, we investigated the relationship between RDW and renal outcome in patients with non-dialysis-dependent CKD (NDD-CKD).

Materials and methods

Ethical considerations

The study was performed according to the ethical principles of the Declaration of Helsinki and received ethical approval for the use of an opt-out methodology by the ethics committee of Hyogo Prefectural Nishinomiya Hospital (approval number: H28-32), based on no additional burden to the patients in clinical practice.

Study population

We enrolled consecutive outpatients with NDD-CKD who were seen between September 1, 2012 and November 30, 2016 in the nephrology department of Hyogo Prefectural Nishinomiya Hospital, Hyogo, Japan. We excluded patients who were younger than 18 years, those without biochemical data, those with an observation period that was shorter than 30 days, and those who had biopsy-proven hematologic diseases. All of the patients' information and laboratory data were de-identified before analyses.

Data collection and laboratory measurement

Data on baseline characteristics, including diabetes mellitus, prior CVD (history of percutaneous coronary intervention, cerebral hemorrhage, and cerebral infarction), medications (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, erythropoiesis stimulating agents [ESAs], and iron supplements), and blood pressure (BP), were collected from patients' medical records. The parameters of blood chemistry were measured with standard automated techniques. We calculated the estimated glomerular filtration rate (eGFR) based on inulin clearance, according to the following standard Japanese formula: $194 \times \text{creatinine}^{-1.094} \times \text{age}^{-0.287}$ (if female: $\times 0.739$) [13]. RDW-CV, which was calculated by dividing the standard deviation (SD) of the mean cell size by the mean cell volume of red cells and multiplying by 100 to convert the value to a percentage, was routinely reported, along with the complete blood count. We used an automatic hematology analyzer (ADVIA2020, Siemens,

München); the reference range for RDW-CV in our laboratory is 11.5%-14.5%. Urinary protein was measured semi-quantitatively with a dipstick test.

Endpoint

Patients were followed until the study end date (May 31, 2017), death, or loss to follow-up. The endpoint for the study was the initiation of dialysis or doubling of the serum creatinine concentration, whichever occurred first.

Statistical analyses

Descriptive data were summarized using proportions, means with SDs, and medians with inter-quartile ranges (IQRs), as appropriate. Between-group differences were analyzed using Student's or Welch's t test and the Mann-Whitney U test when required. Categorical variables were compared using the Chi-squared test or Fisher's exact test when the expected numbers were small. Variables with right-skewed distribution were log-transformed before being applied to analyses. The trend analysis of RDW across CKD stages was performed by using Jonckheere-Terpstra test. Pearson's correlation coefficients were calculated to determine the strength of associations between RDW and other laboratory parameters. For the regression analyses, we used multivariable regression, incorporating restricted cubic splines with 3 knots to investigate the potentially non-linear association between RDW and the decline in eGFR during the first 3 months of observation (defined as [eGFR at 3 months]–[eGFR at baseline]). RDW was categorized into two groups based on the median of baseline RDW (low RDW: RDW < 13.5%; high RDW: RDW ≧ 13.5%). We converted eGFR decline during the first 3 months into a binary variables that indicated negative or non-negative changes in eGFR and performed the multivariable logistic regression analysis to investigate the association between RDW and short-term eGFR decline. For survival analyses, Kaplan-Meier survival curves were generated to compare renal outcomes of patients in the two RDW categories, and the log-rank test was performed to assess the statistical significance. The relationship between RDW and renal outcomes was examined using the Cox proportional hazards model. The covariates for adjustment included (a) RDW only: unadjusted model; (b) RDW, age, sex, diabetes, prior CVD, systolic BP, and medications: adjusted model; and (c) all variables: fully adjusted model. For sensitivity analyses, we applied the Fine and Gray model to analyze the competing risk, considering death as a competing risk for the renal endpoint. Next, the propensity score (PS) of the high RDW was estimated by the logistic regression using parameters at baseline. We performed 1:1 PS matching using the greedy nearest-neighbor algorithm, with a caliper width of 0.25 of the SD of the PS's logit and evaluated the statistical significance of the baseline RDW category as a predictor of renal outcomes. Furthermore, to evaluate the association between the transition of the RDW category and the renal endpoint, we also collected data on RDW at 3 months after the baseline. We divided patients into four groups according to the fluctuation patterns of RDW: (1) low RDW at baseline to low RDW at 3 months: L-L; (2) high-to-low: H-L; (3) low-to-high: L-H; and (4) high-to-high: H-H. We then performed Cox regression analyses to determine the composite renal outcomes. A two-tailed P-value of < 0.05 was considered significant. The statistical analyses were performed using Stata/SE 13.1 software (Stata Corp., College Station, TX).

Results

Patient characteristics

The baseline characteristics of the patients in this study are shown in Table 1. The mean age was 70.4 years (SD: 13.6 years), and about 40% of the patients were female. The proportions of

Table 1. Baseline characteristics categorized by the median of RDW.

