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Red Cell Distribution Width and Mortality in Hemodialysis Patients

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Background: Red cell distribution width (RDW) is an index of red blood cell volume variability that has historically been used as a marker of iron deficiency anemia. More recently, studies have shown that elevated RDW is associated with higher mortality risk in the general population. However, there is lack of data demonstrating the association between RDW and mortality risk in hemodialysis (HD) patients. We hypothesized that higher RDW is associated with higher mortality in HD patients.

Study Design: Retrospective observational study using a large HD patient cohort.

Setting & Participants: 109,675 adult maintenance HD patients treated in a large dialysis organization from January 1, 2007, to December 31, 2011.

Predictor: Baseline and time-varying RDW, grouped into 5 categories: <14.5%, 14.5% to <15.5%, 15.5% to <16.5%, 16.5% to <17.5%, and $\geq 17.5\%$. RDW of 15.5% to <16.5% was used as the reference category.

Outcome: All-cause mortality.

Results: Mean age of study participants was 63 ± 15 (SD) years and the study cohort was 44% women. In baseline and time-varying analyses, there was a graded association between higher RDW and incrementally higher mortality risk. Receiver operating characteristic, net reclassification analysis, and integrated discrimination improvement analyses demonstrated that RDW is a stronger predictor of mortality as compared with traditional markers of anemia, such as hemoglobin, ferritin, and iron saturation values.

Limitations: Lack of comprehensive data that may be associated with both RDW and HD patient outcomes, such as blood transfusion data, socioeconomic status, and other unknown confounders; therefore, the possibility of residual confounding could not be excluded. Also, lack of information for cause of death; thus, cardiovascular mortality outcomes could not be examined.

Conclusions: In HD patients, higher RDW is associated with incrementally higher mortality risk. RDW is also a stronger predictor of mortality than traditional laboratory markers of anemia. Further studies are needed to determine the mechanisms underlying the association between RDW and mortality.

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INDEX WORDS: Red cell distribution width (RDW); red blood cell heterogeneity; hemodialysis (HD); mortality; renal function; end-stage renal disease (ESRD).

Red cell distribution width (RDW) is a quantitative marker of the heterogeneity of red blood cell (RBC) volume.¹ It is routinely reported as a part of the standard complete blood cell count. Although it has traditionally been considered to be a marker of nutritional deficiency (iron, vitamin B₁₂, and folate),²

in more recent years, RDW has emerged as a novel predictor of mortality across various populations.³⁻¹² Although the underlying mechanism of the RDW-mortality association remains unclear, it has been hypothesized that it may also be a marker of malnutrition and inflammation.

Although RDW has been shown to closely correlate with kidney function,^{1,13-15} there is limited understanding of the relationship between RDW and mortality in patients with chronic kidney disease, particularly for those receiving dialysis. To date, only 2 small studies of peritoneal dialysis and hemodialysis (HD) patients have examined this question. In the first of these studies, among 1,293 incident peritoneal dialysis patients from a single center, those with RDW $\geq 15.5\%$ had 60% and 27% higher cardiovascular and all-cause mortality risks, respectively, compared with those with RDW < 15.5%.¹³ In the second prospective study of 100 HD patients from a single center, each 1% increase in RDW was associated with 54% higher all-cause mortality risk after 1 year of follow-up in crude analyses.¹⁵

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Given the limited generalizability and lack of adjustment of potential confounders in the mentioned studies, we sought to re-examine the association between RDW and mortality in a nationally representative population of HD patients receiving care from a large dialysis provider in the United States. We hypothesized that higher RDW is associated with higher mortality risk in HD patients independent of socio-demographics, comorbid conditions, and laboratory confounders and that RDW may have strong predictive value as a marker of mortality.

METHODS

Source Cohort

The study was approved by the institutional review committees of the University of California, Irvine, University of Washington, and DaVita Clinical Research (UCI IRB# 2012-9090). The study was exempt from informed written consent due to its nonintrusive nature and anonymity of patients.

We examined data from a total of 208,820 patients with end-stage renal disease who initiated dialysis therapy from January 1, 2007, through December 31, 2011, in a large dialysis care organization in the United States. We excluded 46,156 patients for whom dialysis vintage was less than 60 days total, 29,502 patients who were not initiated on thrice-weekly HD therapy, and 23,487 patients who did not have RDW measured during the first 3 months of initiating dialysis therapy. The final study population consisted of 109,675 adult HD patients (Fig 1). Patients were followed up from the date of dialysis therapy initiation until death, kidney transplantation, transfer to another dialysis facility, or end of the study period (December 31, 2011), whichever occurred first.

Sociodemographic, Clinical, and Laboratory Measures

Information for sociodemographics, dialysis modality, vascular access type, cause of end-stage renal disease, hospitalization data, comorbid conditions (diabetes mellitus, hypertension, atherosclerotic heart disease, congestive heart failure, other cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, history of cancer, HIV [human immunodeficiency virus], and dyslipidemia), body weight, laboratory values, and intravenous medications were obtained from the large dialysis organization database.

Figure 1. Flow chart of patient selection. Abbreviations: HD, hemodialysis; Q1, quarter 1; RDW, red cell distribution width.

