Elevated red blood cell distribution width as a marker of higher risk for contrast-induced nephropathy: A systematic review and meta-analysis

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Background and objectives: Contrast-induced nephropathy (CIN) after the use of contrast media in patients is a common complication associated with a poorer outcome. The large sample research of the correlation between RDW and CIN is lack. We performed a meta-analysis and systematic review to investigate the value of red cell distribution width (RDW) as a marker in the early prediction of CIN. Methods: Relevant articles were selected from the databases of PubMed, EMBASE and the Cochrane Library until May 28, 2018, to identify eligible cohort and case-control studies evaluating RDW levels to predict CIN. Overall odds ratio (OR) of the effect of RDW for CIN were pooled and shown in forest plots. Results: Seven studies with a total of 3,048 patients were included in this meta-analysis. The combined results based on the pooling of the 7 studies that provided related data indicated that the elevated RDW was related to CIN(OR, 1.35 (95% CI, 1.11-1.65)). Furthermore, similar results were in-analysis stratified by acute coronary syndrome (ACS), ST-segment elevation myocardial infarction (STEMI) and/or non-ST-segment elevation myocardial infarction (NSTEMI) (OR, 1.45 (95% CI, 1.29-1.64)) and ACS only STEMI (OR, 1.58 (95% CI, 1.35-1.85)). For every 1% increase in RDW, the risk of CIN was increased by 45% in ACS patients and increased by 58% in STEMI patients. Conclusions: This meta-analysis demonstrated that RDW could be a potential risk factor in CIN patients, and that higher RDW may have higher risk than those with lower RDW in ACS, especially in STEMI patients.

Key Words: red blood cell distribution width; contrast-induced nephropathy; acute coronary syndrome; ST-segment elevation myocardial infarction; meta-analysis

INTRODUCTION

The use of contrast media in medical practice has been rapidly increasing in radiologic imaging and interventional therapy. Some patients developed contrast-induced nephropathy (CIN) after undergoing these diagnostic and therapeutic procedures. The development of CIN is associated with poor clinical outcomes including prolonged hospitalization and increased cost, risk of end-stage renal failure, and mortality. A 3-fold higher risk of CIN was developed in acute coronary syndrome (ACS). Poor outcome is caused partly by the lack of a predictive marker for CIN. Therefore, strategies for predicting CIN and its prevention are important.

Erythrocyte variability and heterogeneity are measured by red cell distribution width (RDW), which is obtained by the standard complete blood cell counts. Increased RDW indicates un-
uniform size, which is related to them echanism of erythropoiesis obstacle and red cell degradation. Increased RDW reflects chronic inflammation and oxidative stress.\textsuperscript{10,11} RDW was related with high-sensitivity Creative protein (hsCRP), and erythrocyte sedimentation rate (ESR). However, S. Bello et al. found no association between inflammatory markers (CRP, PCT and WBC) and long-term community-acquired pneumonia mortality. Studies have shown that an increased RDW is associated with poor clinical cardiac outcomes in various clinical settings, included patients with heart failure,\textsuperscript{12-14} slow coronary blood flow,\textsuperscript{15} stable coronary artery disease,\textsuperscript{16,17} ACS,\textsuperscript{18-21} and those undergoing percutaneous coronary intervention (PCI).\textsuperscript{22} Due to the potential mechanism of inflammation and oxidative stress in the development of CIN, RDW might be a marker of CIN risk. However, whether RDW is related to CIN risk remains unclear. The large sample research of the correlation between RDW and CIN is lacking. To date, no independent meta-analysis has been carried out to identify. Thus, we performed a systemic review and meta-analysis to investigate whether elevated RDW levels are associated with the development of CIN, especially PCI in patients with ACS.

MATERIALS AND METOOGDS

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were applied in this systemic review and meta-analysis. The databases used in the search for pertinent articles included PubMed, EMBASE, and the Cochrane Library to identify eligible studies published up to May 28, 2018. The search terms for all three databases were “erythrocyte indices”, “red blood cell distribution width”, “RDW”, “contrast-induced nephropathy”, “CIN”, and “radiographic contrast nephropathy”. Manual retrievals were also performed by reviewing the references of the eligible studies. One reviewer performed the retrieval, whereas another confirmed the process.

Study Selection

By using titles, abstracts, and/or full articles, the search yielded 7 articles. The inclusion criterion included studies investigating the RDW values for CIN risk [studies including the odds ratio (OR)]. The outcomes of the studies were reported in terms of the CIN rate. The full text was considered in terms of its eligibility for inclusion. The criteria for exclusion included patients lacking laboratory RDW data, studies without OR, animal studies, abstracts, duplicated publications, or those published in languages other than English. While screening the citations, two reviewers independently reviewed the search results to determine article inclusion. In cases of discord, a consensus was reached through discussion with the articles’ authors.