Variables	All patients (N = 703)	Low RDW (<13.5) (N = 328)	High RDW (≥13.5) (N = 375)	P value
RDW (%)	13.9±1.41	12.8±0.42	14.9±1.29	<0.001
Age (years)	70.4±13.6	68.7±13.7	71.9±13.2	0.002
Gender (female)	268 (38.1%)	132 (39.1%)	136 (36.2%)	0.279
Diabetes Mellitus	236 (33.6%)	102 (31.1%)	134 (35.7%)	0.194
ESA therapy	102 (14.5%)	25 (7.6%)	77 (20.5%)	<0.001
Oral iron therapy	58 (8.3%)	17 (5.2%)	41 (10.9%)	0.006
ACE-I	53 (7.5%)	27 (8.2%)	26 (6.9%)	0.515
ARB	388 (54.9%)	180 (54.9%)	206 (54.9%)	0.988
Prior CVD	111 (15.8%)	39 (11.9%)	72 (19.2%)	0.008
sBP (mmHg)	140±22.0	138±20.1	141±23.4	0.032
dBP (mmHg)	76.2±13.4	77.2±12.5	75.3±14.1	0.051
eGFR (mL/min/1.73m^2)	29.9±19.5	33.7±19.8	26.7±18.7	<0.001
CKD stage				
CKD stage 1&2 (eGFR ≥60)	60 (8.6%)	37 (11.3%)	23 (6.1%)	<0.001
CKD stage 3 (eGFR 30–59)	227 (32.3%)	124 (37.8%)	103 (27.5%)	
CKD stage 4 (eGFR 15–29)	247 (35.1%)	117 (35.7%)	130 (34.7%)	
CKD stage 5 (eGFR <15)	169 (24.0%)	50 (15.2%)	119 (31.7%)	
Hemoglobin (g/dL)	11.6±2.04	12.2±1.87	11.0±2.00	<0.001
MCV (fL)	93.6±6.12	93.7±4.57	93.5±7.21	0.691
Albumin (g/dL)	3.73±0.63	3.88±0.59	3.60±0.64	<0.001
CRP (mg/dL)	0.09 (0.04, 0.29)	0.07 (0.03, 0.19)	0.12 (0.05, 0.39)	<0.001
TSAT (%)	28.1±11.9	29.6±11.1	26.8±12.5	0.002
Ferritin (ng/mL)	87 (44, 158)	91 (51, 155)	83 (37, 159)	0.014
Proteinuria (≥(2+))	278 (39.6%)	101 (30.7%)	177 (47.3%)	<0.001

Values are n (%), means±SDs, and medians (1st quartiles, 3rd quartiles), RDW: red cell distribution width, ESA: erythropoiesis stimulating agents, ACE-I: angiotensin converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CVD: cardiovascular disease, sBP: systolic blood pressure, dBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, CKD: chronic kidney disease, MCV: mean corpuscular volume, CRP: C-reactive protein, TSAT: transferrin saturation, Proteinuria: measured by the dip stick tests

patients with diabetes mellitus and prior CVD were 33.6% and 15.8%, respectively. Approximately 15% and 8% patients were treated with ESAs and iron supplements, respectively. The mean eGFR was 29.9 mL/min/1.73m^2 (SD: 19.5 mL/min/1.73m^2), and most patients (91.4%) had CKD stages 3, 4, or 5. The mean hemoglobin level was 11.6 g/dL (SD: 2.04 g/dL), and the median RDW was 13.5% (IQR: 12.9%-14.6%) (Fig 1). The patient characteristics across RDW categories showed that the patients in the high RDW group were more likely to be older, receive ESA therapy and iron supplements, have a history of CVD, and be proteinuric than were those in the low RDW group. They also had lower eGFR, hemoglobin, serum albumin, TSAT, and serum ferritin levels, and higher CRP levels than did those in the low RDW group. Fig 2 shows that RDW increased as the CKD stages progressed (p for trend < 0.001).

