META-ANALYSIS

Prognostic Impact of Red Cell Distribution Width on the Development of Contrast-Induced Nephropathy, Major Adverse Cardiac Events, and Mortality in Coronary Artery Disease Patients Undergoing Percutaneous Coronary Intervention

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Abstract: Red cell distribution width (RDW) serves as an independent predictor towards the prognosis of coronary artery disease (CAD) in patients undergoing percutaneous coronary intervention (PCI). A systematic search of databases such as PubMed, Embase, Web of Science, and Cochrane library was performed on October 10th, 2019, to elaborate the relationship between RDW and in hospital and long term follow up, all-cause and cardiovascular mortality, major adverse cardiac events (MACE) and development of contrast-induced nephropathy (CIN) in patients with CAD undergoing PCI. Twenty-one studies qualified this strict selection criterion (number of patients = 56,425): one study was prospective, and the rest were retrospective cohorts. Our analysis showed that patients undergoing PCI with high RDW had a significantly higher risk of in-hospital all-cause mortality (OR 2.41), long-term all-cause mortality (OR 2.44), cardiac mortality (OR 2.65), MACE (OR: 2.16), and odds of developing CIN (OR: 1.42) when compared to the patients with low RDW. Therefore, incorporating RDW in the predictive models for the development of CIN, MACE, and mortality can help in triage to improve the outcomes in coronary artery disease patients who undergo PCI.

1. INTRODUCTION

Red cell distribution width (RDW) is a quantitative measure of the size variation of circulating erythrocytes which plays a vital role as the diagnostic parameter for anemia [1]. High values of RDW (>13.1) are closely associated with pro-inflammatory states. According to recent studies, RDW plays a key role in cardiovascular disease progression as elevated RDW is associated with high mortality and morbidity after myocardial infarction [2] and in patients with heart failure [3], stroke [4], and patients undergoing heart valve surgery. Recent studies have shown that high RDW is not only a predictor for poor prognosis of coronary artery disease and congestive heart failure, but at the same time, it serves as an independent predictor towards the prognosis of coronary artery disease in patients undergoing percutaneous coronary intervention (PCI). The factors underpinning this asso-

ciation are unclear. Therefore, the determination of such factors may provide insight into the risk of coronary events and mortality among patients with CAD undergoing PCI.

Contrast-induced nephropathy (CIN) is an important complication after invasive cardiovascular procedures. Patients with baseline risk factors for renal dysfunction undergoing PCI have a 50% risk of developing CIN. Development of CIN after PCI is associated with worse clinical outcomes, including increased length of hospitalization, repeat revascularization, myocardial infarction, rehospitalizations, and thus higher cost of healthcare. Pathophysiology of CIN involves increased vasoconstriction, reduced renal flow, inflammation, and oxidative stress from the generation of reactive oxygen species. Therefore, it is hypothesized that mediators reflecting inflammation such as RDW might be associated with a greater risk of CIN in patients undergoing PCI for the acute coronary syndrome.

We conducted this meta-analysis to elaborate on the relationship between RDW and in-hospital and long-term follow-up all-cause and cardiovascular mortality, major ad-

verse cardiac events, and development of contrast-induced nephropathy in patients with CAD undergoing PCI.

2. MATERIAL AND METHODS

The systematic review was conducted according to the PRISMA guidelines, and its summary is given in Fig. (**1**).

A systematic search of databases such as PubMed, Embase, Web of Science, and Cochrane library was performed using the medical search terms (MeSH) and their respective keywords with the following search strategy: "coronary artery disease" AND "percutaneous coronary intervention" AND "Mortality" OR "Major adverse cardiac events" AND "Red cell distribution width". Additionally, unpublished trials were identified from the clinicaltrials.gov website, and references of all pertinent articles were also scrutinized to ensure the inclusion of all relevant studies. The search was completed on October 10th, 2019, with no filters applied for language, subjects, or time. After removing 125 duplicates, titles and abstracts of 420 articles were screened for relevance by two independent reviewers, and conflict was settled by discussion. A total of 79 articles were deemed relevant, and their abstracts and full texts were screened for eligibility. The following eligibility criterion was used: Original articles reporting the impact of RDW on mortality, major adverse cardiac events, and CIN in CAD patients undergoing PCI. Twenty-one studies qualified this strict selection criterion (number of patients = 56,425): one study was prospective, and the rest of the 20 studies were retrospective cohorts. The reasons for exclusion of the other 58 articles were: duplicates (1), preclinical studies (5), irrelevance (42), reviews (6), and others (4). The exclusion criteria were: Preclinical studies (5), studies showing no subjective data regarding required outcomes (6), Interim reports of studies, other than the most recent one, evaluating the impact of RDW on mentioned outcomes (4).

