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ORIGINAL ARTICLE

Red blood cell distribution width and mortality and hospitalizations in peritoneal dialysis patients

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ABSTRACT

Background. Red blood cell distribution width (RDW) is found to be associated with different types of anemia and has recently been studied as a prognostic marker of mortality in hemodialysis patients. However, the relationship of RDW with mortality and hospitalization rate in peritoneal dialysis (PD) patients is less known.

Methods. Among 14 323 incident PD patients between 2007 and 2011 in the USA, we examined the relationship of baseline and time-varying RDW with the risk of mortality and time to first hospitalization using adjusted Cox models. In addition, we examined the relationship of baseline RDW and hospitalization rate using an adjusted negative-binomial regression model. Sensitivity analyses included competing risk models and subgroup analyses.

Results. The study population comprised patients 56 ± 16 years of age, including 43% females, 23% African Americans and 62% diabetics, with a mean RDW of 15.3 ± 1.6%. In models adjusted for clinical characteristics and laboratory parameters, RDW exhibited an incremental relationship with the mortality risk, where RDW ≥16.5% had a 40% and 69% higher risk of death in baseline and time-varying analyses, respectively, compared with an RDW of 14.5–15.5%. Moreover, higher baseline RDW ≥16.5% was also associated with a higher risk of time to first hospitalization {hazard ratio 1.22 [95% confidence interval (CI) 1.14–1.29]} and a higher rate of hospitalizations [incidence rate ratio 1.16 (95% CI 1.09–1.23)]. These results were consistent across numerous sensitivity analyses.

Conclusions. Higher RDW is associated with a higher risk of mortality and hospitalizations among incident PD patients. Further studies are needed to examine the mechanism behind RDW and adverse outcomes.

Keywords: hospitalization, mortality, peritoneal dialysis, red blood cell distribution width

INTRODUCTION

Red blood cell distribution width (RDW) is an index that reflects the degree of heterogeneity of circulating red blood cell size or anisocytosis. A higher baseline RDW is indicative of more variability in erythrocyte size and suggestive of dysfunctional erythropoiesis [1]. In clinical practice, RDW has classically been used as another useful indicator of anemia in conjunction with mean corpuscular volume and is commonly available in standard blood tests [2]. However, despite its widespread availability, only recently has it been studied as a novel marker of morbidity and mortality. Some studies have suggested that higher RDW is associated with greater hospitalization risk, including cardiovascular (CV)-related hospitalizations [3–5]. Moreover, studies have shown that higher RDW is associated with a higher risk of mortality in a variety of cohorts, including the general community and patients with cardiovascular disease, cancer and chronic kidney disease, including those on hemodialysis (HD) [1, 6–14].

Recently, in a large cohort of incident HD patients, Vashistha *et al.* [15] showed that both higher baseline and time-varying RDW were associated with a higher risk of all-cause mortality, and RDW was a strong indicator of anemia in that population compared with other classical anemia markers. Although a majority of end-stage renal disease (ESRD) patients initiate treatment with HD, a growing number of patients have turned to peritoneal dialysis (PD) as the modality of choice in renal replacement therapy [15]. To date, there have only been a few studies that have investigated the association of RDW with

mortality in PD patients [16–18]; one study found that RDW ≥15.5% was associated with higher CV mortality, yet an attenuated risk of all-cause mortality [16], and two other studies reported that higher RDW (≥15.3%, and per 1% increase, respectively) was associated with greater all-cause mortality risk [17, 18]. However, each of these studies centered on smaller cohorts of Asian patients (<1300 patients each) and only investigated baseline RDW values. It is unknown whether this relationship applies to a more diverse PD population, where racial differences have already been suggested in the general population [19] and short-term changes in RDW have been associated with worse mortality outcomes among hospitalized patients [14, 20]. Ultimately the relationship of RDW and morbidity and mortality remains understudied in PD patients.

Thus we sought to investigate the association of both baseline and time-varying RDW with all-cause mortality, time to first hospitalization and hospitalization rate in a large, contemporary cohort of incident PD patients receiving treatment in the USA. We hypothesize that higher RDW, both in the long and short term, is associated with worse outcomes in PD patients.