Univariate correlations between RDW and other laboratory parameters

Table 2 shows the univariate correlations between RDW and other laboratory parameters. RDW had a significant, positive correlation with age and log-transformed CRP, whereas there were negative correlations between RDW and hemoglobin, mean corpuscular volume, eGFR, serum albumin, TSAT, serum iron, log-transformed ferritin, and diastolic BP. RDW had the
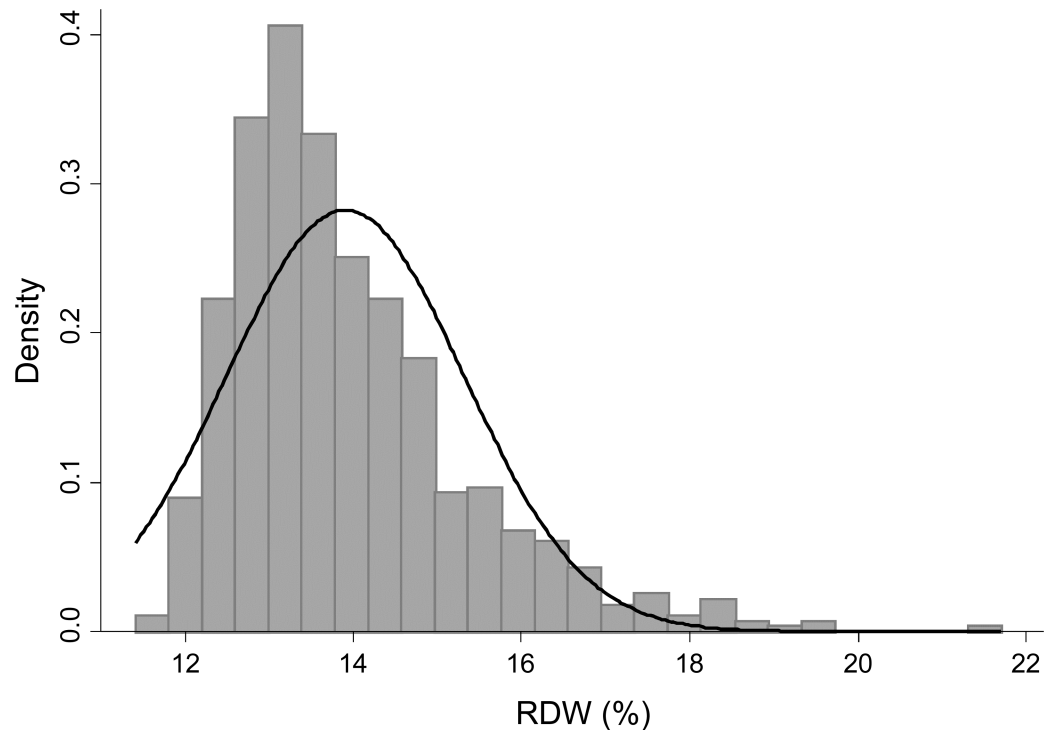
Fig 1. Histogram of baseline RDW. Histogram of baseline RDW of all patients (N = 703); the corresponding normal distribution is shown in the bar chart and density plot. The median RDW was 13.5%.

strongest, statistically significant, negative correlation with hemoglobin and, to the lesser extent, with eGFR, serum albumin, TSAT, and serum iron levels in patients with NDD-CKD.

Association between RDW and short-term eGFR decline

The eGFR decline during the first 3 months of observation had a non-linear association with baseline RDW, with a greater negative correlation in the lower half of the RDW distribution than in the greater half (Fig 3). The inflection point was located near the median of baseline RDW, which was the cut-off value of the RDW category. The multivariable logistic regression analysis showed that the patients in the high RDW group had a higher risk of worsened renal function than did those in the low RDW group (Odds Ratio: 1.49, 95% confidence interval [CI]: 1.05–2.13).

Association between RDW and long-term renal outcome

The median follow-up period was 665 days (IQR: 345–910 days). During the observational period, 178 patients (25.3%) experienced renal outcomes (initiation of dialysis only [n = 41], doubling of the serum creatinine concentration only [n = 64], or both [n = 73]). The Kaplan-Meier survival curves of renal outcomes showed that the high RDW was associated with an increased risk compared with the low RDW (Fig 4). In the unadjusted and adjusted Cox proportional hazards models, the high RDW was consistently associated with worsened renal outcomes than did the low RDW (fully adjusted hazard ratio [HR]: 1.47, 95% CI: 1.05–2.07, Table 3). Twenty-five patients (3.6%) died without achieving the renal endpoint. Even after considering the competing risk of death, we observed a consistent, statistically significant association between the high RDW and renal outcomes (fully adjusted sub-distribution-HR: 1.47,
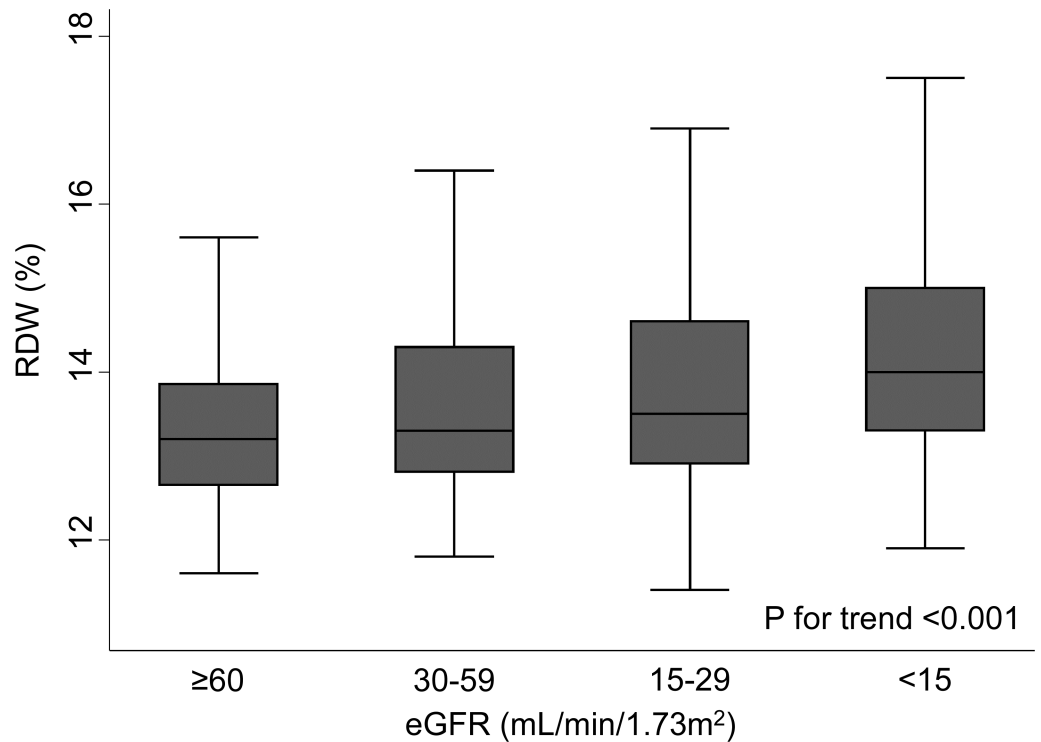
Fig 2. Box plots of RDW according to the eGFR categories. The box plot shows that the median RDW increased as CKD progressed. Outliers were omitted in this figure. Abbreviations: RDW, red cell distribution width; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Table 2. Univariate correlations between RDW and other laboratory parameters.

