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Original Investigation

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 ≥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 B_{12}, 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 ≥ 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 sociodemographics, 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.

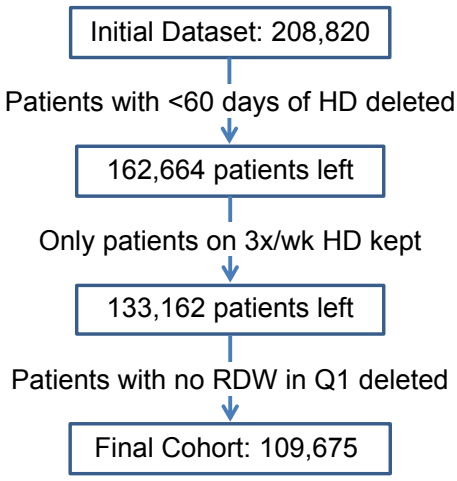

Figure 1. Flow chart of patient selection. Abbreviations: HD, hemodialysis; Q1, quarter 1; RDW, red cell distribution width.

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 ± 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 ≥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 ≥ 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