The quality of the included studies and their risk of inherent bias were assessed using the NIH tool for quality assessment. The NIH tool for quality assessment evaluates an article based on the following variables: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and any other sources of bias. The bias risk assessment using this tool is mostly subjective. Two independent reviewers performed the risk assessment. The primary endpoint was all-cause in-hospital and long-term (>6 months) mortality. Secondary endpoints were the incidence of CIN, cardiovascular mortality, and major adverse cardiovascular events. The main summary estimate was random effects relative risk (RR) with 95% confidence intervals (CIs).
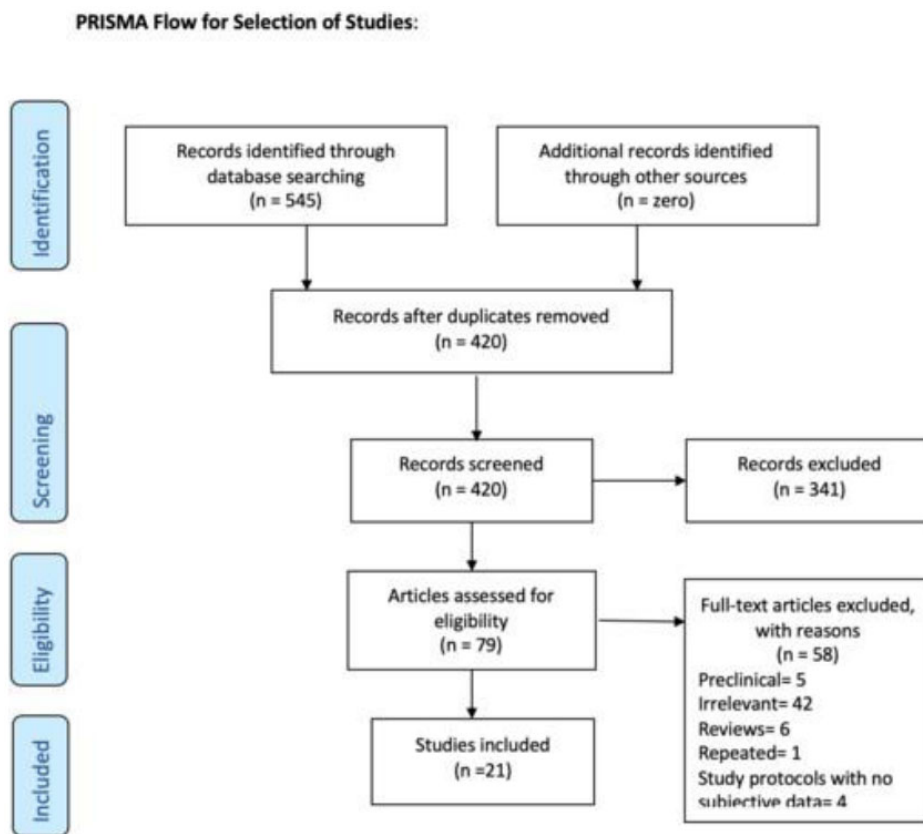
PRISMA Flow for Selection of Studies:

Fig. (1). Prisma flow diagram showing the selection of studies.

2.1. Definitions

The CAD includes patients with acute coronary syndrome and patients who are either symptomatic or have >70% narrowing or blockage of coronary arteries. The ACS refers to any group of clinical symptoms compatible with acute myocardial ischemia, including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction. The CIN is an acute kidney injury that is defined as a 25% or 0.5 mg/dL increase over the baseline of the serum creatinine level 24 h to 72 h after intravascular administration of contrast in the absence of other causes. Major adverse cardiac events (MACE) were defined as the composite of death, nonfatal myocardial infarction (MI), target vessel revascularization, and target lesion revascularization by PCI or coronary artery bypass graft surgery. Long-term mortality is mortality from any cause after 6 months of PCI. High RDW means a value of >13.1, while low RDW refers to a value of <13.1.

3. RESULTS

3.1. Baseline Characteristics

Twenty-one studies (one prospective and twenty protective studies) qualified for inclusion. A summary of baseline characteristics of involved patients is given in Tables **1**-**3**.