MATERIALS AND METHODS

Study population and data source

The study population comprised incident ESRD patients who initiated treatment at any outpatient facility of large dialysis organization (LDO) in the USA between 1 January 2007, and 31 December 2011. The development of this cohort has been previously described [21]. Patients were excluded if treated for a total of <60 days with PD throughout follow-up. Patient follow-up was divided into consecutive intervals of 91-day patient quarters from the start of PD. Of the 17 844 patients ever treated with PD, we further excluded patients who did not have at least one RDW measurement in the first 91 days of PD treatment. The final cohort comprised 14 323 PD patients (Supplementary data, Figure S1).

All data including patient characteristics, comorbid conditions and laboratory measurements were obtained from the electronic medical records of the LDO. Race/ethnicity was self-identified into five categories. Blood samples were drawn using standardized techniques at the LDO facility and analyzed with automated and uniform methods at a central laboratory in Deland, FL, USA, within 24 h. Most laboratory measurements were made monthly, if not quarterly. To minimize measurement variability, all repeated laboratory measurements and parenteral medication dosages were summarized and averaged for each 91-day period of PD through follow-up. Data from the first 91 days of PD treatment were considered as baseline.

Exposure and outcome variables

The primary exposure was RDW during PD treatment. All patients had a baseline RDW measurement. For time-varying analyses in patients with a subsequent missing RDW value, the last measured RDW was carried forward. In all analyses, RDW was categorized into five groups: <13.5, 13.5–<14.5, 14.5–<15.5, 15.5–<16.5 and ≥16.5%. The RDW categories as well as the reference of RDW (14.5–<15.5%) were chosen, considering the median of the cohort and prior studies [16–18].

The three primary outcomes of this study were (i) hospitalization incidence rate, (ii) time to first hospitalization and (iii) all-cause mortality during PD treatment. CV mortality was also examined in a proportion of patients with an available cause of death. Patients with a recorded death, yet a missing or unknown cause of death, were excluded in these sensitivity analyses. The cause of death was obtained from the LDO electronic medical records. We considered the following causes as CV: acute myocardial infarction, pericarditis, atherosclerotic heart disease (ASHD), cardiomyopathy, cardiac arrhythmia, cardiac arrest—cause unknown, valvular heart disease, pulmonary edema due to exogenous fluids, congestive heart failure (CHF), pulmonary embolus, cerebrovascular accident and ischemic brain damage. Data on all censoring events and outcomes were obtained from the LDO electronic medical records. Patients were followed from the initiation of PD treatment and censored for death or hospitalization in the respective analyses, kidney transplantation, recovered renal function, transfer to another dialysis modality or another dialysis organization or 31 December 2011, whichever occurred first. The use of another dialysis modality was recognized as treatment with the new modality for at least 60 continuous days. All outcomes within 60 days of transfer from PD were attributed as a PD outcome.

Statistical analyses

Baseline characteristics are presented as mean ± SD, median [interquartile range (IQR)] or proportion, as appropriate. Standardized differences were calculated between included and excluded patients.

Negative binomial and Poisson regression models, as our primary and sensitivity analyses, respectively, were used to examine the association of baseline RDW and hospitalization rate.

In time-to-event analyses, separate Cox proportional hazards models as well as competing risk regression models such as sensitivity analyses using the Fine and Gray method [22] were used to evaluate the association of baseline or time-varying RDW with each outcome. In analyses where all-cause mortality was the outcome, competing events were transplant and transfer to in-center hemodialysis. In analyses where time to first hospitalization was the outcome, all-cause mortality, transplantation and transfer to in-center hemodialysis were treated as competing events. In sensitivity analyses investigating CV causes of death, Cox proportional hazards models were used to model a CV cause of death against a non-CV cause of death.