In all large dialysis care organization clinics, blood samples were drawn using standardized techniques and transported to a centralized laboratory in Deland, FL, typically within 24 hours, where they were measured using automated and standardized methods. Serum creatinine, phosphorus, calcium, serum urea nitrogen, albumin, bicarbonate, total iron-binding capacity, and RDW were measured monthly. Serum intact parathyroid hormone (iPTH) and ferritin were measured at least quarterly. Hemoglobin was measured weekly to biweekly in most patients. Delivered dialysis dose was estimated by single-pooled Kt/V using the urea kinetic model. Body mass index was calculated as post-HD body weight in kilograms divided by height in meters squared. Data were averaged over 91-day intervals from dialysis therapy initiation (dialysis patient quarters). Measurements during the first 91 days on dialysis therapy were used as baseline values.

RDW was routinely reported along with complete blood cell count and was calculated by dividing the standard deviation of the mean cell size by the mean cell volume of RBCs and multiplying by 100 to convert to a percentage. The reference range for RDW is approximately 11.5% to 15.5%.¹⁶

STATISTICAL METHODS

Descriptive data were summarized using proportion, mean $\pm$ standard deviation, and median with interquartile range as appropriate and were compared using tests for trend, analysis of variance (Kruskal-Wallis test for nonparametric variables), or χ^2 tests.

Linear regression was used to calculate the expected change in baseline RDW with each unit change in a laboratory variable, and correlation coefficients were calculated to determine the strength of these associations.

The relationship between baseline and time-varying RDW with all-cause mortality was examined using Cox proportional hazard models. RDW was categorized into 5 different groups (<14.5%, 14.5%–<15.5%, 15.5%–<16.5%, 16.5%–<17.5%, and $\geq 17.5\%$). The RDW category 15.5% to <16.5% was used as the reference category because it was the category with the largest proportion of patients. Three levels of adjustment were analyzed: (1) unadjusted models that included RDW, the main predictor variable; (2) case-mix-adjusted models that additionally included age, sex, race/ethnicity (non-Hispanic white, African American, Hispanic, Asian, and other), comorbid conditions, cause of end-stage renal disease, dialysis access, primary insurance, delivered dialysis dose, and number of days in the hospital per dialysis patient quarter; and (3) case-mix-plus-malnutrition-inflammation complex syndrome (MICS)-adjusted models that included all covariates in the case-mix model as well as 17 surrogates of nutritional and inflammatory status: hemoglobin, serum albumin, calcium, phosphorus, iPTH, iron saturation, total iron-binding capacity, ferritin, bicarbonate, white blood cell count, lymphocyte percentage, creatinine, alkaline phosphatase, body mass index, normalized protein catabolic rate, cumulative iron dose per quarter, and erythropoiesis-stimulating agent (ESA) median dose per week. Time-varying models included time-updated values of dialysis dose, number of hospital days per dialysis patient quarter, and all MICS laboratory measurements. Associations of RDW as a continuous predictor with mortality were also modeled using restricted cubic splines with best placed knots at the 25th, 50th, and 75th percentiles. We examined possible effect modification in the baseline RDW-mortality association across strata of demographics, comorbid conditions, and laboratory measurements with higher baseline RDW $\geq 15.5\%$ versus lower referent RDW < 15.5%.

The added value of RDW to case-mix covariates in predicting all-cause mortality was evaluated using receiver operating characteristic (ROC) analysis with area under the curve (AUC). This was compared with ROCs of other markers of anemia (ie, hemoglobin, iron saturation, and ferritin values) and albumin level because it is a

