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Variability of red blood cell size predicts all-cause mortality, but not progression to dialysis, in patients with chronic kidney disease: A 13-year pre-ESRD registry-based cohort

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ABSTRACT

Background: Prognostic role of red blood cell distribution width (RDW) in patients with chronic kidney disease (CKD) is unclear. Little evidence provides a comprehensive predictive analysis considering both baseline values and longitudinal trajectories of RDW along with mean corpuscular volume (MCV).

Methods: We conducted a comprehensive risk assessment of RDW and MCV in a registry-based cohort of 4621 patients with CKD (age, 20–90 y) receiving multidisciplinary care during 2003 to 2015. Both baseline and longitudinal trajectories of RDW and MCV were modeled as predictors for end-stage renal disease (ESRD) and mortality by using multiple Cox proportional hazards regression models, incorporating time-varying covariates and adjustments for imperative confounding variables.

Results: Fully adjusted hazard ratio (HR; 95% CI) of progression to ESRD for each unit increase in RDW and MCV at baseline was 0.97 (0.93–1.02) and 1.00 (0.99–1.01), respectively. Longitudinally, neither RDW nor MCV trajectory was associated with progression to ESRD. For all-cause mortality, fully adjusted HRs (95%CI) were 1.09 (1.04–1.14) for each percent increase in RDW with a linear dose–response relationship and 1.95 (1.47–2.59) for a stable-high RDW trajectory compared with normal RDW trajectory. The effects of RDW on mortality were further augmented in patients with concomitantly high MCV status. Incorporating point-of-care RDW significantly improves the discrimination performance quantified using Harrell C statistics into the existing CKD mortality predictive equation (from 0.770 to 0.784, $P = .018$).

Conclusions: We support the clinical utility of RDW in predicting all-cause mortality among patients with CKD. The mechanism underlying our findings is critical for CKD risk assessment and management, particularly from malnutrition, inflammation, and atherosclerosis perspectives.

1. Introduction

Anisocytosis, an increased degree of variability in red blood cell (RBC) size, is commonly reported in daily practice and indicated by red blood cell distribution width (RDW)—a part of automated complete blood count reports. Although RDW are readily available, its low sensitivity in differentiating the etiologies of anemia limits its clinical utility. However, additional prognostic insight into mortality risks associated with a higher degree of anisocytosis in both general [1] and clinical populations, including patients with acute heart failure [2,3], under critical care [4], and with end-stage renal disease (ESRD) [5], is required. High RDW may also be a risk factor for incident myocardial infarction [6], stroke [7], thromboembolic disease [8], metabolic syndrome [9], and albuminuria [10]. Although the exact underlying pathogenic mechanism remains unclear, most studies have suggested a relationship of RDW with chronic inflammation [11], nutritional insufficiency [12], and impaired microcirculation [13]. The aforementioned observations can also be indicative of the lethal triad, the malnutrition–inflammation–atherosclerosis (MIA) syndrome, in patients with ESRD [14].

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Whether variability in RBC size can be used as a biomarker to summarize MIA status in patients with chronic kidney disease (CKD) remains unclear. Only one study examined the prognostic role of RDW in mortality of patients with CKD [15]. Most studies have failed to demonstrate a clear dose–response relationship between RDW and clinical events. Furthermore, researchers are generally unaware of the potential role of mean corpuscular volume (MCV), indicative of average RBC size, in predicting adverse events in patients with CKD. A possible link between high MCV and all-cause mortality in patients with CKD was reported recently [16]. However, no study has examined the conjoint trajectories or patterns of change in RDW and MCV related to the CKD progression and mortality in patients with CKD.

2. Methods

2.1. Study population

In 2002, Taiwan National Health Insurance Administration launched the Project of Integrated Care of CKD; since 2007, this program has used a multidisciplinary approach to focus on patients with CKD stages 3b to 5 [17]. China Medical University Hospital (CMUH) joined this project in 2003 and has consecutively enrolled patients with CKD based either on nephrologists' working diagnoses or according to the criteria outlined in the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [18]. Additional detailed information regarding the CMUH Pre-ESRD Program was published recently [19]. All patients enrolled in this program were followed up until the initiation of maintenance dialysis (hemodialysis or peritoneal dialysis), loss to follow-up, mortality, or December 31, 2015, whichever occurred first. ESRD was defined as the requirement for maintenance dialysis therapy during follow-up. The date of ESRD initiation was verified through active contact and review of electronic medical records (EMRs) when patients were lost to follow-up for > 6 months. The mortality status was determined based on national mortality database, which are systematically maintained by Health and Welfare Data Science Center of Ministry of Health and Welfare. The study was approved by the Research Ethical Committee/Institutional Review Board of China Medical University Hospital.

In this study, 4621 patients aged at least 20 years with available RDW information and 1688 patients who had at least 2 RDW measurements during the follow-up before the event or the study end were selected from 10,277 pre-ESRD program participants and their last RDW measurement were at least 6 months after pre-ESRD enrollment (see Supplementary Fig. S1 for detailed selection process). All RDW measurements within 30 days of packed RBC transfusion were excluded. The index date was defined as the first day of pre-ESRD program enrollment. The study was approved by the Big Data Center of CMUH and the Research Ethical Committee/Institutional Review Board of CMUH (CMUH105-REC3-068).

2.2. RBC count, kidney function, and inflammatory marker measurements

CHUH's clinical laboratory has received full accreditation from the Taiwan Accreditation Foundation and the College of American Pathologists Laboratory Accreditation Program since September 2003 and December 2008, respectively. Hemoglobin concentration, RDW, and MCV were measured using an automatic analyzer Sysmex HST-302N (Sysmex HST-series). The reference ranges for hemoglobin for 13.7 to 17.0 g/dL in men and 11.1 to 15.0 g/dL in women; for RDW and MCV, they are 11.5% to 14.5% and 80 to 99 fL, respectively, in both sexes. Rigorous quality control procedures and calibration were performed every 3 months. All prospective RDW measurements (until the endpoints) were considered. We calculated the quarterly average RDW in cases where the patient had data for more than one RDW within a 3-month period, and the RDW trajectory of each individual was modeled based on the serial RDW measures (Fig. 1). The same approach was applied to model the trajectory of MCV (Supplementary Fig. S2).