For all analyses, three hierarchical models were used for adjustment: (i) unadjusted models; (ii) case mix, including age, gender, primary insurance, race/ethnicity, dialysis vintage at the start of PD, year incident to ESRD, facility region and the following comorbid conditions: diabetes, hypertension, CHF, ASHD and other CV disease; and (iii) case mix + malnutrition-inflammation-cachexia syndrome, including the variables in the case-mix model as well as hemoglobin, albumin, uncorrected calcium, phosphorus, parathyroid hormone, iron

saturation, total iron binding capacity, ferritin, bicarbonate, white blood cell count, lymphocyte percentage, alkaline phosphatase, median weekly doses of erythropoietin and iron, total weekly *Kt*/*V*, residual kidney function, 4-h dialysate:plasma creatinine ratio from the peritoneal equilibration test and treatment with automated PD. In time-varying analyses, time-updated values were also used for geographic region, laboratory measurements, medication use and use of automated PD.

We also examined effect modification of the association of baseline RDW [dichotomized at the median RDW level as higher versus lower RDW (referent): ≥15.0 versus <15.0%, respectively] with the three outcomes across strata of demographics and laboratory measurements. Wald's tests for interaction were performed in fully adjusted models. Finally, we used restricted cubic splines to model the association of baseline and time-varying RDW with all-cause mortality and time to first hospitalization, with 4 best placed knots.

Data on baseline characteristics of gender, race/ethnicity and geographic region (baseline and time varying) were missing for <0.3% of the cohort and were not imputed. In addition, most data on laboratory variables for baseline and time-varying analyses were missing for <6% of the cohort, with the exception of 34% for baseline dialysate:creatinine ratio and <16% for baseline and time-varying total weekly *Kt*/*V* and residual kidney function. These variables were imputed using multiple imputation of five sets and combined using Rubin's rules to obtain a hazard ratio (HR) or incidence rate ratio (IRR). All analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA). Restricted cubic spline functions were performed using Stata 14.1 (StataCorp, College Station, TX, USA). This study was approved by the institutional review board of the University of California, Irvine. Given the large sample size, patient anonymity and nonintrusive nature of the study, the written consent requirement was waived.

RESULTS

PD patient characteristics

Baseline clinical characteristics of PD patients are presented in Table 1. The cohort was on average 56 ± 16 years old, including 43% females, 23% African Americans and 62% diabetics. Patients initiated PD therapy at a median of 33 (IQR 10–174) days from the first dialysis treatment. The mean RDW was 15.3 ± 1.6%. Patients with a greater RDW value were more likely to be female, African American and have CHF and ASHD. Moreover, higher RDW patients tended to have lower hemoglobin, iron saturation (ISAT), lymphocyte percentage and total iron binding capacity during the baseline PD period.

RDW and mortality

The median follow-up was 12 (IQR 7–22) months while on PD and the crude death rate for the cohort was 97 (IQR 93–102) per 1000 person-years. Across all levels of adjustment, baseline RDW was linearly associated with all-cause mortality on PD, where RDW <13.5% had the lowest risk of mortality after full adjustment [HR 0.75 (95% CI 0.60–0.95); reference 14.5–<15.5%] (Supplementary data, Table S1A; Figure 1A). Moreover, this linear relationship was similar in competing risk analyses (Supplementary data, Table S1B) and in unrestricted cubic splines (Supplementary data, Figure S2A). Likewise with CV mortality, a similar yet attenuated linear relationship was observed, where RDW <14.5% was not associated with a lower risk as observed with all-cause mortality (Supplementary data, Table S2A and Figures S2B and S3A).

In subgroup analyses, higher RDW (≥15.0%) versus lower RDW was associated with a higher risk of all-cause mortality across most strata of demographics and clinical characteristics (Supplementary data, Figure S4). There was a significant interaction for ISAT; among patients with ISAT ≥30%, higher RDW was not significantly associated with mortality (P for interaction <0.01).

Moreover, examining the short-term risk of time-varying RDW and mortality also showed a linear relationship in unadjusted and case-mix models (Supplementary data, Table S3A; Figure 1B). After adjustment for demographics and comorbidities, time-varying RDW was linearly associated with mortality, where RDW ≥16.5% was associated with an almost 3-fold higher risk of mortality [HR 2.75 (95% CI 2.43–3.12)]. However, this relationship was attenuated towards a slightly flatter linear shape after additional adjustment for laboratory covariates. Likewise, low RDW <13.5 and 13.5–<14.5% had a lower risk of all-cause mortality [HR 0.77 (95% CI 0.62–0.96) and 0.75 (0.65–0.88), respectively]. In sensitivity analyses, the time-varying RDW and mortality relationship was similar when considering competing events and spline analyses (Supplementary data, Table S3B and Figure S2D). Finally, higher time-varying RDW was also associated with a higher risk of CV mortality, although the relationship resembled a slight J-shaped association (Supplementary data, Table S2B and Figures S2E and S3B).