Variables	Coefficient	95% CI	P value
Age (years)	0.142	(0.068, 0.213)	<0.001
Hemoglobin (g/dL)	-0.367	(-0.430, -0.302)	<0.001
MCV (fL)	-0.092	(-0.165, -0.018)	0.015
Platelet (10^4/μL)	0.030	(-0.044, 0.104)	0.429
eGFR (mL/min/1.73m^2)	-0.177	(-0.248, -0.105)	<0.001
Albumin (g/dL)	-0.215	(-0.285, -0.144)	<0.001
Log CRP (mg/dL)	0.139	(0.066, 0.211)	<0.001
TSAT (%)	-0.197	(-0.267, -0.125)	<0.001
Fe (μg/dL)	-0.252	(-0.320, -0.182)	<0.001
TIBC (μg/dL)	-0.036	(-0.110, 0.038)	0.339
Log Ferritin (ng/mL)	-0.149	(-0.221, -0.076)	<0.001
sBP (mmHg)	0.067	(-0.007, 0.140)	0.077
dBP (mmHg)	-0.081	(-0.154, -0.007)	0.032

RDW: red cell distribution width, MCV: mean corpuscular volume, eGFR: estimated glomerular filtration rate, CRP: C-reactive protein, TSAT: transferrin saturation, TIBC: total iron binding capacity, sBP: systolic blood pressure, dBP: diastolic blood pressure, CI: confidence interval
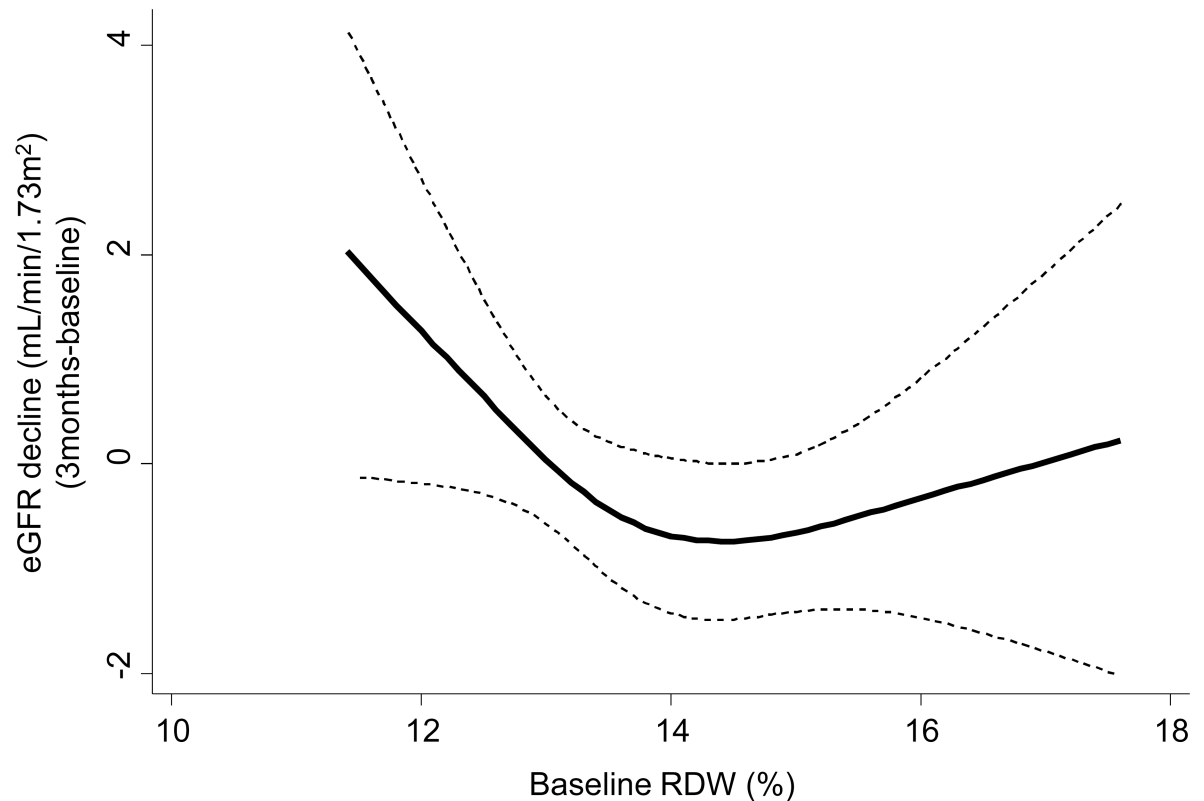
Fig 3. Restricted cubic spline curves for eGFR decline during the first 3 months across baseline RDW. A non-linear association between decline in the eGFR during the first 3 months and baseline RDW was observed in the multivariable regression analysis (adjusted for age, sex, diabetes mellitus, baseline eGFR, and hemoglobin, albumin, C-reactive protein, and proteinuria levels). The inflection point was located near the median of baseline RDW (13.5%). Abbreviations: RDW, red cell distribution width; eGFR, estimated glomerular filtration rate.