Table 1. Summary of important characteristics of included studies on development of contrast-induced nephropathy in coronary artery disease patients undergoing percutaneous coronary intervention.

Studied Variables		Akin, F 2014	Akkoyun, DC. 2015	Kurtul, A. 2015	Mizuno, A. 2015	Zhao, K. 2015	Rubinkiewicz, K.Z. 2017	Elhosseiny, S. 2018
		Baseline Characteristics						
Total Num of patients (N)	CIN	79	49	81	10	78	50	12
	No-CIN	551	307	581	92	601	207	149
Males/ females	CIN	--	41/ 8	51/ 30	7/ 3	49/ 29	27/ 23	8/ 4
	No-CIN	--	261/ 46	406/ 175	73/ 19	420/ 181	143/ 64	109/ 40
Mean Age in Years	CIN	--	--	71.7 + 12.5	68.9 +/- 17.3	69.8 ± 10.9	74.7 ± 11.6	66.2 ± 11
	No CIN	--	--	59.8 + 12.3	60.4 +/- 13.6	60.2 ± 11.3	67.8 ± 11.0	62.5 ± 11
Hypertension % (N)	CIN	--	26/ 49	42/ 81	7/ 10	35/ 78	42/ 50	11/ 12
	No-CIN	--	118/ 307	236/ 581	49/ 92	242/ 601	180/ 207	103/ 149
Diabetes % (N)	CIN	--	21/ 49	32/ 81	1/ 10	33/ 78	26/ 50	7/ 12
	No-CIN	--	55/ 307	174/ 581	19/ 92	153/ 601	70/ 207	31/ 149
Smoking % (N)	CIN	--	22/ 49	13/ 81	2/ 10	42/ 78	2/ 50	--
	No CIN	--	175/ 307	288/ 581	49/ 92	295/ 601	30/ 207	--
		Laboratory Parameters						
RDW (%)	CIN	--	16.9± 2	15.19± 1.81	14.2 ± 1.7	15.12 ± 1.81	14.85 ± 4.6	14.83 ± 1.21
	No-CIN	--	14.8± 2.14	13.98 ± 1.17	13.2 ± 0.8	13.92 ± 1.12	13.62 ± 1.3	14.035 ± 1.48
Hb (g/ dl)	CIN	--	12.7± 2.13	12.6 ± 2.1	13.7 ± 3	13.97 ± 1.56	--	12.75 ± 2.49
	No-CIN	--	13.2± 1.62	14.3 ± 1.7	15.0 ± 1.7	14.05 ± 1.68	--	14.13 ± 1.78
Serum Cr (mg/dl)	CIN	--	1.1± 0.43	1.34± 0.38	2.6 ± 4.3	1.51 ± 0.52	120.9 ± 87.6	1.96 ± 0.61
	No-CIN	--	0.8± 0.16	1.06± 0.25	0.9 ± 0.3	0.93 ± 0.45	96.1 ± 31.8	1.08 ± 0.41
eGFR (ml/ min/ 1.72 m²)	CIN	--	68.7± 17	52± 18	46.7 ± 24.7	66.8 ± 30.2	58.13 ± 24.0	35.75 ± 16.91
	No CIN	--	89.7± 20	73 ± 19	74.7 ± 23.8	97.3 ± 26.9	66.85 ± 17.1	72.42 ± 21.45
Amount of Contrast (ml)	CIN	--	258± 60	174 ± 76	215.3 ± 132.1	172 ± 63	233.3 ± 88.9	108.75 ± 112.94
	No-CIN	--	212± 65	162 ± 63	217.7 ± 70.6	163 ± 71	246.75 ± 92.16	142.72 ± 66.49
		Indications for PCI						
STEMI	CIN	100% (n= 79)	100% (n= 49)	49/81	100% (n= 10)	--	30/ 50	8/ 12
	No-CIN	100% (n= 551)	100% (n= 307)	375/ 581	100% (n= 92)	--	88/ 207	72/ 149
CAD other than STEMI	CIN	--	--	32/ 81	--	100% (n= 78)	18/ 50	4/ 12
	No-CIN	--	--	206/ 581	--	100% (n= 601)	121/ 207	76/ 149

Abbreviations: CAD= Coronary Artery Disease, CIN= Contrast Included Nephropathy, Cr= Creatinine, eGFR= Estimated Glomerular Filtration Rate, STEMI= ST-segment Elevation Myocardial Infarction, N= Number, PCI= Percutaneous Coronary Intervention, RDW= Random Distribution Width, Hb= Hemoglobin

Table 2. Summary of important characteristics of included studies on short-term (in-hospital), long-term all-cause and cardiovascular mortality in coronary artery disease patients undergoing percutaneous coronary intervention.