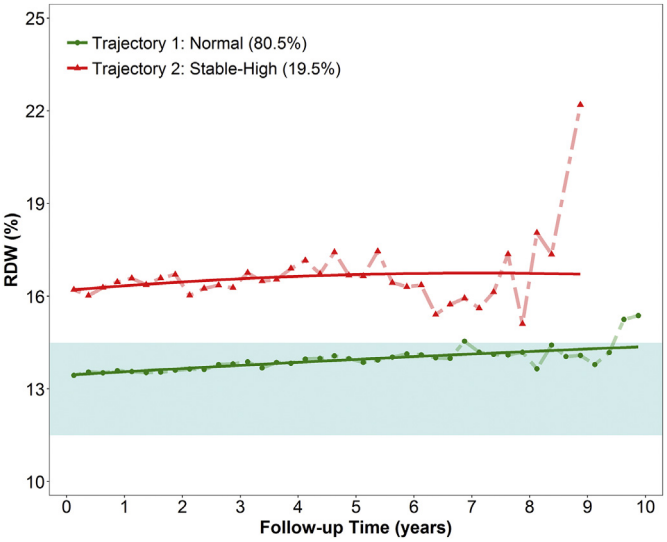

Fig. 1. RDW trajectories as defined through GBTM by using serial quarterly average levels of RDW over the course of CKD. The solid line represents the averaged estimated trajectory, whereas the points represent the averaged observed trajectories. The light green band represents the normal range of RDW. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Serum creatinine levels were measured using the Jaffe rate method (kinetic alkaline picrate) at the CMUH Central Laboratory on a Beckman UniCel DxC 800 immunoassay system. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [20]. Serum creatinine levels at enrollment were used to define baseline eGFR and corresponding CKD stages by using the following cutoff values: > 90, 60 to 89.9, 30 to 59.9, 15 to 29.9, and < 15 mL/min/1.73 m^2. Serum iron concentration was determined through a timed-endpoint method by using a commercially available kit (Beckman Synchron Systems). The main inflammatory maker used here was serum ferritin, measured using a chemiluminescent immunoassay sandwich method and quantitated on a UniCel DxI 800 system (Beckman Coulter Inc.). Protein–creatinine ratio (PCR) measurements were used not only to quantify proteinuria but also as a marker to represent microcirculatory endothelial function.

2.3. Other variables

Sociodemographic variables collected during the enrollment interview included age, sex, education level, smoking status, and alcohol consumption. Smoking status and alcohol consumption were categorized as never, former, and current. Diabetes mellitus and hypertension were defined using physicians' clinical diagnoses according to the patients' International Classification of Diseases, Ninth Revision, Clinical Modification codes and glucose-lowering or antihypertensive agent use. History of cardiovascular disease (CVD) was defined as coronary artery disease, myocardial infarction, stroke, and heart failure documented in the EMRs. Baseline comorbidities, medication use, and relevant biochemical measures were determined according to registry data or information obtained from the EMRs within 1 y before enrollment.

2.4. Statistical analyses

2.4.1. General analysis

Continuous variables are expressed as medians and interquartile ranges (IQRs) and compared using the Kruskal–Wallis test, whereas categorical variables are expressed as frequency (percentage) and compared using the x^2 test. The associations among the baseline RDW,

ESRD risk, and all-cause mortality were estimated using multivariable Cox regression analysis with time-varying interaction with erythropoietin-stimulating agent (ESA) use and dosage, hemoglobin level, and eGFR. We used the unit of epoetin alpha as the reference, and the equivalent dose from darbepoetin and methoxy polyethylene glycol-epoetin beta to epoetin alpha was estimated at a dose ratio of 250:1 and 300:1, respectively [21,22]. Baseline RDW was modeled as both continuous and categorical (tertile) exposures. The dose–response relationship was characterized using a restricted cubic spline model with 3 knots located at the 10th, 50th, and 90th percentiles of the overall RDW distribution. Similar approaches were applied to model MCV, including the group-based trajectory modeling (GBTM) described in the subsequent sections. All statistical analyses were performed using SAS (ver9.4). The 2-sided statistical significance level was set at $\alpha = 0.05$. We performed a four-stage analysis to reveal the relationships of RDW trajectories and ESRD risk and all-cause mortality.

2.4.2. Stage 1. Identifying distinctive RDW and MCV trajectories from pre-ESRD program enrollment to endpoint

Semiparametric GBTM was used to characterize RDW and MCV trajectories among the patients enrolled in the CMUH Pre-ESRD Program throughout the follow-up period. Briefly, the PROC TRAJ macro (developed using SAS) fits a semiparametric mixture model to longitudinal data using the maximum-likelihood method [23,24]. This approach is useful when the number of subgroups and other information, such as the shape of trajectories in subgroups, are unknown. We empirically compare 1-, 2-, 3-, and 4-group solutions and then optimized the number of subgroups by using Bayesian information criterion values (values close to zero indicate good fit), wherein the shapes of the trajectories was determined according to the order of the polynomial (e.g., linear, quadratic, and cubic). Assignment to RDW and MCV trajectory subgroups was determined by balancing clinical knowledge against latent hypotheses regarding the presence of distinct trajectories and their number or shape to facilitate meaningful interpretation. The determination of RDW and MCV trajectories was performed before the analysis of dialysis and mortality risk.

2.4.3. Stage 2. Associating RDW and MCV trajectories with the risk of dialysis and all-cause mortality

We evaluated the prospective relationships of RDW trajectories with dialysis and mortality risks using hazard ratios (HRs) with 95% confidence intervals (CIs) based on the Cox proportional hazards model. The models were adjusted hierarchically (see footnotes of Table 2). To account for renal function being a critical confounding factor pertaining to the influence of RDW or MCV levels on the dialysis and mortality risks, we formulated multiple domains of renal function, including time varying eGFR, and primary CKD etiologies within a multivariable model to minimize residual confounding. We characterized the relationship of RDA and MCV trajectories with dialysis risk by using competing risk analysis according to the methods outlined by Fine et al. [25].