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95% CI: 1.03–2.10). Furthermore, we performed 1:1 PS matching, in which 482 patients (S1 Table) were successfully matched. The HR of the high RDW for renal outcomes remained significant (HR: 1.68, 95% CI: 1.16–2.41).

Association between the transition of the RDW category and renal outcome

We investigated the transition of the RDW category during the first 3 months of observation. About one-third of the patients were categorized into the L-L group, and 45% were categorized into the H-H group. The remaining 25% transitioned to the other RDW category at 3 months (8.5% and 16.5% in the L-H and H-L groups, respectively). As shown in Fig 5, survival curves of renal outcomes were significantly different among these groups (p<0.001), with the highest risk in the H-H group. As seen in the multivariable Cox regression analyses, patients in the H-H group showed a significantly higher risk of renal outcomes than did those in the L-L group (fully adjusted HR: 1.65, 95% CI: 1.02–2.67, Table 4).

Discussion

In this study, we demonstrated that higher RDW was independently associated with the decline in renal function in the short-term observational period. In addition, patients with NDD-CKD and higher RDW showed poor renal outcomes, which was defined as a composite
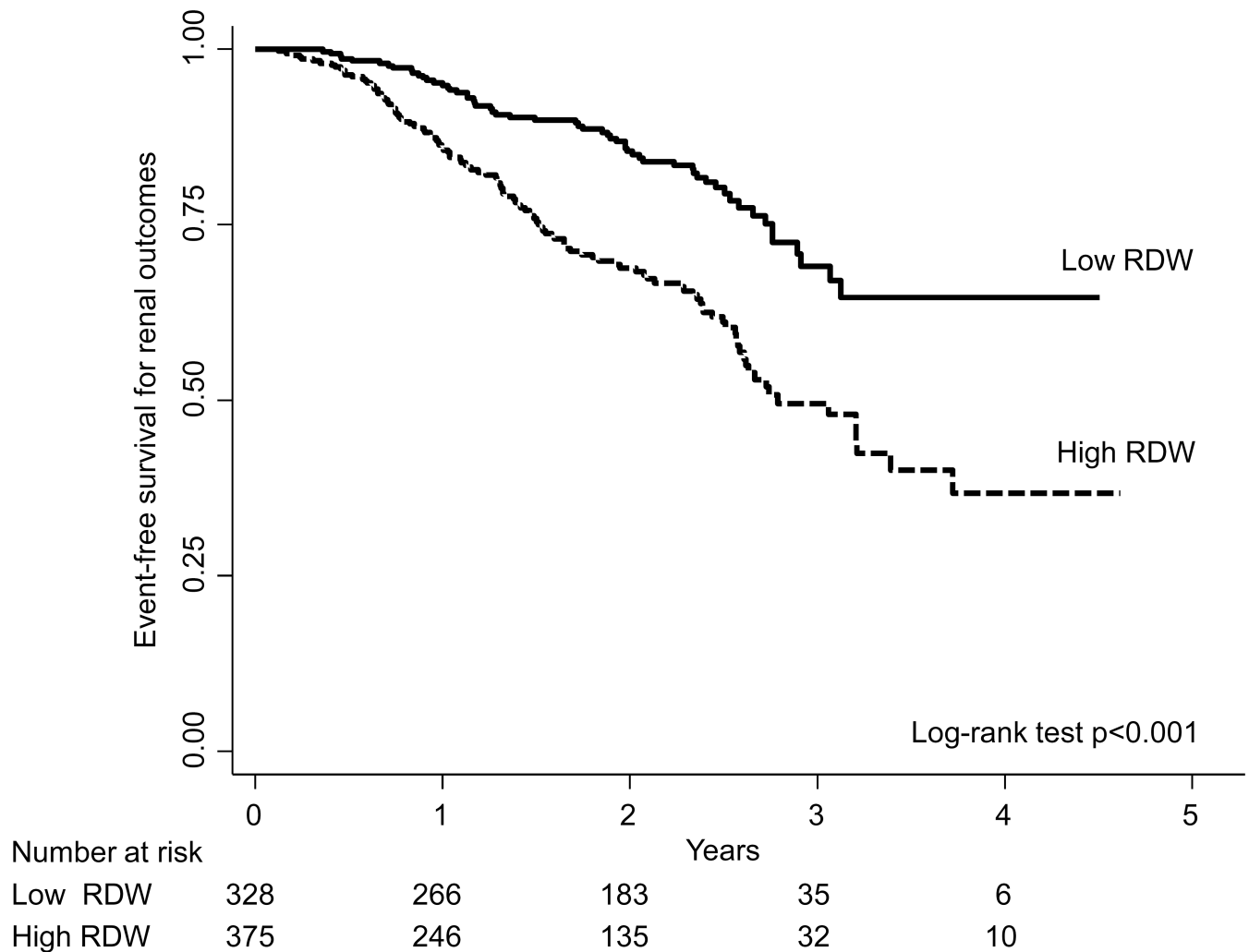
Fig 4. Kaplan-Meier survival curves of renal outcomes, stratified by the median of baseline RDW. RDW was categorized into two groups according to the median of baseline RDW (low RDW: < 13.5%, high RDW: ≥ 13.5%). The Kaplan-Meier survival curves of renal outcomes showed that the patients in the high RDW group had a significantly higher risk than did those in the low RDW group (p<0.001). Abbreviation: RDW, red cell distribution width.