Table 1. Baseline Characteristics of Patients Stratified by RDW

	Total	RDW					P
		<14.5%	14.5%–<15.5%	15.5%–<16.5%	16.5%–<17.5%	≥17.5%	
No. of participants	109,675 (100)	12,704 (12)	24,973 (23)	27,852 (25)	20,260 (18)	23,886 (22)	
Age, y	63 ± 15	59 ± 15	61 ± 15	63 ± 15	64 ± 15	64 ± 15	<0.001
Female sex	47,761 (44)	3,850 (30)	9,766 (39)	12,261 (44)	9,733 (48)	12,151 (51)	<0.001
Diabetes	64,060 (58)	6,755 (53)	14,856 (59)	16,654 (60)	12,058 (60)	13,737 (58)	<0.001
Race							<0.001
White	51,124 (47)	5,777 (46)	11,374 (46)	13,183 (47)	9,609 (48)	11,181 (47)	
African American	34,366 (31)	3,192 (25)	6,750 (27)	8,419 (31)	6,917 (34)	9,088 (38)	
Hispanic	16,334 (15)	2,582 (20)	4,783 (19)	4,310 (15)	2,448 (12)	2,211 (9)	
Asian	3,530 (3)	500 (4)	906 (4)	875 (3)	590 (3)	659 (3)	
Other	3,977 (4)	603 (5)	1,063 (4)	982 (4)	637 (3)	692 (3)	
Insurance							<0.001
Medicare	58,859 (54)	5,977 (47)	12,693 (51)	14,947 (54)	11,367 (56)	13,875 (58)	
Medicaid	7,647 (7)	1,068 (8)	1,803 (7)	1,931 (7)	1,339 (7)	1,506 (6)	
Other	43,169 (39)	5,659 (45)	10,477 (42)	10,974 (39)	7,554 (37)	8,505 (36)	
Single-pool Kt/V	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	1.5 ± 0.3	0.004
URR	68 ± 7	68 ± 7	68 ± 7	68 ± 7	69 ± 7	69 ± 7	0.008
Comorbid conditions							
ASHD	15,773 (14)	1,418 (11)	3,176 (13)	4,050 (15)	3,133 (15)	3,996 (17)	<0.001
CHF	40,339 (37)	3,875 (31)	8,582 (34)	10,345 (37)	7,888 (39)	9,649 (40)	<0.001
Other CVD	16,643 (15)	1,424 (11)	3,277 (13)	4,141 (15)	3,378 (17)	4,423 (19)	<0.001
CBVD	1,942 (2)	179 (1)	440 (2)	500 (2)	360 (2)	463 (2)	<0.001
HTN	56,153 (51)	6,340 (50)	12,617 (51)	14,163 (51)	10,492 (52)	12,541 (53)	<0.001
COPD	5,595 (5)	447 (4)	1,079 (4)	1,457 (5)	1,136 (6)	1,476 (6)	<0.001
Cancer	2,538 (2)	206 (2)	427 (2)	584 (2)	527 (3)	794 (3)	<0.001
HIV	543 (0.5)	44 (0.3)	59 (0.2)	95 (0.3)	119 (0.6)	226 (1.0)	<0.001
Dyslipidemia	27,709 (25)	2,908 (23)	6,091 (24)	7,123 (26)	5,180 (26)	6,407 (27)	<0.001
Access type							<0.001
CVC	81,966 (75)	8,494 (67)	18,215 (73)	21,000 (75)	15,567 (77)	18,690 (78)	
AV fistula	16,389 (15)	2,957 (24)	4,350 (18)	4,055 (15)	2,494 (13)	2,533 (11)	
AV graft	4,545 (4)	551 (4)	1,037 (4)	1,121 (4)	868 (4)	968 (4)	
AV other	105 (0.09)	15 (0.1)	30 (0.1)	16 (0.05)	26 (0.1)	18 (0.07)	
Unknown	6,583 (6)	678 (5)	1,320 (5)	1,632 (6)	1,289 (6)	1,664 (7)	

(Continued)

Table 1 (Cont'd). Baseline Characteristics of Patients Stratified by RDW

	Total	RDW					P
		<14.5%	14.5%-<15.5%	15.5%-<16.5%	16.5%-<17.5%	≥17.5%	
Cause of ESRD							<0.001
Diabetes	50,350 (46)	6,157 (48)	12,532 (50)	13,328 (49)	8,886 (43)	9,447 (40)	
HTN	32,513 (30)	3,644 (29)	7,120 (29)	8,111 (29)	6,219 (31)	7,419 (31)	
GN	10,155 (9)	1,026 (8)	1,853 (7)	2,404 (9)	2,001 (10)	2,871 (12)	
Cystic kidney disease	1,642 (1)	401 (3)	433 (2)	379 (1)	215 (1)	214 (1)	
Other	15,015 (14)	1,476 (12)	3,035 (12)	3,630 (12)	2,939 (15)	3,935 (16)	
Albumin, g/dL	3.5 ± 0.5	3.7 ± 0.5	3.8 ± 0.5	3.5 ± 0.5	3.5 ± 0.5	3.4 ± 0.5	<0.001
Calcium, mg/dL	9.09 ± 0.6	9.05 ± 0.5	9.05 ± 0.6	9.08 ± 0.6	9.12 ± 0.6	9.18 ± 0.6	<0.001
Phosphorus, mg/dL	4.9 ± 1.2	5.0 ± 1.1	5.0 ± 1.1	5.0 ± 1.2	4.9 ± 1.2	4.8 ± 1.2	<0.001
Ferritin, ng/mL	283 [164-486]	249 [153-402]	266 [159-434]	283 [166-478]	303 [170-529]	315 [171-584]	<0.001
iPTH, pg/mL	313 [197-486]	339 [222-507]	330 [216-503]	315 [198-487]	301 [187-472]	286 [174-460]	<0.001
Hemoglobin, g/dL	11.1 ± 1.2	11.4 ± 1.1	11.3 ± 1.1	11.1 ± 1.1	10.9 ± 1.2	10.8 ± 1.3	<0.001
WBC count, ×10 ³ /μL	7.8 ± 2.7	7.5 ± 2.1	7.7 ± 2.3	7.8 ± 2.4	7.9 ± 2.8	8.0 ± 3.3	<0.001
CRP, mg/dL	1.5 [0.6-3.6]	0.6 [0.3-1.6]	1.1 [0.4-2.4]	1.3 [0.6-3.6]	2.0 [0.8-5.2]	2.4 [1-4.7]	<0.001
ALP, IU/L	87 [69-115]	80 [65-101]	84 [67-108]	86 [69-113]	90 [70-120]	95 [74-130]	<0.001
Bicarbonate, mEq/L	23.6 ± 2.7	23.4 ± 2.6	23.4 ± 2.6	23.4 ± 2.7	23.6 ± 2.7	23.8 ± 2.8	<0.001
Creatinine, mg/dL	5.5 [4.2-7.1]	5.7 [4.5-7.3]	5.6 [4.4-7.3]	5.5 [4.2-7.1]	5.3 [4.1-7.1]	5.2 [3.9-6.8]	<0.001
TIBC, μg/dL	225 ± 49	241 ± 43	231 ± 45	224 ± 47	219 ± 50	214 ± 54	<0.001
Iron saturation, %	23.0 ± 9.1	24.4 ± 8.2	23.0 ± 7.9	22.4 ± 8.2	22.6 ± 9.1	23.9 ± 11.4	<0.001
Vitamin B ₁₂ , pg/mL	638 [454-930]	579 [424-830]	609 [440-889]	631 [451-917]	664 [484-962]	684 [481-1,015]	<0.001
Folate, ng/mL	14.4 [8.5-20.0]	13.2 [8.2-20.0]	13.8 [8.2-20.0]	13.9 [8.3-20.0]	14.7 [8.5-20.0]	15.9 [8.9-20.0]	<0.001
ESA dose, IU/wk	4,692 [1,493-11,931]	4,401 [1,307-11,104]	4,444 [1,429-11,413]	4,620 [1,437-11,727]	4,800 [1,500-12,099]	5,135 [1,666-12,949]	<0.001
Iron dose, IU	1,000 [400-1,400]	950 [450-1,350]	1,000 [500-1,400]	1,000 [450-1,500]	1,000 [450-1,450]	900 [250-1,400]	<0.001
nPCR, g/kg/d	0.8 [0.6-0.9]	0.8 [0.7-0.9]	0.8 [0.7-0.9]	0.8 [0.6-0.9]	0.8 [0.6-0.9]	0.8 [0.6-0.9]	<0.001
BMI, kg/m ²	27 [23-32]	27 [24-32]	27 [23-32]	27 [23-32]	26 [23-32]	26 [22-31]	<0.001
Lymphocyte, %	20.7 ± 7.5	22.8 ± 7.0	21.5 ± 7.1	20.7 ± 7.2	20.1 ± 7.5	19.2 ± 8.3	<0.001

Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean ± standard deviation if normally distributed or median [interquartile range] if skewed. Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; creatinine in mg/dL to μmol/L, ×88.4; phosphorus in mg/dL to mmol/L, ×0.3229; TIBC in μg/dL to μmol/L, ×0.179; folate in ng/mL to nmol/L, ×2.266.

Abbreviations: ALP, alkaline phosphatase; ASHD, atherosclerotic heart disease; AV, arteriovenous; BMI, body mass index; CBVD, cerebrovascular disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CVC, central venous catheter; CVD, cardiovascular disease; ESA, erythropoiesis-stimulating agent; ESRD, end-stage renal disease; GN, glomerulonephritis; HIV, human immunodeficiency virus; HTN, hypertension; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; RDW, red cell distribution width; TIBC, total iron-binding capacity; URR, urea reduction ratio; WBC, white blood cell.

Table 2. Correlations and Linear Regressions of Baseline RDW With Various Laboratory Data

Laboratory Variable	Coefficient (95% CI)	Correlation (95% CI)
Albumin, per 1-g/dL greater	-0.731 (-0.752 to -0.710)	-0.200 (-0.207 to -0.193)
Ferritin, per 100-ng/mL greater	0.060 (0.057 to 0.062)	0.135 (0.128 to 0.142)
Platelets, per 10,000-cells/ μ L greater	-0.009 (-0.011 to -0.007)	-0.049 (-0.062 to -0.036)
WBC count, per 1,000-cells/ μ L greater	0.040 (0.036 to 0.043)	0.060 (0.054 to 0.066)
nPCR, per 1-g/kg/d greater	-0.470 (-0.520 to -0.430)	-0.059 (-0.064 to -0.053)
CRP, per 1-mg/L greater	0.050 (0.030 to 0.090)	0.149 (0.088 to 0.210)
Hemoglobin, per 1-g/dL greater	-0.250 (-0.260 to -0.240)	-0.172 (-0.178 to -0.167)
Iron saturation, per 1% greater	0.004 (0.003 to 0.005)	0.021 (0.014 to 0.029)
Phosphorus, per 1-mg/dL greater	-0.100 (-0.108 to -0.090)	-0.065 (-0.071 to -0.060)
iPTH, per 100-pg/mL greater	-0.020 (-0.023 to -0.017)	-0.038 (-0.044 to -0.033)
BMI, per 1-kg/m ² greater	-0.012 (-0.013 to -0.010)	-0.049 (-0.055 to -0.043)
Bicarbonate, per 1-mEq/L greater	0.036 (0.030 to 0.040)	0.055 (0.050 to 0.061)
Lymphocytes, per 1% greater	-0.034 (-0.035 to -0.033)	-0.146 (-0.153 to -0.139)
TIBC, per 1- μ g/dL greater	-0.006 (-0.006 to -0.005)	-0.161 (-0.168 to -0.154)
Median ESA dose, per 1,000-IU greater	0.004 (0.003 to 0.005)	0.028 (0.023 to 0.033)
Iron dose, per 100-IU greater	-0.007 (-0.008 to -0.005)	-0.028 (-0.035 to -0.022)
Creatinine, per 1-mg/dL greater	-0.061 (-0.065 to -0.056)	-0.082 (-0.087 to -0.077)
Calcium, per 1-mg/dL greater	0.275 (0.257 to 0.293)	0.089 (0.083 to 0.094)
ALP, per 1-IU/L greater	0.003 (0.003 to 0.003)	0.133 (0.126 to 0.140)
Single-pool Kt/V, per 1-U greater	0.001 (-0.030 to 0.032)	0.002 (-0.006 to 0.007)
Vitamin B ₁₂ , per 100-pg/mL greater	0.036 (0.030 to 0.043)	0.091 (0.074 to 0.109)
Folate, per 1-ng/mL greater	0.0179 (0.013 to 0.023)	0.061 (0.045 to 0.077)