2.4.4. Stage 3. Performing exploratory subgroup analysis and developing risk matrices combining RDW and MCV categories

Exploratory subgroup analysis was used to evaluate effect modification in the adjusted models. Patients were stratified according to (1) age (> 65 vs. < 65 y), (2) sex, (3) diabetes, (4) hypertension, (5) CKD stage, (6) hemoglobin tertile with cutoff values of 9.9 and 12.1 g/dL, and (7) MCV tertile with cutoff values of 86.1 and 90.7 fL. We created an interaction term (baseline or longitudinal RDW and MCV × each factor) in Cox regression models to assess the multiplicative interaction based on the *p*-values of the regression coefficient of the product terms. We also mapped risk matrices for adverse outcomes by combining RDW and MCV categories. For baseline RDW and MCV, we applied both statistical classification (in tertile) and clinical cutoffs to map the risks of progression to ESRD and mortality. We also developed a risk matrix according to longitudinal RDW and MCV trajectories derived from GBTM. In detail, we combined 3 longitudinal MCV trajectories with longitudinal RDW trajectories (normal and stable high) to obtain a risk matrix for outcomes of progression to ESRD and all-cause mortality using the group within normal RDW trajectory and normal-high MCV trajectory as the reference cell.

2.4.5. Step 4. Predictive performance of RDW for mortality in the point-of-care setting

To evaluate the predictive performance of RDW in the point-of-care setting, we applied Harrell C statistic to manage the time-dependent receiver operating characteristics curve for right-censored survival data [26,27]. Based on evidence, we constructed a reference predictive model for 3-year mortality risk, which included age; sex; baseline serum creatinine, hemoglobin, albumin, calcium, and phosphate levels; urine PCR; diabetic status; hypertension; and CVD. We then evaluated the predictive performance of the new risk model incorporating the baseline RDW tertiles [28]. To minimize the negative effects of missing data on risk prediction (e.g., reduced statistical power), we performed multiple imputation through the fully conditional specification method in SAS, an iterative Markov chain Monte Carlo procedure, to replace the missing values for variables in our proposed formula with imputed values. We specified the imputation number as 20 and iteration number as 100. Moreover, we plotted the observed vs. predicted risk probability to show the differences in calibrations between the reference and the proposed risk models for 3-y all-cause mortality.

3. Results

3.1. Clinical characteristics across baseline RDW tertile and prospective trajectory

The median (IQR) age at enrollment of all 4621 participants was 67.41 (56.70–76.58) years; median follow-up duration was 19.50 months; and median (IQR) number of RDW and MCV measurements was 4 (3–8) and 5 (3–9), respectively. At baseline, the patients were classified using RDW tertiles with cutoff values of ≤13.1%, 13.1% to 14.1%, and > 14.1%, respectively. We identified 2 RDW trajectories among the 1688 participants by using GBTM (Fig. 1): one that consistently below the reference upper limit of 14.5% was labeled to have a "normal" trajectory (trajectory 1, n = 1358, 80.5%), whereas the other that stably exceeded 14.5% was labeled to have "stable-high" trajectory (trajectory 2, n = 330, 19.5%; Table 1 and Fig. 1). Similarly, baseline MCV was categorized into tertiles; 3 distinct prospective trajectories were identified on the basis of prospective MCV measurements (Supplementary Fig. S2). Supplementary Table S1 lists the clinical characteristics across the baseline MCV tertiles and prospective trajectories. The correlation between RDW and MCV based on the hemoglobin cutoffs at 9.5 and 11 g/dL is presented in SupplementaryFig. S3 (overall $\gamma = -0.394$, $P < .001$).

Compared with patients with the low tertile of baseline RDW (≤13.1%), those with the middle or high tertile of baseline RDW were older, less educated, more anemic, and more likely to have advanced CKD (stages 4 and 5), diabetes, and CVD (Table 1). Correspondingly, patients with the high tertile of baseline RDW used more folic acid, vitamin B complex, antiplatelet agents, diuretics, angiotensin-converting enzyme inhibitors (ACEIs), insulin, and ESAs (Table 1). Marginally significantly decreasing trends of serum iron and total iron binding capacity were observed across the increasing order of RDW tertiles; similarly, significantly decreasing trends were observed in total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), albumin, and calcium. Moreover, increasing trends of serum creatinine, PCR, uric acid, and phosphate were consistently found across increasing baseline RDW tertiles (Table 1).

Patients with a stable-high RDW trajectory over the CKD course showed generally similar characteristics to those with a high baseline

Table 1
Baseline demographic and clinical characteristics according to RDW defined by baseline level and group-based trajectory modeling (GBTM).