Studied Variables		Uyarel, 2011	I'lhan, 2012	Tsuboi, 2013	Osadnik, 2103	Sun, 2014	Yao, 2014	Liu, 2015	Bekler, 2015	Bozorgi, 2016	Li, 2016	Liu, 2017	Wu, 2019
Baseline Characteristics													
-	RDW Cutoff for high-/low %	> 14.8/≤14.8	> 14.8/≤14.8	>13.1/<13.1	≥ 14.1/<14.1	≥ 13.0/<13.0	≥13.5/<13.5	≥ 12.3/<12.3	>14.0/≤14.0	≥13.6/<13.6	>14/≤14	≥ 12.2/<12.2	≥ 13.1/<13.1
Total Num of patients (N)	High RDW	370	65	288	706	362	506	992	100	--	123	1015	3125
	Low RDW	2136	698	272	1844	329	1663	899	102	--	186	1170	2894
Males/ females	High RDW	281/89	49/16	230/58	494/212	268/94	315/314	629/363	72/28	157	121/2	695/320	2280/872
	Low RDW	1794/342	615/83	216/56	1305/539	247/82	1153/510	623/276	87/15	337	129/43	888/282	2215/679
Mean Age in Years	High RDW	61.1	57.15±14.79	68.0	65.6 ± 9.1	65.30 ± 12.76	62.3±10.8	68.5 ± 5.4	62.9±11.1	59.97±12.1	62±11	61.6 ± 10.6	60.9± 10.7
	Low RDW	55.8	54.27±11.83	65.2	62.3 64.4±9.3	63.02 ± 12.13	58.3-60.1	67.8 ± 5.3	57.5±11.8	56.07±12.3	56±12	59.2 ± 10.2	58± 10.7
Hypertension (N)	High RDW	162	25	206	491	233	348	604	56	118	74	704	1386
	Low RDW	823	172	198	1336	202	746	681	45	218	79	743	1169
Diabetes (N)	High RDW	102	34	288	280	123	157	289	29	45	40	276	713
	Low RDW	514	297	272	663	149	336	210	27	136	37	296	738
Smoking (N)	High RDW	185	27	69	344	--	152	441	40	67	89	377	1183
	Low RDW	1264	267	64	821	--	552	421	47	140	94	410	1236
LVEF %	High RDW	45	--	60.8	43.8 ± 11.4	--	--	59.9 ± 11.4	50	40.85±12.39	56±7	61.6 ± 10.4	61± 7
	Low RDW	47.9	--	63.4	46.4 ± 10.0	--	--	61.5 ± 11.2	55	44.23±10.86	59±6	62.7 ± 10.1	61± 7
Laboratory Parameters													
WBC count (x10^9 /L)	High RDW	--	--	--	7.4 ± 2.2	--	15.12 ± 1.81	7.2 ± 2.2	9.8 (4-19)	--	10.9±3.8	7.1 ± 2.0	7.34± 2.41
	Low RDW	--	--	--	7.4 ± 2.6	--	13.92 ± 1.12	7.2 ± 2.1	8.8 (4.6-17.4)	--	10.9±3.6	7.1 ± 2.0	7.39± 2.42
Hb (g/ dl)	High RDW	12.7	14.04±1.39	12.9 (11.8-14.2)	13.7±1.6	14.0.7±1.26	13.97 ± 1.56	13.64 ± 1.56	13.5 (12-17.3)	14.48±1.90	13.7±2.0	13.6 ± 1.6	--
	Low RDW	13.8	14.67±5.06	--	13.8±1.4	14.1±1.23	14.05 ± 1.68	13.24 ± 1.66	14 (12-17.1)	14.90±1.62	14.4±1.8	14.0 ± 1.5	--
Mortality													
In-hospital %	High RDW	7.6	--	--	--	--	1.6	--	--	13.3	12.2	2.7	--
	Low RDW	3.6	--	--	--	--	0.5	--	--	5.9	4.8	1.0	--
Long term %	High RDW	--	--	7.3	16.0	9.6	5.7	4.3	--	19.7	8.1	--	6.2
	Low RDW	--	--	2.9	6.5	3.6	2.2	2.0	--	7.9	2.7	--	3.9
Cardiac %	High RDW	11.4	9.2	4.5	--	7.2	3.8	--	16.0	--	--	--	5.2
	Low RDW	4.4	3.0	0.4	--	1.5	1.6	--	5.0	--	--	--	3.0

Table 3. Summary of important characteristics of included studies on major adverse cardiac events in coronary artery disease patients undergoing percutaneous coronary intervention.