Abbreviations: ALP, alkaline phosphatase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; RDW, red cell distribution width; TIBC, total iron-binding capacity; WBC, white blood cell.

strong predictor of mortality. Likelihood ratio tests were used to compare goodness of fit of case-mix models with case-mix models with the added predictor. Net reclassification improvement (NRI) was performed to examine the effect of case-mix variables alone versus case-mix variables and RDW on different cutoff points (5%, 15%, and 30%) in predicting all-cause mortality. We also calculated integrated discrimination improvement (IDI) to compare discrimination ability between the 2 logistic regression prediction models (case-mix variables alone vs case-mix variables and RDW). NRI and IDI were also calculated for other markers of anemia (ie, hemoglobin, iron saturation, and ferritin values) and albumin levels.

In the primary analysis, data were missing for 1.3%, 4.6%, and 1.5% of patients for serum ferritin, creatinine, and normalized protein catabolic rate, respectively, and data were missing for <1% for all other covariates. In sensitivity analysis, data for vitamin B₁₂ and folate levels were missing for 88% and 87% of

patients, respectively. For all analyses, complete case methods were used, for which each model analysis was limited to patients with complete data for all model variables. All analyses were carried out with Stata, version 13.1 (StataCorp LP).

RESULTS

Baseline Demographics and Clinical Characteristics According to RDW

The cohort included 109,675 HD patients. Baseline characteristics stratified by the 5 RDW categories are shown in Table 1. Mean age was 63 ± 15 (standard deviation) years. At baseline, patients with higher RDW were more likely to be African

Figure 2. Association of baseline red cell distribution width with all-cause mortality over 5 years of follow-up. Abbreviation: MICS, malnutrition-inflammation complex syndrome.

Figure 3. Association of time-varying red cell distribution width with all-cause mortality over 5 years of follow-up. Abbreviation: MICS, malnutrition-inflammation complex syndrome.

Figure 4. Association of time-varying red cell distribution width (RDW) with all-cause mortality over 5 years of follow-up using restricted cubic splines ([A] unadjusted model, [B] case-mix-adjusted model, and [C] case-mix-plus-malnutrition-inflammation complex syndrome-adjusted model).

American, have diabetes and cardiovascular comorbid conditions, and use a central venous catheter at the time of initiation of HD therapy. As RDW increased, serum ferritin, vitamin B₁₂, and C-reactive protein (CRP) levels increased, whereas iPTH levels decreased. Interestingly, hemoglobin, ESA, and iron dose values were essentially similar across all RDW groups.

Association of RDW With Different Laboratory Variables

Table 2 shows the correlation and association between RDW and different laboratory variables. RDW had positive correlations with values for ferritin, white blood cell count, CRP, iron saturation, bicarbonate, median ESA dose, calcium, alkaline phosphatase, single-pool Kt/V, vitamin B₁₂, and folate. It had negative correlations with albumin, platelet, creatinine, hemoglobin, phosphorus, iPTH, body mass index, lymphocyte, total iron-binding capacity, and iron dose values. However, these correlations between RDW and various laboratory variables were weak. The strongest correlation was found to be between RDW and albumin level. With every 1-g/dL increase in albumin level, RDW decreased by 0.7% (correlation coefficient, -0.20).

Association of RDW With Mortality

Using RDW of 15.5% to <16.5% as a reference, there was a linear association between baseline RDW and mortality in unadjusted, case-mix-adjusted, and case-mix-plus-MICS-adjusted models. In case-mix-plus-MICS-adjusted models, baseline RDW $\geq 17.5\%$ was associated with the highest risk for mortality compared to the reference group (15.5%–<16.5%; adjusted hazard ratio [HR], 1.28; 95% confidence

interval [CI], 1.24–1.33; Fig 2; Table S1 [provided as online supplementary material]). Higher time-varying RDW was incrementally associated with higher all-cause mortality risk in all levels of adjustment (Figs 3 and 4; Table S2). In the fully adjusted case-mix-plus-MICS model, lower time-varying RDW groups of <14.5% and 14.5% to <15.5% were associated with lower mortality risk compared to the reference group (adjusted HRs of 0.64 [95% CI, 0.60–0.68] and 0.84 [95% CI, 0.79–0.88], respectively), whereas higher time-varying RDW groups of 16.5% to <17.5% and $\geq 17.5\%$ were associated with higher mortality risk (adjusted HRs of 1.16 [95% CI, 1.10–1.22] and 1.47 [95% CI, 1.40–1.55], respectively). Subgroup analyses demonstrated that patients with RDW $\geq 15.5\%$ had higher all-cause mortality in unadjusted, case-mix-adjusted, and case-mix-plus-MICS-adjusted models compared with patients with RDW < 15.5% (Figs 5 and 6).