Variables	Baseline RDW					RDW Trajectory		
	Q1: ≤13.1 (n = 1577)	Q2: 13.1 < ~ ≤ 14.1 (n = 1498)	Q3: > 14.1 (n = 1546)	P-value	P for trend	Traj 1: Normal (n = 1358)	Traj 2: Stable-High (n = 330)	P-value
Age at entry (year)	65.0 (54.6, 74.7)	68.6 (58.2, 77.3)	68.7 (58.3, 77.7)	< **0.001**	< **0.001**	67.0 (56.6, 76.2)	71.2 (61.8, 78.7)	< **0.001**
Female	718 (45.53)	647 (43.19)	697 (45.08)	NS	NS	608 (44.77)	142 (43.03)	NS
Follow-up duration (month)	24.0 (12.6, 43.0)	18.4 (8.7, 33.5)	15.0 (6.4, 28.6)	< **0.001**	< **0.001**	33.8 (20.3, 55.7)	25.9 (15.3, 41.2)	< **0.001**
No. of records	–	–	–	–	–	4 (3, 8)	5 (3, 8)	NS
Body mass index (kg/m^2)	24.1 (21.9, 26.8)	24.1 (21.5, 27.1)	23.9 (21.3, 26.7)	0.080	NS	24.1 (21.4, 26.7)	23.3 (20.8, 26.5)	**0.038**
Initial CKD stage				< **0.001**	–			**0.007**
1	64 (4.07)	43 (2.87)	34 (2.20)			43 (3.18)	10 (3.03)	
2	109 (6.93)	76 (5.08)	62 (4.02)			82 (6.06)	10 (3.03)	
3	657 (41.77)	549 (36.67)	479 (31.04)			565 (41.73)	114 (34.55)	
4	381 (24.22)	406 (27.12)	442 (28.65)			397 (29.32)	111 (33.64)	
5	362 (23.01)	423 (28.26)	526 (34.09)			267 (19.72)	85 (25.76)	
Smoking				NS	–			NS
Never	1341 (85.03)	1243 (82.98)	1272 (82.28)			1146 (84.39)	275 (83.33)	
Former	105 (6.66)	107 (7.14)	120 (7.76)			92 (6.77)	28 (8.48)	
Current	131 (8.31)	148 (9.88)	154 (9.96)			120 (8.84)	27 (8.18)	
Alcohol consumption				NS	–			NS
Never	1450 (91.95)	1377 (91.92)	1410 (91.20)			1251 (92.12)	300 (90.91)	
Former	73 (4.63)	78 (5.21)	97 (6.27)			73 (5.38)	20 (6.06)	
Current	54 (3.42)	43 (2.87)	39 (2.52)			34 (2.50)	10 (3.03)	
Education level (year)				< **0.001**	–			NS
< 9	405 (25.68)	446 (29.77)	478 (30.92)			377 (27.76)	102 (30.91)	
9 ≤ ~ < 12	605 (38.36)	577 (38.52)	625 (40.43)			518 (38.14)	131 (39.70)	
12 ≤ ~ < 16	381 (24.16)	317 (21.16)	321 (20.76)			313 (23.05)	66 (20.00)	
16+	186 (11.79)	158 (10.55)	122 (7.89)			150 (11.05)	31 (9.39)	
Diabetes	565 (35.85)	614 (41.02)	604 (39.12)	**0.012**	NS	537 (39.54)	127 (38.60)	NS
Hypertension	883 (56.03)	888 (59.32)	918 (59.46)	NS	NS	797 (58.69)	188 (57.14)	NS
Cardiovascular disease	542 (34.39)	628 (41.98)	692 (44.85)	< **0.001**	< **0.001**	544 (40.06)	150 (45.73)	NS
Baseline medication profiles								
EPO	180 (11.45)	225 (15.04)	316 (20.47)	< **0.001**	< **0.001**	157 (11.56)	57 (17.33)	**0.005**
Pentoxifylline	316 (20.10)	343 (22.93)	340 (22.02)	NS	NS	278 (20.47)	71 (21.58)	NS
NSAIDs	486 (30.92)	480 (32.09)	513 (33.23)	NS	NS	483 (35.57)	124 (37.69)	NS
Contrast media	278 (17.68)	302 (20.19)	359 (23.25)	**0.001**	< **0.001**	280 (20.62)	87 (26.44)	**0.022**
Dipyidamole	119 (7.57)	93 (6.22)	94 (6.09)	NS	NS	102 (7.51)	16 (4.86)	NS
Folic acid	278 (17.68)	322 (21.52)	366 (23.70)	< **0.001**	< **0.001**	245 (18.04)	78 (23.71)	**0.019**
Vitamin B	193 (12.28)	218 (14.57)	279 (18.07)	< **0.001**	< **0.001**	197 (14.51)	62 (18.84)	NS
Anti-platelet	448 (28.50)	500 (33.42)	541 (35.04)	< **0.001**	< **0.001**	448 (32.99)	124 (37.69)	NS
Anti-diabetic agents								
OAD	455 (28.94)	491 (32.82)	469 (30.38)	NS	NS	426 (31.37)	99 (30.09)	NS
Insuline	329 (20.93)	391 (26.14)	471 (30.51)	< **0.001**	< **0.001**	326 (24.01)	97 (29.48)	**0.040**
Anti-hypertension agents								
ACEI	409 (26.02)	346 (23.13)	434 (28.11)	**0.007**	0.187	366 (26.95)	91 (27.66)	NS
ARBs	679 (43.19)	622 (41.58)	637 (41.26)	NS	NS	616 (45.36)	133 (40.43)	NS
Trichlorethiazide	160 (10.18)	175 (11.70)	198 (12.82)	NS	**0.021**	153 (11.27)	44 (13.37)	NS
Furosemide, Spironolactone, Amizide, Indapamide	592 (37.66)	750 (50.13)	936 (60.62)	< **0.001**	< **0.001**	620 (45.66)	189 (57.45)	< **0.001**
Baseline biochemical profiles								
RDW (%)	12.7 (12.4, 12.9)	13.6 (13.4, 13.9)	15.2 (14.6, 16.1)	< **0.001**	< **0.001**	13.3 (12.7, 13.9)	15.2 (14.1, 16.2)	< **0.001**
MCV (fL)	89.7 (86.5, 93.0)	88.9 (85.6, 92.2)	86.1 (79.5, 90.7)	< **0.001**	< **0.001**	89.3 (85.9, 92.8)	84.6 (71.0, 90.6)	< **0.001**
Serum Iron (ug/dL)	57.0 (40.0, 79.0)	53.5 (41.0, 74.0)	50.0 (33.0, 72.0)	0.066	NS	53.0 (42.0, 76.0)	53.0 (31.0, 77.0)	NS
Ferritin (ng/mL)	209 (105, 385)	189 (98, 376)	200 (80, 453)	NS	NS	181 (78, 364)	210 (73, 452)	NS
TIBC (ug/dL)	270 (228, 309)	259 (225, 302)	252 (207, 303)	NS	NS	266 (227, 308)	256 (210, 320)	NS
T-CHO (mg/dL)	186 (159, 218)	181 (153, 217)	173 (144, 208)	< **0.001**	< **0.001**	184 (157, 218)	175 (141, 208)	< **0.001**
TG (mg/dL)	134 (93, 191)	130 (90, 187)	121 (83, 176)	< **0.001**	NS	129 (92, 187)	121 (79, 178)	**0.022**
LDL-C (mg/dL)	106 (85, 129)	103 (82, 129)	97 (74, 124)	< **0.001**	**0.001**	104 (84, 131)	102 (74, 131)	NS
HDL-C (mg/dL)	38.9 (32.5, 48.6)	39.6 (33.5, 48.9)	39.7 (33.2, 48.2)	0.675	NS	38.5 (31.9, 48.1)	37.9 (31.5, 47.6)	NS
eGFR (mL/min/1.73m^2)	31.2 (17.0, 46.9)	25.9 (14.3, 39.7)	22.4 (12.3, 36.0)	< **0.001**	< **0.001**	29.2 (18.4, 43.4)	24.6 (14.5, 37.3)	< **0.001**
Hemoglobin (g/dL)	11.8 (10.1, 13.6)	11.1 (9.6, 12.8)	10.1 (8.9, 11.8)	< **0.001**	< **0.001**	11.3 (9.9, 13.1)	10.2 (8.9, 11.7)	< **0.001**
Serum uric acid (mg/dL)	7.30 (6.10, 8.50)	7.40 (6.10, 8.70)	7.50 (6.30, 9.10)	< **0.001**	< **0.001**	7.30 (6.10, 8.50)	7.50 (6.30, 9.10)	**0.001**
Serum creatinine (mg/dL)	2.00 (1.40, 3.50)	2.20 (1.50, 4.07)	2.60 (1.64, 4.66)	< **0.001**	< **0.001**	2.07 (1.46, 3.30)	2.33 (1.61, 3.72)	**0.001**

