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Association Between Red Blood Cell Distribution Width and All-cause Mortality in Chronic Kidney Disease Patients: A Systematic Review and Meta-analysis

Tao Zhang,[a,*] Jing Li,[b,*] Yan Lin,[a] Hongtao Yang,[a] and Shili Cao[a]

[a]*Department of Nephrology, The First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, People's Republic of China*
[b]*Department of Transplantation, The First Central Hospital of Tianjin, Tianjin, People's Republic of China*

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Background. Considering results among previous studies regarding the relationship of red blood cell distribution width (RDW) and all-cause mortality in chronic kidney disease (CKD) patients, we aimed to perform a comprehensive meta-analysis to evaluate the potential association between RDW and all-cause mortality in CKD patients.

Methods. We conducted a systematic literature using electronic databases (PubMed, Ovid, Embase and Web of Science) to identify the studies reporting the association between RDW and all-cause mortality in CKD patients. We searched the literatures published December 2016 or earlier. We used both fix-effects and random-effects models to calculate the overall effect estimate. A sensitivity analysis and subgroup analysis were performed to find the origin of heterogeneity.

Results. We retrieved 9 studies with a total of 117,047 patients. For every 1% increase in RDW, the risk of all-cause mortality increased by 47% (HR 1.47, 95% CI 1.35−1.61) with no statistical heterogeneity among the studies (I^2 = 44.5%, p = 0.094). When RDW was entered as a categorical variable, mortality risk was significantly increased (HR 1.84, 95% CI 1.21−2.81). Heterogeneity among the studies was observed for all-cause mortality (I^2 = 82.3%, p = 0.001). We also performed a predefined subgroup analyses according to study population. We found that for every 1% increase in RDW, the risk of all-cause mortality in hemodialysis (HD) patients increased by 36% (HR 1.36, 95% CI 1.20−1.53).

Conclusions. Our meta-analysis suggests that high levels of RDW probably increase the risk of all-cause mortality in CKD patients.

Key Words: Red blood cell distribution width, Chronic kidney disease, Peritoneal dialysis, Hemodialysis, Mortality, Meta-analysis.

Introduction

Red blood cell distribution width (RDW) is a quantitative measure of variability in the size of circulating erythrocytes with higher values reflecting greater heterogeneity in cellular sizes at no additional cost. This parameter, in conjunction with mean corpuscular volume, was first introduced as an aid to the differential diagnosis of hypochromic anemia. High values of RDW have been implicated in the pro- inflammatory state (1,2). In more recent years, as a part of complete blood count (CBC) test, RDW has received a lot of attention in various populations. Of note, a number of studies reported that RDW has been associated with mortality and other adverse outcomes in various clinical conditions, including acute and chronic heart failure (3), acute dyspnea (4), acute pancreatitis (5), severe sepsis and septic

*These authors contributed equally to this study.

Address reprint requests to: Shili Cao, Professor, Department of Nephrology, The First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300112, People's Republic of China; Phone: (+86) 22-27986563; FAX: (+86) 22-27986573; E-mail: caozt1949@163.com

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shock (6,7), trauma (8), acute pulmonary embolism (9), older adulthood (10), and even acute kidney injury or kidney transplantation (11,12).

Chronic kidney disease (CKD) is considered as a status of increased inflammation, oxidative stress and endothelial dysfunction. However, renal failure is the end stage of several kidney diseases, which increases disproportionately high mortality and economic burden around the world attributed to untraditional risk factors. To date, a number of studies have shown that higher RDW levels are associated with renal function (13) and adverse outcomes in end-stage renal disease (ESRD) patients (14,15). Although the relevant mechanisms involved in the relationship between RDW and mortality in CKD patients, particularly for those ongoing dialysis, are not well clarified, it is of critical relevance to recognize the high risk population. Given that inconsistent results regarding the association between RDW and adverse impacts in CKD patients, we systematically reviewed the current literatures and performed a systematic review and comprehensive meta-analysis to evaluate prognostic value of RDW in CKD patients.

Methods

Search Strategies and Inclusion Criteria

Two reviewers (TZ. and JL.) systematically and independently searched the online databases of PubMed, Ovid, Embase and Web of Science to identify relevant studies published until December 5, 2016. We used the following keywords 'red blood cell distribution width' or 'RDW' and 'renal failure' or 'chronic kidney disease or CKD' or 'end-stage renal disease or ESRD' or 'hemodialysis or HD' or 'peritoneal dialysis or PD'. Titles and abstracts as well as the reference lists of all of the identified reports were examined independently by 2 reviewers (TZ. and JL.) to include potentially relevant studies that reported the association between RDW and all-cause mortality in CKD patients.

The inclusion criteria were as follows: a) the study design was a prospective or retrospective cohort study and case−control study. Individual case reports, editorials, and review articles were excluded; b) measured RDW at baseline and documented clinical outcome during follow-up in CKD patients; c) clearly defined the death events in CKD patients; d) reported the hazard ratio(HR)or odds ratio (OR) and the corresponding 95% confidence interval (CI) for RDW levels and all-cause mortality in CKD patients; e) only studies that included patients with a diagnosis of CKD that is clearly defined and in accordance with current guideline based definitions were selected. We also excluded the studies that only reported unadjusted HR or that reported HR without 95% CI. We included published and unpublished studies without language restriction.

Data Extraction

Two reviewers (TZ. and JL.) independently screened the abstracts or titles of the studies from the electronic search to identify all potential eligible studies. Potentially relevant reports were then retrieved as complete manuscripts and assessed for compliance with the inclusion criteria. Data extraction was performed from eligible studies by two blinded reviewers (TZ. and JL.) using a standard data extraction. Any uncertainties or discrepancies between the two reviewers were resolved through consensus after rechecking the source data and consultation with the third reviewer (SC.). In each primary study, the results were reported with different variable types (categorical or continuous), so we extracted and analyzed all the multivariate adjusted HR/OR and the corresponding 95% CI in two ways (categorical or continuous) to evaluate RDW in predicting the risk of all-cause mortality in CKD patients. The extracted data elements of this study included first author's last name, publication year, country, study design, study population, sample size, participants' age and sex, the proportion of combined diabetes mellitus, duration of follow-up and end point events.

Quality Assessment

To limit the heterogeneity secondary to differences among study designs, the quality of each study was evaluated according to the guidelines developed by the United States Preventive Task Force (16) and the Evidence-Based Medicine Working Group (17). A point score system was applied according to the quality of the study. The following characteristics were assessed: (1) clear description of inclusion and exclusion criteria; (2) study sample representative for mentioned population; (3) clear description of sample selection; (4) full specification of clinical and demographic variables; (5) follow-up duration more than one year; (6) reporting the loss of follow-up; (7) clear definition of CKD, ESRD, hemodialysis or peritoneal dialysis; (8) clear definition of outcomes and outcome assessment; (9) temporality (assessment of RDW at the baseline); and (10) adjustment of possible confounders on the multivariate analysis. Studies were graded as poor quality if they met <5 criteria, fair if they met 5 to 7 criteria, and good if they met ≥ 8 criteria.

Statistical Analysis

Pooled effect sizes were presented as the HR with 95% CI. The OR value in each primary study was directly considered as HR. Because the results were reported with different variable types (categorical or continuous) in each study, we displayed our estimates in two ways (categorical or continuous) to evaluate the association between RDW and all-cause mortality in CKD patients. To evaluate the heterogeneity across studies, we used I^2 derived from the