Studied Variables		Uyarel, 2011	Kobayashi, 2014	Bekler, 2015	Bozorgi, 2016	Turcato, 2016	Li, 2016	Liu, 2017	Wu, 2019
Baseline Characteristics									
-	RDW Cutoff for high/low %	> 14.8 /≤14.8	18.3/13.8	>14.0/≤14.0	≥13.6/<13.6	>14/≤14	>14/≤14	≥ 12.2/<12.2	≥ 13.1/<13.1
Total Num of patients (N)	High RDW	370	31	100	--	244	123	1015	3125
	Low RDW	2136	340	102	--	631	186	1170	2894
Males/ females	High RDW	281/89	--	72/28	157	131/113	121/2	695/320	2280/872
	Low RDW	1794/342	--	87/15	337	449/182	129/43	888/282	2215/679
Mean Age in Years	High RDW	61.1	--	62.9±11.1	59.97±12.1	72 (51-82)	62±11	61.6 ± 10.6	60.9± 10.7
	Low RDW	55.8	--	57.5±11.8	56.07±12.3	56 (37-76)	56±12	59.2 ± 10.2	58± 10.7
Hypertension (N)	High RDW	162	93%	56	118	158	74	704	1386
	Low RDW	823	73%	45	218	328	79	743	1169
Diabetes (N)	High RDW	102	--	29	45	46	40	276	713
	Low RDW	514	--	27	136	73	37	296	738
Smoking (N)	High RDW	185	--	40	67	88	89	377	1183
	Low RDW	1264	--	47	140	170	94	410	1236
LVEF %	High RDW	45	--	50	40.85±12.39	--	56±7	61.6 ± 10.4	61± 7
	Low RDW	47.9	--	55	44.23±10.86	--	59±6	62.7 ± 10.1	61± 7
Laboratory Parameters									
WBC count (x10⁹ /L)	High RDW	--	--	9.8 (4-19)	--	--	10.9±3.8	7.1 ± 2.0	7.34± 2.41
	Low RDW	--	--	8.8 (4.6-17.4)	--	--	10.9±3.6	7.1 ± 2.0	7.39± 2.42
Hb (g/ dl)	High RDW	12.7	11.3±1.6	13.5 (12-17.3)	14.48±1.90	13.1 [11.8-14.0]	13.7±2.0	13.6 ± 1.6	--
	Low RDW	13.8	13.2±1.7	14 (12-17.1)	14.90±1.62	--	14.4±1.8	14.0 ± 1.5	--
Major Adverse Cardiac Events									
-	High RDW	24.3	12.9	52	30	36.5	12.2	26.8	14.9
	Low RDW	20.4	2.9	31.4	17.4	30.3	4.8	13.4	12.4

Abbreviations: N= Number, RDW= Random Distribution Width, Hb= Hemoglobin

3.2. RDW and All-cause Mortality

3.2.1. RDW and In-hospital All-cause Mortality

Five retrospective studies [5-9], including 7,169 patients (2014 with high RDW and 5155 with low RDW), were included. The risk of in-hospital all-cause mortality was significantly higher in patients with high RDW when compared to patients in the low RDW group with an odds ratio of 2.41 (95% CI; 1.80-3.23, p value= <0.00001) (Fig. **2**).

3.2.2. RDW and Long-term All-cause Mortality

Eight retrospective studies [5-8, 10-13], including 12,324 patients (5137 with high RDW and 7187 with low RDW), were included. The risk of long-term all-cause mortality was significantly higher in patients with high RDW when compared to patients in the low RDW group with an odds ratio of 2.44 (95% CI; 1.96-3.04, p value= <0.00001) (Fig. **3**).

3.3. RDW and Cardiovascular Mortality

Seven studies (six retrospectives and one prospective) [8-12, 14, 15], including 13,937 patients (4843 with high RDW and 8094 with low RDW), were included. Patients in the high RDW group were at a high statistically significant risk of cardiac mortality compared to patients in the low RDW group with an odds ratio of 2.65 (95% CI; 1.90-3.71, p value= <0.00001) (Fig. **4**).