RDW and hospitalization

During follow-up, patients experienced a median of 1 (IQR 0–2) hospitalizations while treated with PD. In unadjusted and case-mix analyses, RDW was linearly associated with a higher rate of hospitalizations during follow-up (Supplementary data, Table S4A; Figure 2). Additional adjustment for laboratory variables slightly attenuated this association, however, a linear relationship still remained. The lowest RDW was associated with the lowest rate of hospitalizations [IRR 0.77 (95% CI 0.70–0.84)]. Moreover, in sensitivity analyses under a Poisson model, the linear relationship was also evident. Finally higher RDW ≥15.0% was associated with a higher rate of hospitalization across strata of demographics and clinical characteristics compared with RDW <15.0%, yet patients with a longer vintage had an even greater hospitalization rate (P for interaction <0.01) (Supplementary data, Figure S5).

In addition to hospitalization rate, baseline RDW was also linearly associated with risk of time to first hospitalization (Supplementary data, Table S5A; Figure 3A). Over a median follow-up of 6 (IQR 3–13) months while on PD, the cohort had a crude hospitalization rate of 762 (IQR 746–779) per 1000 person-years. After full adjustment as well as in competing risk analyses, baseline RDW ≥16.5% had an ∼20% higher risk

Table 1. Baseline characteristics of 14 323 PD patients stratified by baseline RDW strata