(*continued on next page*)

Table 1 (*continued*)

Variables	Baseline RDW			RDW Trajectory				
	Q1: ≤13.1 (n = 1577)	Q2: 13.1 < ~ ≤ 14.1 (n = 1498)	Q3: > 14.1 (n = 1546)	P-value	P for trend	Traj 1: Normal (n = 1358)	Traj 2: Stable-High (n = 330)	P-value
Serum Albumin (g/dL)	3.80 (3.40, 4.20)	3.80 (3.30, 4.10)	3.55 (3.00, 4.00)	< **0.001**	< **0.001**	3.70 (3.30, 4.10)	3.60 (3.10, 4.00)	< **0.001**
Sodium (mmol/L)	138 (135, 140)	138 (135, 140)	138 (135, 140)	0.207	NS	138 (135, 140)	138 (135, 140)	NS
Potassium (mmol/L)	4.20 (3.80, 4.50)	4.20 (3.80, 4.65)	4.20 (3.70, 4.60)	0.056	NS	4.20 (3.70, 4.50)	4.20 (3.80, 4.60)	NS
Calcium (mg/dL)	8.90 (8.40, 9.20)	8.80 (8.30, 9.20)	8.60 (8.20, 9.10)	< **0.001**	< **0.001**	8.80 (8.40, 9.20)	8.70 (8.20, 9.10)	**0.002**
Phosphate (mg/dL)	4.00 (3.50, 4.70)	4.20 (3.60, 4.90)	4.30 (3.60, 5.10)	< **0.001**	< **0.001**	4.00 (3.40, 4.60)	4.10 (3.60, 4.70)	**0.040**
Urine creatinine (mg/dL)	78.6 (49.1, 118.3)	77.6 (50.1, 116.7)	67.4 (45.7, 104.1)	< **0.001**	< **0.001**	75.6 (48.3, 115.1)	67.5 (43.2, 101.7)	**0.013**
Urine PCR (mg/g)	804 (198, 2501)	935 (233, 3102)	1275 (336, 3816)	< **0.001**	< **0.001**	849 (230, 2640)	1198 (459, 2646)	**0.007**

Abbreviations: ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blockers; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; GBTM, group-based trajectory modeling; EPO, erythropoietin; IQR, inter-quartile range; NSAID, nonsteroidal anti-inflammatory drugs; OAD, oral antidiabetic agents; PCR, protein/creatinine ratio; RDW, red cell distribution width; T-CHO, total cholesterol.

RDW tertile, even when some baseline characteristic differences across baseline RDW tertile, such as those in education level, diabetic prevalence, antiplatelet agent and ACEI use, and LDL-C level, became nonsignificant (Table 1). Notably, the decreasing trend of BMI across baseline RDW tertiles became significant between longitudinal RDW trajectory groups (Table 1).

3.2. Progression to ESRD, all-cause mortality, and baseline RDW and prospective RDW trajectories

Over the 10,181 person-years of follow-up, 1000 ESRD events and 519 mortalities occurred. ESRD and all-cause mortality incidence was 98.2 and 50.5 per 1000 person-years, respectively (Table 2). For every percent increase in baseline RDW, the adjusted all-cause mortality risk increased by 9% (95%CI = 1.04–1.14), but that of dialysis did not increase significantly (HR = 0.97, 95%CI = 0.93–1.02). A significant dose–response relationship between baseline RDW and all-cause mortality, which began at 13% and then plateaued at nearly 15%, was also observed, even after adjustment for time-varying hemoglobin concentration (Fig. 2C). Among patients with RDW of 13.1% to 14.1%, the HR of progression to ESRD was 1.22 (95%CI = 1.04–1.43); however, no significant trend differences in risks of progression to ESRD across tertiles for the change in baseline RDW were found after introducing the time-varying covariates of eGFR, hemoglobin, and weekly epoetin alfa dosage (Table 2, Models 3).

From the perspective of RDW trajectory, as illustrated by the Kaplan–Meier curve in Supplementary Fig. S4 and S5, patients with a stable-high RDW trajectory had shorter overall survival (log-rank test, $P < .001$), but no difference in the risk of progression to ESRD. Compared with those with a normal RDW trajectory, these patients' adjusted HRs (95%CI) for mortality and incidental ESRD were 1.95 (1.47–2.59) and 0.77 (0.57–1.04), respectively (Table 2). For MCV, we noted no significant association of MCV (both baseline tertile and prospective trajectories) with incident ESRD and mortality (Supplementary Table S2).

In the subgroup analysis, we observed a similar association of baseline and prospective RDW trajectories with incident ESRD and mortality, with regard to age, sex, diabetes, hypertension, and CKD stage. However, in patients with hemoglobin level lower than 9.9 g/dL, the stable-high RDW trajectory significantly reduced the risk of progression to ESRD (HR = 0.64, 95%CI = 0.42–0.97;Fig. 3). By contrast, a trend of increasing mortality risk with increasing baseline RDWs was noted across categories of increasing MCV tertiles (Fig. 3).

3.3. Risk matrices with RDW and MCV and RDW-based all-cause mortality risk prediction

In the risk matrix using tertiles of the baseline RDW and MCV, the patients concomitantly in the highest tertile of RDW and MCV exhibited the highest all-cause mortality risk (Fig. 4A), revealing the significant interaction among tertiles of MCV and RDW in a continuous scale (P for interaction = 0.012, Fig. 3). Similarly, in the risk matrix using clinical cutoffs commonly used by clinicians, patients with both the highest tertiles of RDW and MCV showed the highest all-cause mortality risk (Fig. 4B). When constructing the risk matrix based on the longitudinal trajectories of RDW (stable-high vs. normal) and MCV (decreasing-low, normal-low, and normal-high), the pattern was consistent with not only the risk matrices using baseline values but also the larger effect size in patients concomitantly with stable-high RDW and normal-high MCV trajectories (HR = 3.08, 95%CI = 1.95–4.86; Fig. 4C). The discrimination performance quantified using Harrell C statistics after addition of baseline RDW tertiles into the reference risk equation increased significantly from 0.770 to 0.784 ($P = .018$; Supplementary Fig. S6).