3.4. RDW and MACE

Eight studies (seven retrospectives and one prospective) [6-10, 14, 16, 17], including 12,478 patients (4526 with high RDW/7952 with low RDW), were included. Patients in the high RDW group had a significantly higher odds of having MACE post PCI compared to the control group with low RDW; OR: 2.16 (95% CI 1.47-3.16, p-value = <0.0001) (Fig. **5**).

3.5. RDW and CIN

Seven retrospective studies [18-26] having a total patient population of 2847 (359/2488) in the CIN and no CIN group were included. Patients in CIN group showed a higher baseline value of RDW (CIN= 14.2-16.9 *verses* No-CIN= 13.2-14.8, p < 0.01). Both groups did not significantly differ in the previous history of CAD, amount of contrast used, and

duration of the procedure (p > 0.05). Our analysis showed that patients who had higher baseline RDW values have a significantly higher odds of developing CIN [OR: 1.42, (95% CI: 1.30-1.6), p ≤ 0.001, I^2 = 0) (Fig. **6**).
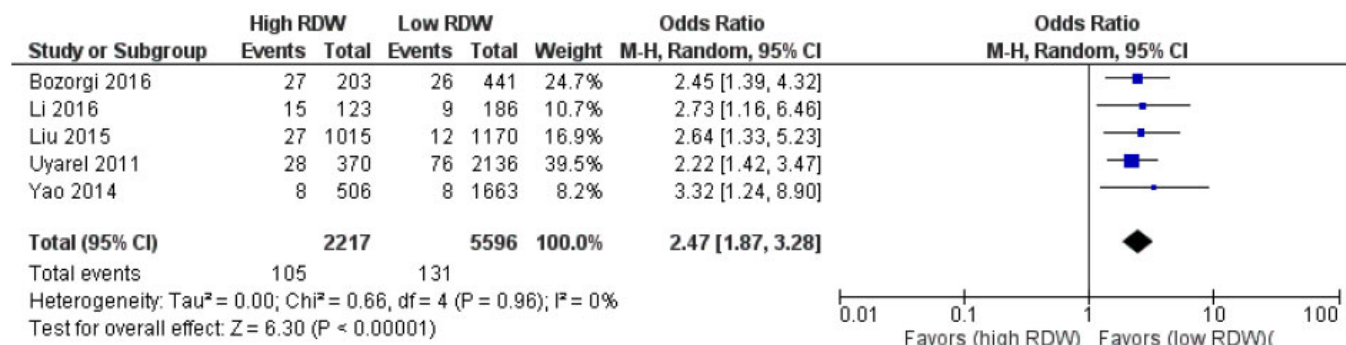

Fig. (2). Forest plot showing the risk of all-cause in-hospital mortality in patients with high red cell distribution width.
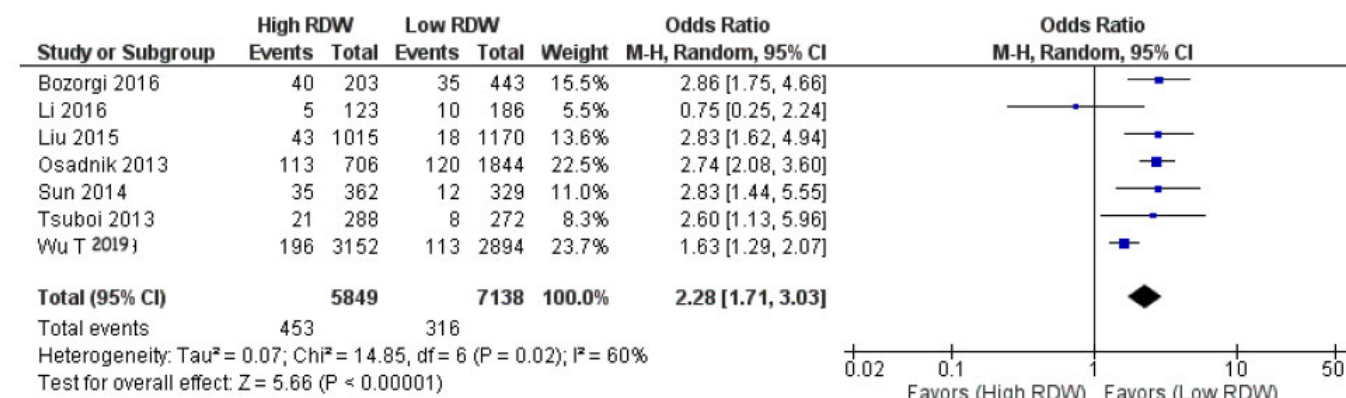