Characteristic	Total	RDW (%) strata				
		<13.5	13.5–<14.5	14.5–<15.5	15.5–< 16.5	≥16.5
n (%)	14 323	1475 (10.3)	3456 (24.1)	3907 (27.3)	2686 (18.8)	2799 (19.5)
Age (years)	56 ± 16	54 ± 16	55 ± 16	56 ± 16	56 ± 16	56 ± 16
Gender (female), %	43	41	40	42	44	49
Vintage (days)	33 (10–174)	32 (11–237)	38 (11–219)	31 (10–169)	31 (9–146)	34 (10–142)
Ever treated with HD (%)	42	35	41	41	45	46
Race/ethnicity (%)						
White	57	64	60	59	54	50
African American	23	13	18	20	27	34
Hispanic	13	14	15	13	13	10
Asian	4	5	4	4	3	3
Other	3	4	4	3	2	3
Insurance (%)						
Medicare	46	44	45	46	46	47
Medicaid	4	4	5	4	4	4
Other	50	52	50	50	49	49
Comorbidities (%)						
Diabetes	62	56	61	63	66	62
Hypertension	53	50	52	53	55	55
CHF	20	13	17	18	23	26
ASHD	17	14	17	17	17	20
Other CV disease	15	12	14	15	16	18
Year of incidence (%)						
2007	19	14	14	17	20	28
2008	19	19	21	19	19	19
2009	21	18	20	22	24	21
2010	24	25	25	25	23	20
2011	17	24	20	16	14	13
Geographic location (%)						
Northeast	11	12	10	11	11	13
Midwest	19	20	19	18	19	18
South	47	42	45	47	49	51
West	23	27	26	23	21	17
IV medications						
Iron dose (mg/month)	0 (0–400)	0 (0–200)	0 (0–300)	0 (0–400)	50 (0–400)	100 (0–500)
ESA (U/week)	3108 (0–7952)	777 (0–3451)	2588 (0–5908)	4074 (0–8400)	4349 (0–9639)	4046 (0–10 836)
Laboratory measurements						
Albumin (g/dL)	3.6 ± 0.5	3.8 ± 0.4	3.7 ± 0.4	3.6 ± 0.5	3.6 ± 0.5	3.5 ± 0.5
Alkaline phosphatase (U/L)	82 (60–107)	76 (61–98)	80 (63–103)	83 (65–107)	83 (66–108)	87 (67–114)
Body mass index (kg/m^2)	28.5 ± 6.5	27.9 ± 5.8	28.7 ± 6.3	28.7 ± 6.5	28.8 ± 6.8	28.0 ± 6.6
Uncorrected calcium (mg/dL)	8.7 ± 0.7	8.9 ± 0.6	8.8 ± 0.6	8.7 ± 0.7	8.7 ± 0.7	8.7 ± 0.7
CO_2 (mEq/L)	25.1 ± 2.9	25.2 ± 2.8	25.2 ± 2.8	25.1 ± 2.9	25.0 ± 3.0	25.1 ± 3.1
Ferritin (ng/mL)	324 (163–588)	283 (141–539)	321 (159–572)	316 (164–562)	339 (172–610)	357 (167–645)
Hemoglobin (g/dL)	11.6 ± 1.3	12.1 ± 1.2	11.9 ± 1.2	11.7 ± 1.2	11.5 ± 1.3	11.3 ± 1.4
ISAT (%)	30.8 ± 12.6	33.4 ± 11.7	31.8 ± 11.9	30.8 ± 12.6	29.9 ± 12.7	29.4 ± 12.3
Lymphocyte (%)	21.0 ± 7.3	22.7 ± 7.2	21.6 ± 7.0	21.0 ± 7.0	20.4 ± 7.3	19.9 ± 7.7
Phosphorus (mg/dL)	5.0 ± 1.3	4.7 ± 1.1	4.9 ± 1.2	5.1 ± 1.3	5.1 ± 1.3	5.2 ± 1.4
PTH (pg/mL)	302 (191–486)	286 (184–456)	305 (199–477)	306 (193–481)	307 (189–501)	302 (189–499)
TIBC (mg/dL)	245.2 ± 46.3	257.0 ± 42.0	251.8 ± 44.3	246.0 ± 45.6	239.7 ± 46.4	235.2 ± 49.0
WBC (mm^3)	7.5 ± 2.4	7.2 ± 2.2	7.5 ± 2.3	7.5 ± 2.2	7.5 ± 2.3	7.6 ± 2.9
Weekly total *Kt*/*V*	2.5 ± 0.7	2.7 ± 0.8	2.6 ± 0.7	2.5 ± 0.7	2.4 ± 0.7	2.4 ± 0.7
Residual kidney function (L/week/1.73 m^2)	55.5 (25.7–91.4)	78.0 (43.6–113.4)	62.2 (33.2–98.4)	55.6 (27.0–88.2)	48.9 (21.1–84.5)	41.8 (15.0–75.8)
4-h D:P creatinine ratio	0.65 ± 0.12	0.62 ± 0.12	0.64 ± 0.12	0.65 ± 0.12	0.66 ± 0.12	0.65 ± 0.12
Use of automated PD (%)	68	70	70	69	68	65

Data presented as mean ± SD or median (IQR) unless stated otherwise.
D:P creatinine, 4-h dialysate:plasma ratio of creatinine; IV, intravenous; WBC, white blood cell.

of hospitalization compared with RDW 14.5–<15.5% (Supplementary data, Table S5B). We also observed a similar, yet linear association between continuous RDW and hospitalization risk (Supplementary data, Figure S2C). In subgroup analyses, RDW ≥15.0% was associated with a higher risk of time to first hospitalization across most strata after full adjustment (Supplementary data, Figure S6). However, there was significant effect modification on the basis of race, where RDW