4. Discussion

We evaluated the individual and joint roles of RDW and MCV both at baseline and in the prospective trajectory on the risk of progression to ESRD and all-cause mortality among patients with CKD. First, we found that baseline RDW was associated with all-cause mortality, consistent with the related studies; however, the effect size was almost half of that in other studies (comparable with Model 2 in Table 2). Second, the prospective trend of RDW, particularly among those with RDW stably above 15%, was more pronounced and significantly associated with all-cause mortality. Third, the risk matrix combining the trajectories of RDW and MCV revealed that the prospective effect of RDW on mortality was further augmented among patients with CKD with relatively high longitudinal MCV. Finally, RDW significantly improved the predictive performance of the mortality risk in patients with CKD. Our findings of extend the potential practicality of commonly neglected anemic markers from readily available complete blood count reports.

Our findings support that RDW could serve as an integrative marker of MIA syndrome and that it is correlated with nutritional and inflammatory markers, such as ferritin, serum albumin, and urine PCR, particularly in patients with CKD (Supplementary Fig. S7). An important systematic review has nicely summarized the adverse

Table 2
Hazards ratios (95% confidence interval) of progression to dialysis and all-cause mortality by baseline level and trajectory group of RDW.

						Model 1	Model 2	Model 3
Baseline RDW and longitudinal trajectory group	N	Cases	Person-years	Incidence	Crude HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
N (baseline level/Trajectory)						4621/1688	4600/1682	4017/1466
Risk of dialysis[†]								
Baseline RDW (RDW-mean RDW/per 1 unit increase)	4621	1000	10,181.23	98.22	**1.04 (1.00, 1.07)**	**1.05 (1.01, 1.08)**	1.01 (0.97, 1.05)	0.97 (0.93, 1.02)
Baseline RDW (tertile)								
≦13.1	1577	321	4255.94	75.42	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
13.1 < ~≦14.1	1498	326	3171.57	102.79	**1.24 (1.07, 1.45)**	**1.35 (1.16, 1.58)**	1.10 (0.93, 1.29)	**1.22 (1.04, 1.43)**
> 14.1	1546	353	2753.72	128.19	**1.38 (1.19, 1.60)**	**1.50 (1.29, 1.74)**	**1.19 (1.01, 1.39)**	1.00 (0.85, 1.19)
P for trend					< 0.001	< 0.001	0.036	0.924
RDW trajectory group								
Normal	1358	353	4793.90	73.64	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Stable-High	330	77	892.81	86.24	0.96 (0.74, 1.23)	1.03 (0.80, 1.33)	0.87 (0.66, 1.16)	0.77 (0.57, 1.04)
P for trend					0.73	0.816	0.343	0.085
All-cause mortality								
Baseline RDW (RDW-mean RDW/per 1 unit increase)	4621	519	10,269.34	50.54	**1.21 (1.17, 1.26)**	**1.21 (1.17, 1.26)**	**1.18 (1.13, 1.23)**	1.09 (1.04, 1.14)
Baseline RDW (tertile)								
≦13.1	1577	115	4307.36	26.70	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
13.1 < ~≦14.1	1498	153	3193.81	47.91	**1.79 (1.41, 2.29)**	**1.48 (1.16, 1.89)**	**1.30 (1.01, 1.66)**	1.24 (0.96, 1.60)
> 14.1	1546	251	2768.16	90.67	**3.40 (2.72, 4.24)**	**2.84 (2.27, 3.55)**	**2.31 (1.83, 2.90)**	**1.58 (1.24, 2.01)**
P for trend					< 0.001	< 0.001	< 0.001	< 0.001
RDW trajectory group								
Normal	1358	155	4815.89	32.19	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Stable-High	330	93	893.81	104.05	**3.46 (2.67, 4.48)**	**3.01 (2.32, 3.91)**	**2.98 (2.27, 3.90)**	**1.95 (1.47, 2.59)**
P for trend					< 0.001	< 0.001	< 0.001	< 0.001

Incidence = No. of incident dialysis cases/person-years*1000.
Model 1: Adjusted for age at entry, gender, smoking, alcohol, and education.
Model 2: Further adjusted for diabetes, hypertension, cardiovascular disease, primary etiologies of chronic kidney disease and baseline medications listed in Table 1.
Model 3: Further adjusted for time-dependent variable eGFR, EPO dosage, and hemoglobin.
Abbreviations: eGFR, estimated glomerular filtration rate; EPO, erythropoietin; GBTM: group-based trajectory modeling; RDW, red cell distribution width.
[†] With competing risk analysis for death.

prognostic role of RDW in disease development and relevant adverse outcomes in a range of health conditions including cardiovascular disease, metabolic disorders, cancer, and critical illness [29]. The most compelling evidence that exists is for cardiovascular diseases, particularly in coronary artery disease and heart failure, and almost all point that a wide variability in the size of RBC may be induced by chronic low-grade inflammation that mediates impaired iron metabolism and blunted erythropoietin response, leading to RBC immaturity [30]. Although the observational evidence is limited, all the relevant studies have shown that a high level of RDW was significantly associated with a high risk of mortality among CKD populations, including patients requiring renal replacement therapy [5]. Our findings confirm this proposition and strengthen the basis of causal inference that a longitudinal trajectory of RDW stably above 15% contributes significantly to all-cause mortality with a large effect size. Moreover, neither RDW nor MCV could predict progression to ESRD. The discrepancy in risk prediction with regard to CKD progression and mortality in patients with CKD suggests RDW to be a systemic marker of increased mortality but not when associated with progression of ESRD in patients with CKD. More attention may be given to CVD and infection prevention among patients with CKD with persistently high RDW.

In contrast to the findings of the only relevant study on patients with CKD, we did not observe any significant associations among high MCV (both baseline and prospective trajectory), progression to ESRD, and mortality in the CKD population. The main differences between the 2 studies are that the sample size in the present study was 3 times that in the other study and that time-varying variables, including hemoglobin, weekly epoetin alfa dosage, and eGFR, were considered in the present study. Possible explanations of poor prognosis related to relatively high MCV (≥90.8 fL) include malnutrition (e.g., folic acid or vitamin B12 deficiency), impaired hematopoiesis, or endothelial dysfunction [16]. However, we noted that high MCV could modify the mortality risk associated with high RDW, possibly because patients with high MCV must have an even wider standard deviation in RDW to derive the same coefficient of variation of RDW. In other words, the degree of RBC volume heterogeneity would be particularly high among patients with both high MCV and RDW. Further research should focus on the pathophysiological mechanisms underlying the association between RDW and mortality and identify effective intervention strategies to control RDW. Although some inherent determinants of RDW have been reported, including aging, epoetin alfa deficiency or hyporesponsiveness, iron deficiency, and black ethnicity, evidence on modifiable factors is limited [31–33]. An inverse association between physical exercise and RDW recently observed in the general population reveals the potential role of physical exercise in optimizing RDW in patients with CKD [34].