Predictive Value of RDW

ROC analysis demonstrated a modest improvement in AUC after adding RDW to the case-mix model in predicting mortality within the first year of initiating dialysis therapy (AUC of 0.734 [95% CI, 0.730–0.739] vs 0.763 [95% CI, 0.758–0.767] without and with RDW, respectively). Similarly, adding albumin level to the case-mix model changed the AUC from 0.734 (95% CI, 0.730–0.739) to 0.758 (95% CI, 0.753–0.762). AUC was unchanged after adding hemoglobin, ferritin, and percent iron saturation values to case-mix models individually (Table 3). Using IDI, the discrimination slope of the case-mix with RDW model was 1.8% and 2.5% higher when compared to the case-mix model alone in predicting 1- and 5-year mortality, respectively. Reclassification analysis for all-cause mortality using NRI showed an improvement after adding RDW to the model (cutoff < 5%, 5%–<15%, 15%–<30%, and $\geq 30\%$: NRIs of 13.9% [95% CI, 13.0%–14.9%] and 13.6% [95% CI, 12.9%–14.2%] for 1- and 5-year mortality, respectively; $P < 0.001$; Table 4). In the same model, albumin level had the highest predictive value for all-cause mortality, and all other markers of anemia (eg, ferritin, hemoglobin, and iron saturation) had much lower predictive ability compared to RDW. The reclassification table for models without and with RDW as a predictor of event (event is defined as mortality within 5 years of initiating HD therapy) is shown in Table 5. Event rates for the case-mix model are 3%, 10%, 22%, and 42% for risk categories of 0% to <5%, 5% to <15%, 15% to <30%, and $\geq 30\%$, respectively. However, event rates for the case-mix model with RDW are 2.5%, 10%, 16%, and 44% for risk categories of 0% to <5%, 5% to <15%, 15% to <30%, and $\geq 30\%$, respectively. Hence, the

Figure 5. Subgroup analyses show all-cause mortality hazard ratio in patients with baseline red cell distribution width (RDW) $\geq 15.5\%$ (RDW $< 15.5\%$ as reference group) by demographics and comorbid conditions. Abbreviations: CHF, congestive heart failure; CV, cardiovascular; CVA, cerebrovascular accident; HTN, hypertension; MICS, malnutrition-inflammation complex syndrome.

case-mix model with RDW seems to be a better model because it classified more people in the highest risk group.

Sensitivity Analyses

We performed sensitivity analysis in which we additionally adjusted for vitamin B₁₂ and folate levels

in addition to case-mix-plus-MICS covariates in the time-varying analysis. Due to a large proportion of patients with missing data for vitamin B₁₂ and folate (88% of patients), these two variables were not included in the main case-mix-plus-MICS model. After restricting the subcohort to patients with available vitamin B₁₂ and folate measurements, the linear

Figure 6. Subgroup analyses show all-cause mortality hazard ratio in patients with baseline red cell distribution width (RDW) $\geq 15.5\%$ (RDW $< 15.5\%$ as reference group) by laboratory values. Abbreviations: CRP, C-reactive protein; iPTH, intact parathyroid hormone; MICS, malnutrition-inflammation complex syndrome; WBC, white blood cell.

relationship between RDW and mortality persisted but was blunted, in particular for the MICS model additionally adjusted for vitamin B₁₂ and folate levels. These results represent associations in a small subset of the analytical cohort and therefore may be subject to selection biases (Table S3).

Baseline characteristics of patients with complete data for all variables included in the baseline case-mix

and MICS-adjusted models ($n = 99,303$) were compared with those with complete data across all variables, including vitamin B₁₂ and folate ($n = 10,372$). The 2 groups were similar except there was a higher proportion of whites and lower proportion of Hispanics in the group with complete information. Dyslipidemia was also more prevalent in the group with complete information (Table S4).

Table 3. AUC Using ROC Analysis to Predict All-Cause Mortality Within First Year of Initiating Hemodialysis Using Different Laboratory Variables in Addition to Case-Mix Variables as Listed

	1-y Mortality	P
Case-mix variables	0.734 (0.730-0.739)	
Case-mix + RDW	0.763 (0.758-0.767)	<0.001
Case-mix + albumin	0.758 (0.753-0.762)	<0.001
Case-mix + hemoglobin	0.734 (0.731-0.741)	<0.001
Case-mix + ferritin	0.734 (0.731-0.741)	<0.001
Case-mix + % iron saturation	0.734 (0.731-0.471)	<0.001

Note: Associations given as AUC (95% confidence interval). Case-mix variables include age, sex, race/ethnicity (non-Hispanic white, African American, Hispanic, Asian, and other), comorbid conditions, primary insurance, dialysis access, cause of end-stage renal disease, hospitalization history, and delivered dialysis dose. *P* value represents likelihood ratio comparing case-mix models with case-mix + laboratory variables.

Abbreviations: AUC, area under the curve; RDW, red cell distribution width; ROC, receiver operating characteristic.