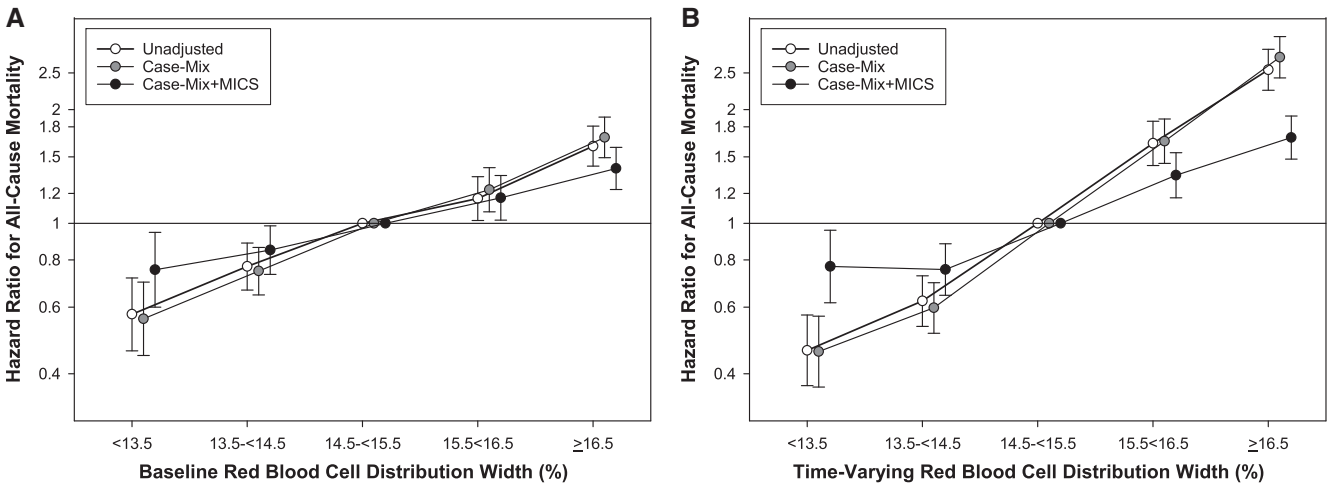

FIGURE 1: Association of (**A**) baseline and (**B**) time-varying RDW with all-cause mortality.

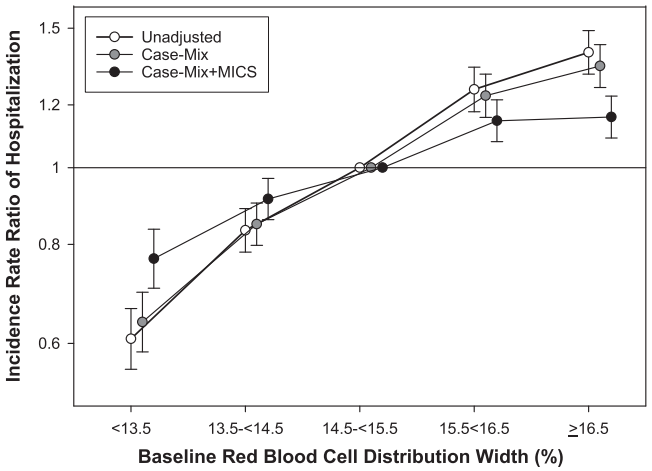

FIGURE 2: Association of baseline RDW with the hospitalization rate.

≥15.0% did not have a higher risk of hospitalization among African American patients compared with an RDW <15.0% (P for interaction <0.01). Moreover, among patients with a longer vintage to PD, RDW ≥15.0% was associated with an even higher risk of hospitalization compared with an RDW <15.0% (P for interaction <0.01). In time-varying analyses there was also a linear relationship between RDW and time to first hospitalization, though slightly attenuated after laboratory adjustment (Supplementary data, Table S6A and S6B; Figure 3B). A time-varying RDW ≥16.5% was associated with a 30% higher risk of hospitalization, although the association was attenuated in restricted cubic spline analyses when examining RDW as a continuous variable (Supplementary data, Figure S2F).

DISCUSSION

In a large, contemporary cohort of incident PD patients in the USA, we observed that both higher baseline and time-varying RDW were associated with a greater risk of mortality, including all-cause and CV, and time to first hospitalization. We also observed that higher RDW is associated with a higher rate of hospitalizations. These associations remained consistent across a series of sensitivity analyses, including subgroup analyses.