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of the initiation of dialysis and doubling of the serum creatinine concentration. We also revealed that sustained, higher RDW within the first 3 months of observation was a significant risk factor of poor renal outcomes in this population.

In 2007, Felker et al. first reported that RDW was associated with mortality in patients with congestive heart failure and cardiovascular disease [2]. Subsequently, various studies confirmed that higher RDW was associated with higher mortality in patients with stroke, peripheral artery disease, and acute kidney injury. Interestingly, this relationship was also observed in the general elderly population [3–6]. Very recently, Vashistha et al. demonstrated that there was a significant association between higher RDW and mortality in a large-cohort study of hemodialysis patients and that RDW had a greater prognostic value for death than did other conventional markers of anemia, such as hemoglobin, TSAT, and serum ferritin levels [8]. Similar results were obtained in patients with peritoneal dialysis [9], patients with NDD-CKD [10], and kidney transplant recipients [14]. Thus, RDW is a reliable risk factor with regard to mortality at any stage of CKD.

Table 3. Cox regression analyses for renal outcomes stratified by the median of RDW at baseline.

	(a) Unadjusted Model		(b) Adjusted Model		(c) Fully Adjusted Model	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
High RDW	2.28 (1.67, 3.12)	<0.001	1.97 (1.42, 2.75)	<0.001	1.47 (1.05, 2.07)	0.026
Age (years)	-	-	0.99 (0.98, 1.00)	0.173	0.99 (0.98, 1.00)	0.191
Gender (Female)	-	-	0.74 (0.54, 1.03)	0.072	0.93 (0.66, 1.31)	0.671
Diabetes mellitus	-	-	2.52 (1.84, 3.44)	<0.001	1.61 (1.15, 2.27)	0.006
eGFR (ml/min/1.73m^2)	-	-	-	-	0.95 (0.94, 0.97)	<0.001
Hemoglobin (g/dL)	-	-	-	-	0.87 (0.78, 0.96)	0.009
Albumin (g/dL)	-	-	-	-	0.73 (0.55, 0.95)	0.022
Proteinuria (≥(2+))	-	-	-	-	3.32 (2.25, 4.90)	<0.001

(a) Unadjusted Model, (b) Adjusted Model: adjusted for age, gender, comorbid conditions, (c) Fully Adjusted Model: adjusted for age, gender, comorbid conditions, hemoglobin, eGFR (estimated glomerular filtration rate), albumin, C-reactive protein, transferrin saturation, ferritin, and Proteinuria, High RDW: RDW≥13.5, Proteinuria: measured by the dip stick tests, HR: hazard ratio, CI: confidence interval

As for the relationship between RDW and renal function, Lippi et al. reported that there was an inverse, step-wise association between RDW and kidney function in a large cross-sectional study of 8,585 adult outpatients [15]. A similar result was observed in kidney transplant recipients [16]. Another cross-sectional study revealed that elevated RDW was independently associated with a higher risk of microalbuminuria, which is a marker of renal injury [17]. However, because of the cross-sectional nature of their study design, the association between RDW and the progression of CKD remained unclear.