In addition, we further evaluated the association of RDW with mortality after excluding patients with hemoglobin levels < 12 g/dL in time-varying analysis. This was done to examine the effect of RDW on

Table 4. Test of Discriminatory Value to Evaluate Predictive Value of RDW in Comparison to Other Laboratory Variables in Hemodialysis Patients Who Died Within the 1-Year and 5-Year Study Period

	1-y Mortality (95% CI)	5-y Mortality (95% CI)
RDW		
IDI	1.8% (1.7%-1.9%)	2.5% (2.4%-2.6%)
NRI ^a	13.9% (13.0%-14.9%)	13.6% (12.9%-14.2%)
Albumin		
IDI	2.7% (2.6%-2.8%)	2.3% (2.2%-2.4%)
NRI ^a	19.4% (18.3%-20.4%)	15.5% (14.9%-16.1%)
Hemoglobin		
IDI	0.40% (0.35%-0.45%)	0.03% (0.02%-0.04%)
NRI ^a	4.5% (3.8%-5.2%)	0.6% (0.4%-1.4%)
Ferritin		
IDI	0.31% (0.26%-0.37%)	0.09% (0.07%-0.12%)
NRI ^a	2.7% (2.2%-3.3%)	1.6% (1.3%-1.8%)
% Iron saturation		
IDI	0.12% (0.10%-0.15%)	0.065% (0.063%-0.066%)
NRI ^a	1.4% (0.9%-1.8%)	1.2% (0.9%-1.4%)

Note: Case-mix variables include age, sex, race/ethnicity (non-Hispanic white, African American, Hispanic, Asian, and other), comorbid conditions, primary insurance, dialysis access, cause of end-stage renal disease, hospitalization history, and delivered dialysis dose. NRI and IDI estimates compare case-mix-adjusted models to case-mix-plus-laboratory variable.

Abbreviations: CI, confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement; RDW, red cell distribution width.

^aCutoff 5%, 15%, and 30%.

mortality prediction in nonanemic patients. RDW remained significantly associated with all-cause mortality in this subcohort of patients (Table S5). In the case-mix-plus-MICS-adjusted model, the lower time-varying RDW groups of <14.5% and 14.5% to <15.5% were associated with lower mortality risk (reference group, 15.5%-<16.5%: adjusted HRs of 0.75 [95% CI, 0.71-0.79] and 0.88 [95% CI, 0.83-0.92]). However, the higher time-varying RDW groups of 16.5% to <17.5% and ≥17.5% were associated with higher mortality risk (adjusted HRs of 1.09 [95% CI, 1.02-1.15] and 1.26 [95% CI, 1.19-1.34], respectively).

DISCUSSION

In this contemporary cohort of 109,675 adult HD patients, we found a robust, consistent, and linear relationship between RDW and mortality. As RDW increased, risk for death also increased. This result remained consistent in patients with hemoglobin levels ≥ 12 g/dL. In addition, there was also an independent and additive effect of RDW in the assessment of survival in patients on maintenance HD therapy. The AUC analyses demonstrated that RDW was a strong predictor of mortality, similar to albumin level. Using reclassification analyses in the mortality prediction model, RDW improved the predictive value of the model by ~14% for 1- and 5-year mortality. Based on our models, RDW might be a better predictor of mortality than hemoglobin, ferritin, and iron saturation values. Furthermore, although previous studies across various non-chronic kidney disease populations found significant correlations between RDW and hemoglobin, CRP, ferritin, and white blood cell values, our study found no significant correlations between RDW, RBC indexes, and various other laboratory/inflammatory markers, suggesting that the pathogenesis of elevated RDW in patients on HD therapy is probably more complex.¹⁵

It has been previously shown that kidney function is closely related to RDW. In 1989, Docci et al¹⁴ were the first to measure and compare RDW values in HD patients versus patients with normal estimated glomerular filtration rates (eGFRs). They concluded that RDW is higher in HD patients and tends to return to normal when HD patients are treated with iron. In 2008, Lippi et al¹⁷ showed that in approximately 8,500 patients with eGFRs > 60 mL/min/1.73 m², there is a strong graded decrease in eGFR with increase in RDW. A similar inverse relationship was found in another study in which both decreased eGFR and increased microalbuminuria were seen with higher RDW.¹⁸ In kidney transplant recipients, results have been similar.¹ More recently, a retrospective analysis has been performed in 296 patients that examined the role of RDW in HD patients without anemia. When

Table 5. Reclassification Table for Models With and Without RDW as a Predictor of Event

	Case-Mix Variables With RDW as Predictor					
Case-Mix Variables Without RDW as Predictor	RDW < 5%	RDW 5%-<15%	RDW 15%-<30%	RDW ≥ 30%	Total	Event Rate
Event						
RDW < 5%	31	15	3	0	49	
RDW 5%-<15%	37	1,625	612	49	2,323	
RDW 15%-<30%	0	922	6,757	2,342	10,021	
RDW ≥ 30%	0	0	1,879	14,489	16,368	
Total	68	2,562	9,251	16,880	28,761	
No event						
RDW < 5%	1,303	293	3	1	1,600	
RDW 5%-<15%	1,392	16,608	2,521	112	20,633	
RDW 15%-<30%	0	6,670	24,313	3,982	34,965	
RDW ≥ 30%	0	2	5,210	17,497	22,709	
Total	2,695	23,573	32,047	21,592	79,907	
All						
RDW < 5%	1,334	308	6	1	1,649	3%
RDW 5%-<15%	1,429	18,233	3,133	161	22,956	10%
RDW 15%-<30%	0	7,592	31,070	6,324	44,986	22%
RDW ≥ 30%	0	2	7,089	31,986	39,077	42%
Total	2,763	26,135	41,298	38,472	108,668	
Event rate	2.5%	10%	22%	44%		

Note: Event is defined as mortality within 5 years of initiating hemodialysis therapy.