The strengths of our study are the large registry-based pre-ESRD cohort with regular hemoglobin and eGFR measurements over a long period and the use of the supplementary in-depth data from the EMRs. For instance, we could exclude the RDW data that may have been contaminated by blood transfusion. Moreover, the advantage of modeling the prospective trajectory of RDW greatly minimized exposure misclassification. We also carefully controlled confounding by the change of kidney function and hemoglobin by considering time-varying characteristics in the Cox proportional modeling. However, the present

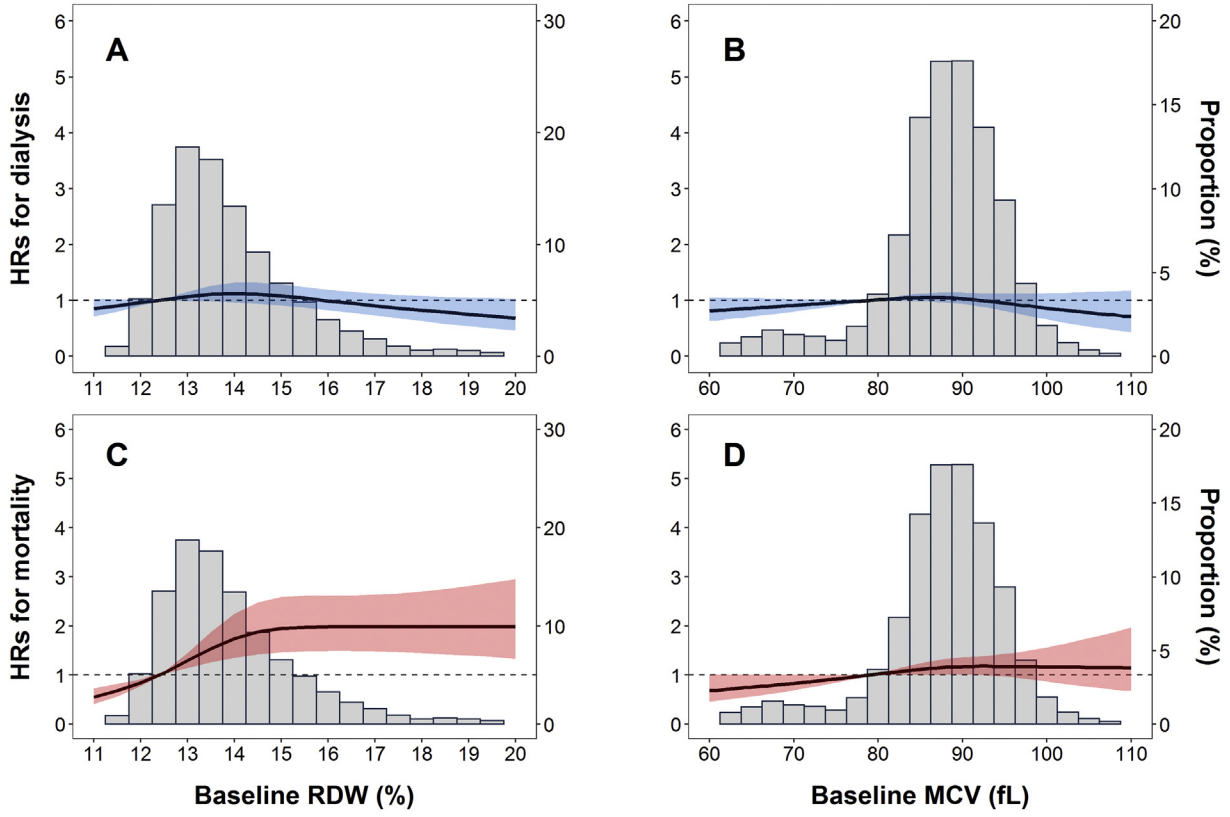

Fig. 2. Adjusted HRs for ESRD requiring dialysis and all-cause mortality according to the baseline serum level of RDW and MCV. Solid lines represent adjusted HRs based on restricted cubic splines for baseline RDW values, with knots at the 10th, 50th, and 90th percentiles. Dotted lines represent upper and lower 95% CIs. Reference was set at the 10th percentile of baseline RDWs. Upper panel (A and B): risk of ESRD requiring dialysis (blue); lower panel (C and D): all-cause mortality (red). Adjusted variables are the same as those shown in Model 3 in Table 2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