In this longitudinal study, we revealed, for the first time, that there was a significant association between higher RDW and poor renal outcome in patients with NDD-CKD. Although we could not determine plausible mechanisms that would explain this association, we have some speculations regarding this relationship. First, anemia is a possible cause of the ability of RDW to predict renal outcome. Anemia was reported to be an important predictor of renal outcome [11, 12], and correction of anemia prevented the progression of CKD [18, 19]. High RDW may indicate alteration of the lifespan of erythrocytes, which usually occurs with the lack of serum erythropoietin levels during the progression of CKD. In addition, iron deficiency and inflammation also play important roles in elevation of RDW in patients with NDD-CKD [20]. In the present study, however, the association between RDW and the progression of CKD was independent of hemoglobin levels, which was considered to be a mediator in those ineffective erythropoiesis, iron deficiency, and inflammatory axes. Second, endothelial dysfunction may be another mechanism that accounts for our observations. Solak et al. demonstrated that RDW was independently related to endothelial dysfunction, as assessed with flow-mediated dilatation and the thickness of the carotid intima in patients with CKD [21]. Endothelial dysfunction might result in renal vascular damage and dysfunction. Finally, oxidative stress is a potential underlying biological mechanism that elevates RDW in the progression of CKD. Previous studies have shown that oxidative stress increased in patients with CKD compared with healthy subjects [22], and that blood selenium, which is known as one of antioxidants in humans, decreased as CKD progressed [23]. Interestingly, in humans with selenium deficiency, selenium supplementation increased glutathione peroxidase activity in erythrocytes [24, 25], thereby improving red cell survival. The interaction between oxidative stress and the erythroid maturation [26–28] might lead to an increase in RDW in patients with CKD.

In the present study, not only higher RDW at baseline but also sustained, higher RDW during the first 3 months of observation was a significant risk factor of poor renal outcome. RDW
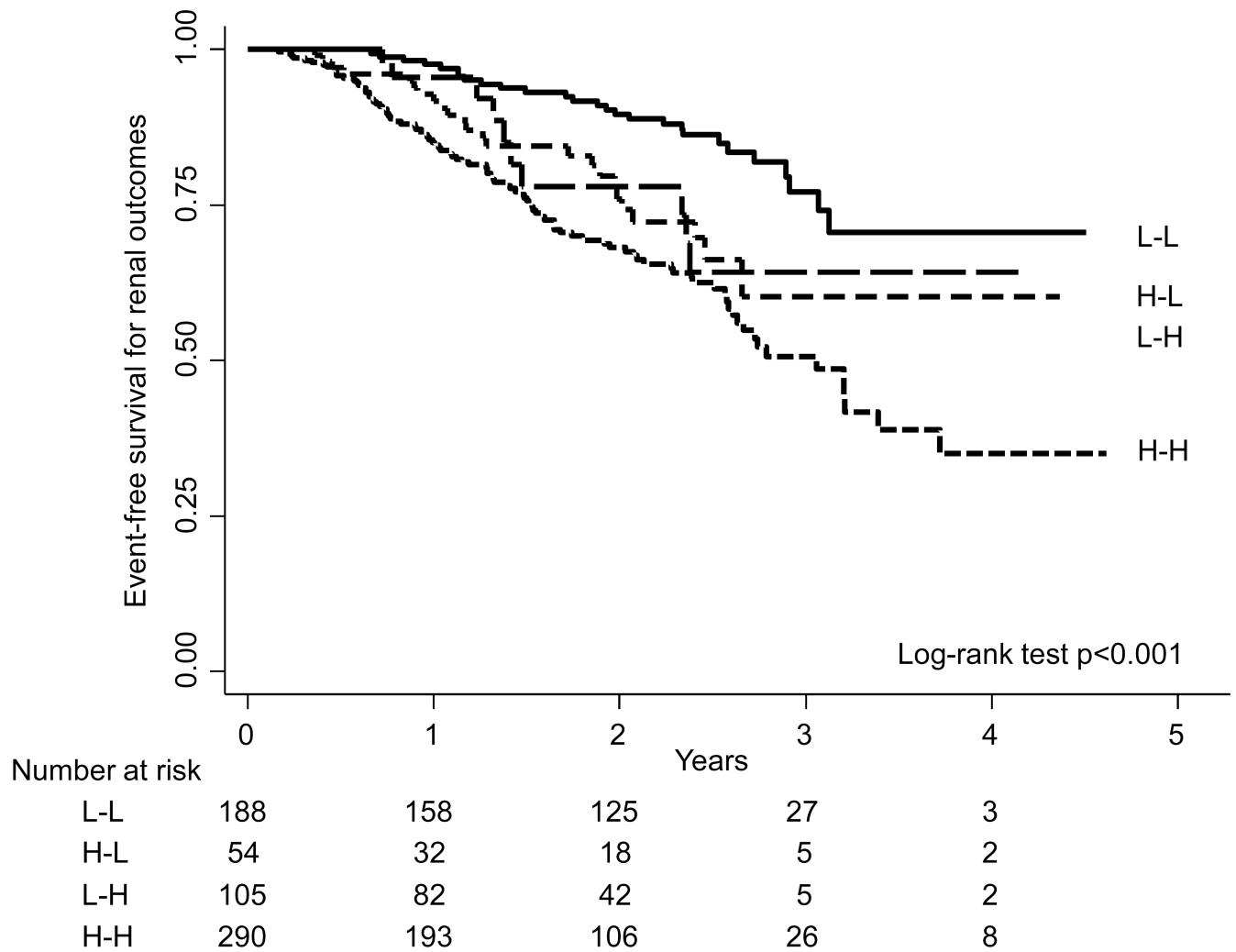
Fig 5. Kaplan-Meier survival curves of renal outcomes, categorized by the fluctuation patterns of RDW. We divided patients into four groups according to the fluctuation patterns of RDW during the first 3 months of observation. Patients in the H-H group showed the highest risk of having renal outcomes among these four groups (p<0.001). Abbreviations: RDW, red cell distribution width; L-L, low RDW at baseline to low RDW at 3 months; H-L, high-to-low; L-H, low-to-high; H-H, high-to-high.