To date, there have been few studies examining the association of RDW and mortality in PD patients. The largest of these studies investigated a cohort of 1293 incident PD patients and observed that baseline RDW ≥15.5% (reference RDW <15.5%) was associated with a 60% higher risk of CV mortality, whereas the relationship with all-cause mortality showed a higher, yet attenuated risk [HR 1.27 (95% CI 0.93–1.75)] [16]. Similarly, in smaller cohorts of <500 PD patients each, Hsieh *et al.* [18] observed a higher risk of all-cause and CV mortality with baseline RDW ≥15.3% (reference RDW <15.3%), and Sun *et al.* [17] reported an almost 3-fold higher risk of all-cause mortality for every unit increase in baseline RDW. Like these studies, we too observed that greater baseline RDW was associated with higher risks of both all-cause and CV mortality in incident PD patients. With the availability of repeated RDW measures in our cohort we were also able to examine the short-term risk of RDW through time-varying analyses, where we report a similar linear pattern with mortality. This incremental relationship of time-varying RDW with mortality among incident PD patients mirrors the linear pattern observed among a large cohort of incident HD patients [14]. Together, our findings that higher RDW is associated with a greater risk of mortality in PD patients are on par with other epidemiological studies investigating RDW in chronic kidney disease and CV disease patients [8, 10, 12, 14, 23, 24].

Moreover, we also observed a higher risk of time to first hospitalization as well as a higher rate of hospitalizations during PD. To date, few studies have investigated the association of RDW and hospitalizations. Of note, in the general population, higher RDW was associated with a greater risk of time to hospitalization for CV reasons, including atrial fibrillation and heart failure [4, 5, 8]. In a small cohort of elderly patients, higher RDW was associated with a higher odds of 1-year all-cause hospitalizations after multivariable adjustment, and this association was stronger than that of other inflammatory markers [3]. Within the general US population, a greater prevalence of hospitalization stays was observed with increasing categories of

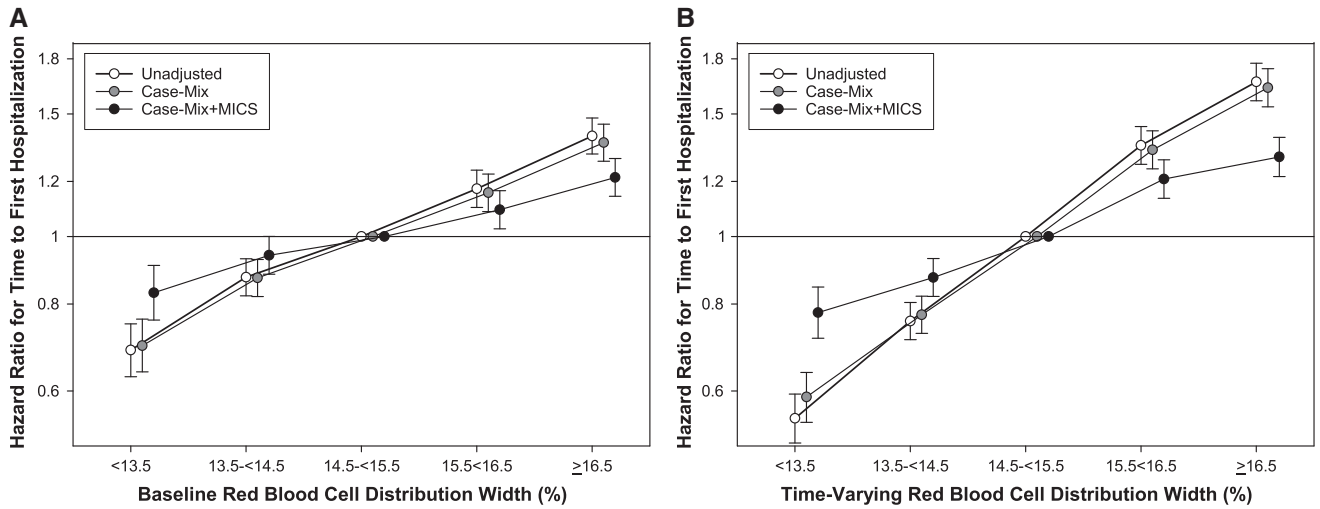

FIGURE 3: Association of (**A**) baseline and (**B**) time-varying RDW with time to first hospitalization.

RDW [6]. Furthermore, in a retrospective study of hospitalized patients, higher RDW was associated with higher odds of all-cause and CV readmission during follow-up [25]. However, our study is the first to investigate the association of RDW and hospitalization in ESRD patients. Similar to the aforementioned studies in other populations, we observed that higher baseline and time-varying RDW was associated with a higher risk and rate of hospitalization in PD patients as well.