Data Extraction and Quality Assessment

Data extraction and quality assessment were performed independently by two authors. The following data were extracted from eligible studies using standardized forms by documenting or recalculating the following variables: names of the first authors, sources of patients, publication year, sample sizes, characteristics of patients, event rates, the corresponding OR and 95% confidence intervals (CIs), CIN definition, timing of RDW measurement, and the confounding factors adjusted for. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies.

Statistical Analysis

This meta-analysis was performed and reported in accordance with the PRISMA guidelines for systematic reviews and meta-analyses.\textsuperscript{23} The systematic review with assessed RDW value was related to CIN risk in people. Meanwhile, subgroup analysis was performed to explore the possible source of heterogeneity. For comparison of different populations of RDW value related to the incidence of CIN, the population of ACS was divided into groups of ACS patients with both ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI), and ACS patients with STEMI only. For the heterogeneity assessment, we used Cochrane’s Q test (significance level of $P<0.10$), as well as the $I^2$ statistics in the eligible studies. If $I^2>50\%$ or $P<0.10$, the OR were pooled using a random-effects model; otherwise, the OR were pooled using a fixed-effects model. Sensitivity analysis was conducted to exclude any single study that may have resulted in a significant change to the final results. Funnel plots was applied to evaluate the potential publication bias.\textsuperscript{23} All analyses were performed using R software.

RESULTS

The search yielded 9 articles that were assessed using titles, abstracts, and/or full articles, and 9 reviewed full-text articles, of which 2 articles were excluded for the reasons shown in Figure 1. Seven studies with a total of 3,048 patients were included for this meta-analysis. [Figure 1, Table 1]

![Figure 1](study_flow_diagram.png)

**Study flow diagram**

**Summary of the Eligible Studies**

As the flowchart in Figure 1 shows, a total of 7 studies\textsuperscript{24-30} meeting
Elevated RDW as CIN Risk Marker

Table 1  The characteristics of included studies

<table>
<thead>
<tr>
<th>First Author(year)</th>
<th>Country</th>
<th>Study population</th>
<th>Sample size</th>
<th>Study design</th>
<th>OR</th>
<th>Selection</th>
<th>Comparability</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atsushi Mizuno (2015)²⁴</td>
<td>Japan</td>
<td>STEMI patients without hemodialysis</td>
<td>102</td>
<td>cohort study</td>
<td>2.029 (1.029-3.999)</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Ertan Vurus¸kan (2017)²⁵</td>
<td>Turkey</td>
<td>Patients with peripheral artery disease</td>
<td>359</td>
<td>case-control study</td>
<td>0.943 (0.822-1.055)</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Katarzyna Zbierska-Rubinkiewicz (2017)²⁶</td>
<td>Poland</td>
<td>NSTEMI and STEMI patients</td>
<td>257</td>
<td>cohort study</td>
<td>1.30 [1.04-1.61]</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Alparslan Kurtul(2015)²⁷</td>
<td>Turkey</td>
<td>ACS (STEMI, NSTEMI) who underwent PCI</td>
<td>662</td>
<td>cohort study</td>
<td>1.379 (1.084-1.753)</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Fatih Akin(2015)²⁸</td>
<td>Turkey</td>
<td>STEMI</td>
<td>630</td>
<td>cohort study</td>
<td>1.406(1.120-1.792)</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Dursun Çayan Akkoyun (2015)²⁹</td>
<td>Turkey</td>
<td>STEMI</td>
<td>359</td>
<td>cohort study</td>
<td>1.716 (1.363-2.157)</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
<tr>
<td>Kai Zhao(2015)³⁰</td>
<td>China</td>
<td>SAP patients who underwent PCI</td>
<td>679</td>
<td>cohort study</td>
<td>1.381 (1.086-1.757)</td>
<td>★★★★</td>
<td>★★</td>
<td>★★★</td>
</tr>
</tbody>
</table>

our included criteria were initially collected through our search strategy. Overall, 6 cohort studies²⁴,²⁶-³⁰ and 1 case-control study,²⁵ with a total of 3,048 CIN patients, were included in our meta-analysis. Six articles²⁴,²⁶-³⁰ were prospective cohort studies, whereas one²⁵ was a retrospective study. Five studies²⁴,²⁶-²⁸ included patients who accepted PCI therapy because of ACS (including STEMI or NSTEMI), one study²⁹ involved stable angina pectoris (SAP) patients, and one study³⁰ addressed patients with peripheral artery disease. The characteristics’ summary of the eligible studies is given in Table 1.

For quality assessment, one of the studies was considered as having mild cohort selection bias because it was designed as a retrospective study.²⁵

Main Findings of the Eligible Studies

We summarized the data from the 7 eligible articles and analyzed them by the forest figure [Figure 2]. The OR values in 6 studies were more than 1.0, indicating that wide RDW is a risk factor of CIN in patients who accepted PCI therapy because of ACS (including STEMI or NSTEMI) and SAP, while only one study of patients with peripheral artery disease showed that elevated RDW had low risk (OR=0.943, 95% CI, 0.822-1.055). Among the 6 studies, the maximum OR value was 2.03(95% CI, 1.03-4.0), while the minimum was 1.30 (95% CI, 1.04-1.62). Meanwhile, when we studied the random effect model for all 7 studies, the OR value was 1.35 (95% CI, 1.09-1.76) [Figure 2].