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Table 4. Cox regression analyses for renal outcomes stratified by the fluctuation patterns of RDW during the first three months of observation.

	(a) Unadjusted Model		(b) Adjusted Model		(c) Fully Adjusted Model	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
L-L	Ref.	-	Ref.	-	Ref.	-
H-L	1.97 (0.95, 4.08)	0.068	1.83 (0.86, 3.90)	0.116	1.26 (0.58, 2.77)	0.557
L-H	2.19 (1.26, 3.80)	0.006	2.10 (1.20, 3.67)	0.009	1.50 (0.83, 2.72)	0.177
H-H	3.21 (2.09, 4.92)	<0.001	2.86 (1.83, 4.46)	<0.001	1.65 (1.02, 2.67)	0.040

(a) Unadjusted Model, (b) Adjusted Model: adjusted for age, gender, comorbid conditions, and medications, (c) Fully Adjusted Model: adjusted for age, gender, comorbid conditions, medications, hemoglobin, estimated glomerular filtration rate, albumin, C-reactive protein, transferrin saturation, ferritin, and proteinuria, RDW: red cell distribution width, L-L: low RDW at baseline to low RDW at 3 months, H-L: high-to-low, L-H: low-to-high, H-H: high-to-high, HR: hazard ratio, CI: confidence interval

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may decrease in response to therapeutic interventions, such as correction of anemia (using ESAs, iron supplements, or other nutritional supplements) and the improvement of underlying diseases (e.g., infection or malignancy). Sustained, higher RDW indicated that there were factors that could not be corrected, or that the patient's problems remained unchanged, which might explain our result that HRs for renal outcomes in the patients with sustained, higher RDW were higher than in the patients with higher RDW only at baseline.

Our study has several limitations. First, given the observational nature of the study, we could not establish that there was a cause-and-effect relationship between RDW and renal outcome. Second, even with thorough adjustments for potential confounders, we might have missed possible important confounders, such as vitamin B12 and folate. Third, since this study was conducted at a single center, our results must be confirmed in other settings before they are generalized externally. Despite these limitations, our study may have a large impact on patients with CKD by discriminating high-risk patients.

In conclusion, we demonstrated that there was a significant association between high RDW and poor renal outcome. Although the pathophysiologic link was not explored in the present study, integrated interactions among anemia, nutritional state, inflammation, endothelial dysfunction, and oxidative stress may explain the observed association. RDW can be measured in daily clinical practice at no additional cost, therefore, this variable could be a convenient method to identify patients at a high risk of having poor renal outcome.

Supporting information

S1 Table. Baseline characteristics categorized by the median of RDW (PS matching cohort).
(DOCX)

Author Contributions

Conceptualization: Sayoko Yonemoto, Takayuki Hamano.

Data curation: Sayoko Yonemoto.

Formal analysis: Sayoko Yonemoto, Naohiko Fujii.

Methodology: Takayuki Hamano, Naohiko Fujii.

Supervision: Takayuki Hamano, Yoshitaka Isaka.

Validation: Takayuki Hamano, Naohiko Fujii.

Writing – original draft: Sayoko Yonemoto.

Writing – review & editing: Karin Shimada, Satoshi Yamaguchi, Ayumi Matsumoto, Keiichi Kubota, Nobuhiro Hashimoto, Tatsufumi Oka, Masamitsu Senda, Yusuke Sakaguchi, Isao Matsui.

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