Although the mechanism between RDW and mortality or hospitalization is unclear, prior research has suggested that RDW plays a role in a number of patient complexities, including inflammation and oxidative stress [2]. It has been suggested that an increase in RDW in ESRD patients may be attributed to inflammation [26, 27]. The inflammatory condition, which is prevalent among ESRD patients, including PD patients, may increase RDW and anisocytosis through impaired iron metabolism and declining erythropoietin response, thus leading to the circulation of immature erythrocytes and ineffective erythropoiesis, and possibly resulting in a greater risk of mortality and morbidity [2, 18, 28]. Moreover, higher RDW may be the result of increased oxidative and inflammatory stress stemming from the release of proinflammatory cytokines [29]. A previous study in PD patients has suggested that oxidative stress is associated with peritonitis, contributing to additional morbidity and mortality [30]. Certain inflammatory markers have also been shown to be well correlated among PD patients and are also suggested in association with higher hospitalization risk [16, 31]. In addition, inflammation may also act by increasing RDW through erythropoietin hyporesponsiveness in ESRD patients, as it has also been suggested that erythropoietin-stimulating agent (ESA) use may affect RDW levels [2, 23, 32, 33]. In our study, we observed higher weekly ESA doses across increasing RDW categories. Yet higher RDW was associated with worse outcomes irrespective of the ESA dose. Although we also adjusted for a number of malnutrition and inflammatory markers, as well as ESA dose, our findings suggest that there are additional confounding factors involved in the RDW and mortality or hospitalization relationships. Thus, given the uncertainty in the pathways in which RDW acts, future studies are needed to elucidate these mechanisms.

There are a number of limitations to this study. Due to the observational nature of the study design, we cannot exclude the possibility of residual confounding nor imply causal relationships. Although these findings may not necessarily be actionable in clinical practice, RDW may continue to serve as a surrogate marker for inflammation, malnutrition or iron deficiency, and studies are needed to investigate mechanisms between RDW and adverse outcomes. Furthermore, the cause of hospitalization was missing for much of these data, thus we could not accurately examine the risk of nonfatal CV- or infection-related events. Although more than a third of PD deaths in the cohort did not have an available cause of death, those patients were excluded rather than included and we also observed a linear relationship between RDW and CV mortality. We adjusted for known and available confounders, including those related to malnutrition, inflammation and cachexia, which may be potential intermediates on the causal pathway, and we were unable to adequately adjust for the presence of nutritional deficiencies such as vitamin B12 and folate or inflammatory markers such as C-reactive protein due to the large number of missing measurements.

Yet our study also comes with a number of strengths. This is the largest study to investigate RDW in incident PD patients, which was racially and ethnically diverse and representative of the US population, as previous RDW studies were sourced from Asian PD patient populations. In addition, the risk of selection bias for patients without an RDW measurement was minimal; however, we do not know the reasons for missing RDW measurements as RDW is available in standard blood panels. Nonetheless, few PD patients were excluded and a comparison between included and excluded patients shows similarities in clinical characteristics and laboratory measures (Supplementary data, Table S7). The most notable difference between groups, however, was the markedly lower proportion of patients on automated PD among excluded patients. Moreover, although RDW values may be subject to the

measurement instrument, all RDW values for this cohort were routinely collected and analyzed using standardized techniques, thus the between-subject variation and differences due to the analytical technique were likely minimized [2].

In conclusion, we observed that baseline and time-varying RDW are linearly associated with a higher risks of mortality and time to first hospitalization, as well as a higher rate of hospitalizations in incident PD patients. These associations remained consistent in numerous sensitivity analyses. Coupled with the growing amount of information regarding RDW as a marker in ESRD patients, additional studies are needed to investigate the mechanism behind these associations.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

M.S., M.Z.M., E.S. and K.K.-Z. contributed to the study concept and design. K.K.-Z. acquired the data. M.S. conducted statistical analyses and interpretation with advice from M.Z.M., A.U., Y.O., C.P.K., K.K.-Z. and E.S. M.S. and E.S. drafted the manuscript and M.Z.M., A.U., Y.O., C.P.K. and K.K.-Z. critically revised it for important intellectual content. All authors contributed to the preparation of the article and approved the final version.

CONFLICT OF INTEREST STATEMENT

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