Abbreviation: RDW, red cell distribution width.

these patients were grouped into 4 categories according to clinical parameters, albumin level, and CRP level, the group with both low serum albumin (<3.5 g/dL) and high CRP values (>5 mg/L) had the highest RDW. This suggests that even in nonanemic HD patients, RDW varies depending on the degree of malnutrition and inflammation.¹⁹

In addition to being closely linked to kidney function, increased RDW has also been associated with higher mortality. In 2007, it was identified as a prognostic marker for all-cause mortality in patients with congestive heart failure.³ In more recent years, RDW has been associated with mortality and other adverse outcomes in various clinical conditions, including chronic and acute heart failure, acute dyspnea, acute pancreatitis, severe sepsis and septic shock, trauma, acute pulmonary embolism, older adulthood, and even acute kidney injury or kidney transplantation.^{4–12} Similarly, results from a single center with 1,293 incident peritoneal dialysis patients demonstrated that patients with RDW ≥ 15.5% had an adjusted HR of 1.60 for cardiovascular mortality (RDW reference group, <15.5%).¹³ However, the impact of RDW on mortality in HD patients has not been well studied. To our knowledge, only one study of 100 HD patients from a single center has examined the RDW-mortality association. In that study, each 1% increase in RDW was associated with 54% higher all-cause mortality risk after 1 year in univariate Cox proportional hazard analyses.¹⁵ The association between RDW and

mortality reported in many diseases may reflect residual confounding from many conditions affecting RBC production and survival.

The exact mechanism by which RDW is linked to mortality is not clear. RDW reflects heterogeneity in RBC size. Disorders causing increased RBC destruction and/or ineffective and increased RBC production, which are both prevalent in patients on dialysis therapy, lead to an increase in RDW. Beyond functioning as a marker of ineffective erythropoiesis, there are other plausible mechanisms that might explain the RDW-mortality risk. First, inflammation inhibits bone marrow function and iron metabolism,²⁰ and proinflammatory cytokines have been determined to inhibit erythropoietin-induced erythrocyte maturation and proliferation and downregulate erythropoietin receptor expression, which is associated with increasing RDW.^{21–23} Second, oxidative stress leads to an increase in heterogeneity of RBCs.^{24,25} Despite having tremendous antioxidant capacity, RBCs are prone to oxidative damage. Patients receiving HD have high levels of inflammation and oxidative stress due to multiple factors, including blood contact with the dialysis membrane, microbial contamination of the dialysate, reduced vitamin C and E levels, and reduced activity of the glutathione system. Third, malnutrition, which is common in HD patients, is known to increase RDW. Finally, RDW has been shown to be an independent predictor of endothelial dysfunction.²⁶

Our study is not without its limitations. First, as an observational study, it cannot prove a causal relationship between RDW and mortality. Second, we did not have comprehensive data that may be associated with both RDW and HD patient outcomes, such as blood transfusion data, socioeconomic status, and other known or unknown confounders. Therefore, we cannot exclude the possibility of residual confounding. We also did not have information for cause of death and therefore could not examine cardiovascular mortality outcomes. Finally, the relevance of these findings is uncertain because it is not necessarily actionable. However, it is possible that similar to ferritin level, RDW is a marker of inflammation and may help in recognizing patients with ESA resistance. Nevertheless, our study is remarkable for its nationally representative cohort, large sample size, and comprehensive data for laboratory values and comorbid conditions.

In summary, we observed that higher RDW is strongly linked to higher mortality risk in HD patients. However, it is not clear whether higher RDW is a risk factor for mortality or an epiphenomenon of underlying biological and metabolic imbalances across RDW categories. Nevertheless, it seems reasonable to infer that assessment of this parameter should be broadened far beyond the differential diagnosis of anemia. Further studies are needed to confirm these findings and determine the mechanisms underlying the RDW-mortality association.

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Contributions: Research idea and study design: TV, ES, MZM, CMR, HM, CPK, KK-Z; data acquisition: TV, ES, KK-Z; data analysis/interpretation: TV, ES, MZM, CMR, HM, MS, CPK, KK-Z; statistical analysis: TV, ES, MZM, MS, KK-Z; supervision or mentorship: KK-Z. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. KK-Z takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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SUPPLEMENTARY MATERIAL

Table S1: Association of baseline RDW with all-cause mortality over 5 y.

Table S2: Association of time-varying RDW with all-cause mortality over 5 y.

Table S3: Association of time-varying RDW with all-cause mortality over 5 y in patients ever with vitamin B₁₂ or folate measurement.

Table S4: Baseline characteristics of cohort with complete data for baseline case-mix and MICS covariates vs those with complete data across all variables.

Table S5: Association of time-varying RDW with all-cause mortality over 5 y in patients with hemoglobin $\geq$ 12 g/dL.

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