![Forest plot](image)

Interestingly, however, we found that the OR value in STEMI patients was higher than that of the ACS (Studies including STEMI and/or NSTEMI) or SAP group. As a consequence, we divided the studies into two subgroups of the ACS (STEMI and/or NSTEMI) subgroup and the STEMI subgroup to explore the possible heterogeneity.

Subgroup Analysis

As referred above, we performed subgroup analysis to explore the possible heterogeneity. We also performed a forest plot (Figure 3) to allow further analysis. The summarized OR values in both ACS (STEMI and/or NSTEMI) and STEMI subgroups were significantly higher, and the OR value in the STEMI subgroup (OR 1.58, 95% CI, 1.35-1.85) was higher than that of the ACS subgroup (OR 1.45, 95% CI, 1.29-1.64).

Publication Bias

Publication bias was described by a funnel plot [Figure 4] for the 7 studies included in the meta-analysis and asymmetry was observed, and indicated that there is no significant publishing bias across the eligible studies.
DISCUSSION

The present systematic review and meta-analysis indicated that increased RDW was significantly associated with increased risk of CIN in patients who had used contrast media. RDW is heterogeneity of erythrocyte measurement. Increased RDW reflected chronic inflammation and oxidative stress, relating to impaired erythropoiesis and erythrocyte degradation.

Although the pathogenesis of CIN is not completely clear, a variety of mechanisms have been found, with inflammation playing an important role. Elevated C-reactive protein, erythrocyte sedimentation rate, and pro-inflammatory cytokines were associated with elevated RDW, and an increased risk of CIN.

The statin treatment for CIN and renal protection link with anti-inflammatory activity. Inflammation may influence red blood cell maturation to elevate RDW, where the increased RDW levels may be associated with oxidative stress, caused by the release of reactive oxygen species (ROS) and CIN. Two studies demonstrated that reducing the production of ROS could lower the risk of CIN. Oxidative stress leads to shortened red cell survival and increase RDW. Consequently, elevated RDW levels may reflect an elevated inflammatory response and a high risk of developing CIN.

RDW at the baseline is associated with higher CIN in patients using contrast media. The results of the 7 studies included in the meta-analysis demonstrated that the pooled OR for CIN was 1.35, which suggests that elevated RDW is associated with higher CIN risk. For every 1% increase in RDW, the risk of CIN in ACS patients was increased by 35%. Meanwhile, only one study of patients with peripheral artery disease showed elevated RDW had a low risk (OR 0.943). Since there was fewer studies focused on CIN due to peripheral artery disease, further research should be conducted. Therefore, we performed subgroup analysis. Similar results were achieved in the analysis stratified by ACS (STEMI and/or NSTEMI) [1.45 (95% CI, 1.29-1.64)] and ACS but only STEMI [1.58 (95% CI, 1.35-1.85)]. For every 1% increase in RDW, the risk of CIN in ACS patients was increased by 45% and the risk of CIN in STEMI patients was increased by 58%.

The subgroup analyses suggest that the summarized OR value in the ACS (STEMI and/or NSTEMI) subgroup is higher (OR 1.45), meaning that for every 1% increase in RDW, the risk of CIN increased by 45% in the ACS patients. The summarized OR value in the STEMI subgroup (OR 1.58) was significantly higher than that of the ACS subgroup, indicating that for every 1% increase in RDW, the risk of CIN increased by 58% in the STEMI patients. The STEMI subgroup (OR 1.58) was higher than that of the ACS (STEMI and/or NSTEMI) subgroup (OR 1.45), suggesting that higher RDW may have a poorer prognosis in STEMI patients than in NSTEMI patients. But, since the subgroup analyses of NSTEMI patients did not identify sufficient data, further studies should be conducted.

Some limitations must be acknowledged in the present systematic review and meta-analysis. First, publication bias existed, that may be that only 7 studies were included in the final and the sample sizes were small. Further studies should be performed, with larger sample sizes and adjusted for confounding factors. Second, the individual studies had their different confounding factors adjusted, such as diabetic patients and nephropathy patients having a higher CIN incidence without subgroup analysis, which may have led to bias. Third, there was a relative paucity of studies on patients with peripheral artery disease and NSTEMI patients, which may have affected the results of the analysis. Lastly, this systematic reviews is not registered online, but our meta-analysis was conducted in strict process accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, so the bias of our research tends to be less.
In conclusion, the results of this systematic review and meta-analysis indicate that elevated RDW may be a risk factor for CIN, and higher RDW may have poorer prognosis than those with lower RDW in ACS, especially in STEMI patients. Further studies are needed to explore the potential mechanisms underlying this association.

Disclosure Statement

The authors report no conflict of interest.

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