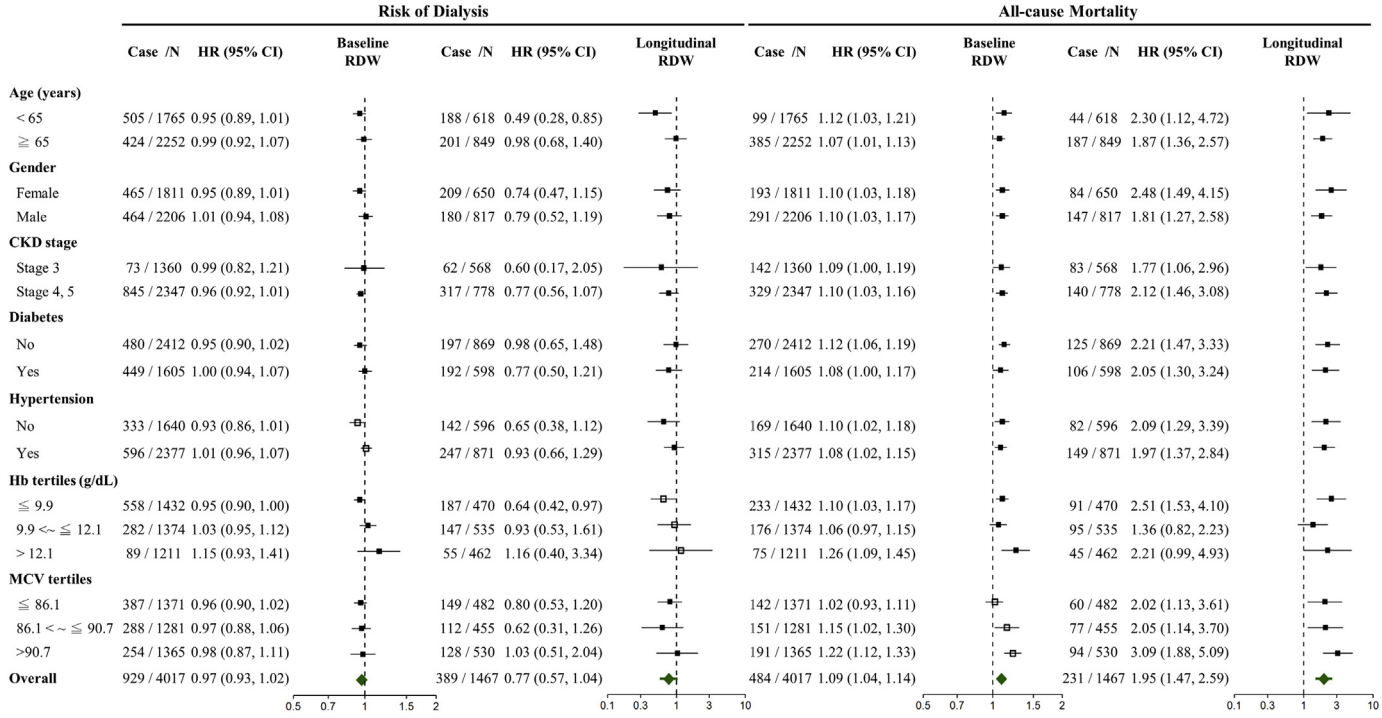

Fig. 3. HRs of the risk of CKD progression to dialysis and all-cause mortality for each unit change of baseline RDW and comparing the stable-high versus reference RDW trajectories. HRs were adjusted for the variables in Model 5 in Table 2, except for the stratifying variables. Estimated 2-sided $P < .05$ for interaction between RDW and participants' characteristics are represented as unfilled squares.

A

	ESRD requiring dialysis			All-cause mortality		
	Baseline RDW (%)			Baseline RDW (%)		
HR (95% CI)	T1: ≦13.1	T2: 13.1<~≦14.1	T3: >14.1	T1: ≦13.1	T2: 13.1<~≦14.1	T3: >14.1
Baseline MCV (fL)						
T1: ≦86.1	1.03 (0.80, 1.34)	**1.31 (1.01, 1.70)**	0.93 (0.72, 1.20)	0.68 (0.40, 1.15)	0.75 (0.46, 1.21)	0.92 (0.63, 1.34)
T2: 86.1<~≦90.7	1.00 (ref)	1.05 (0.80, 1.39)	1.13 (0.85, 1.51)	1.00 (ref)	0.93 (0.61, 1.40)	1.26 (0.83, 1.90)
T3: >90.7	0.90 (0.70, 1.16)	1.17 (0.87, 1.59)	0.87 (0.62, 1.23)	0.58 (0.37, 0.89)	0.97 (0.65, 1.45)	1.42 (0.97, 2.07)

B

	ESRD requiring dialysis			All-cause mortality		
	Baseline RDW (%)			Baseline RDW (%)		
HR (95% CI)	<11.7	11.7≦~<15	≧15	<11.7	11.7≦~<15	≧15
Baseline MCV (fL)						
<85	0.56 (0.07, 4.59)	1.07 (0.90, 1.28)	0.81 (0.64, 1.04)	NA	0.90 (0.67, 1.21)	0.95 (0.69, 1.30)
85≦~<94	1.32 (0.70, 2.50)	1.00 (ref)	0.97 (0.74, 1.28)	NA	1.00 (ref)	**1.51 (1.13, 2.01)**
≧94	0.94 (0.49, 1.82)	0.97 (0.79, 1.19)	0.62 (0.32, 1.18)	0.48 (0.07, 3.46)	1.06 (0.80, 1.39)	**1.76 (1.16, 2.67)**

C

	ESRD requiring dialysis		All-cause mortality	
	Longitudinal RDW (%)		Longitudinal RDW (%)	
HR (95% CI)	Trajectory 1: Normal	Trajectory 2: Stable-High	Trajectory 1: Normal	Trajectory 2: Stable-High
Longitudinal MCV (fL)				
Trajectory 1: Decreasing-Low	1.07 (0.54, 2.13)	1.08 (0.59, 1.99)	1.04 (0.36, 3.03)	1.22 (0.67, 2.23)
Trajectory 2: Normal-Low	**1.45 (1.12, 1.89)**	1.02 (0.66, 1.58)	1.12 (0.78, 1.61)	**2.09 (1.34, 3.25)**
Trajectory 3: Normal-High	1.00 (ref)	0.79 (0.44, 1.43)	1.00 (ref)	**3.08 (1.95, 4.86)**

Fig. 4. A. HRs (95% CI) of CKD progression to dialysis and mortalities based on baseline RDW-MCV tertile combination using the group with the lowest tertile of RDW and mid-tertile of MCV as the reference. B. HRs (95% CI) of CKD progression to dialysis and mortalities based on baseline RDW-MCV clinical categorical combination using the group within the normal range of baseline RDW and MCV between 85 and 94 fL as the reference. C. HRs (95% CI) of CKD progression to dialysis and mortalities based on prospective GBTM trajectory of RDW-MCV combination using the group within normal RDW trajectory and normal-high MCV trajectory as the reference.

study also has several limitations. Neither nutritional data (e.g., serum levels of folate, vitamin B12, and serial iron profiles) nor of bone marrow function parameters (e.g., reticulocyte and platelet count) were routinely examined in our dataset. Other limitations include the possibility of residual confounding (e.g., environmental factors) and overadjustment for variables that could be in the causal pathway (CVD and serial hemoglobin concentrations).

5. Conclusions

Both baseline and longitudinal trajectory of RDW were significantly associated with all-cause mortality in patients with CKD, particularly among those with relatively high MCV. Incorporating point-of-care RDW can significantly improve the predictive performance of existing CKD mortality predictive models. Our current findings support the clinical utility of incorporating the readily available characteristics of RBCs into comprehensive CKD risk assessments in primary care settings. Elucidating the mechanisms underlying the effects of elevated RDW on mortality risk is crucial for developing effective CKD treatment and prevention interventions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2019.07.035.

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