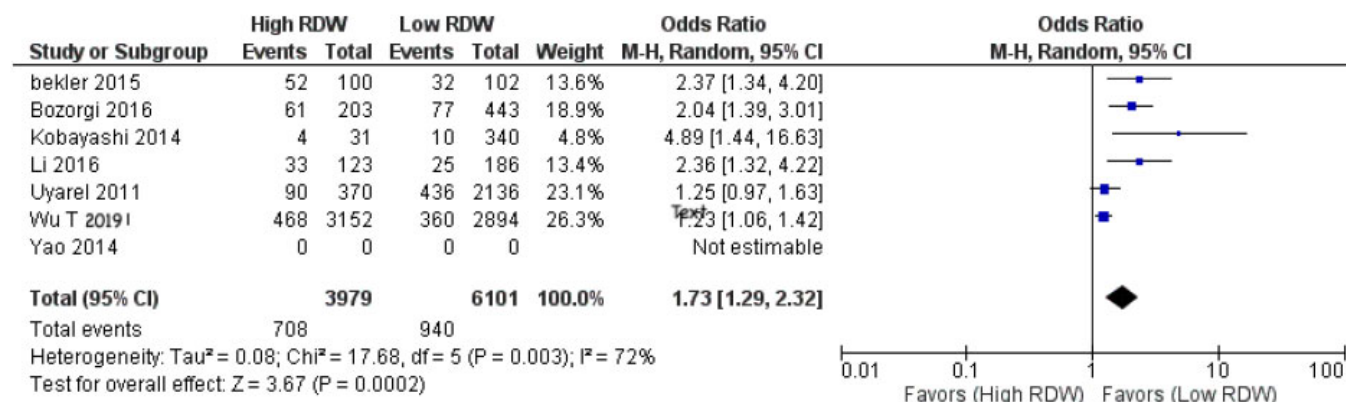**Fig. (3).** Forest plot showing the risk of long-term all-cause mortality in patients with high red cell distribution width.

Fig. (4). Forest plot showing the risk of cardiovascular mortality in patients with high red cell distribution width.
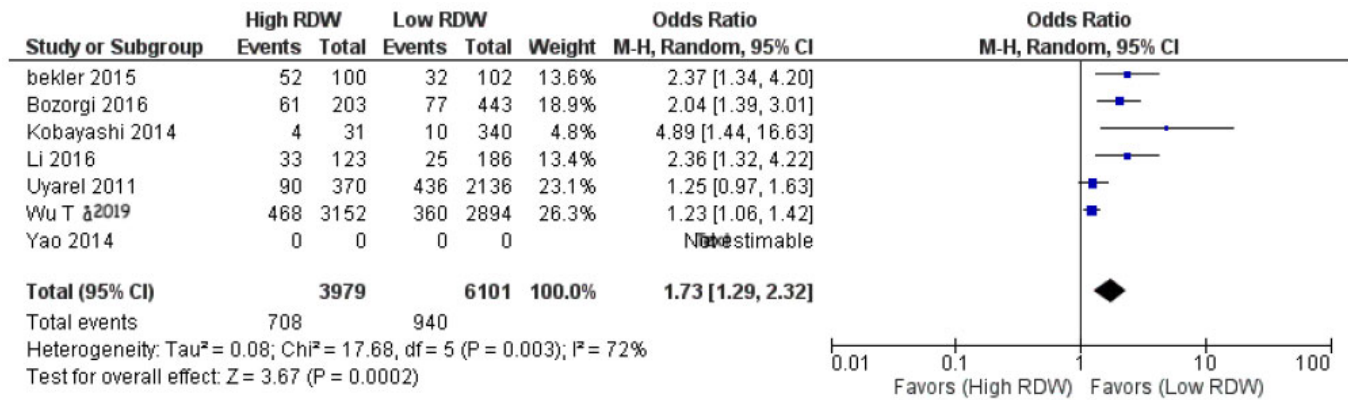
Fig. (5). Forest plot showing the risk of major adverse cardiovascular events in patients with high red cell distribution width.
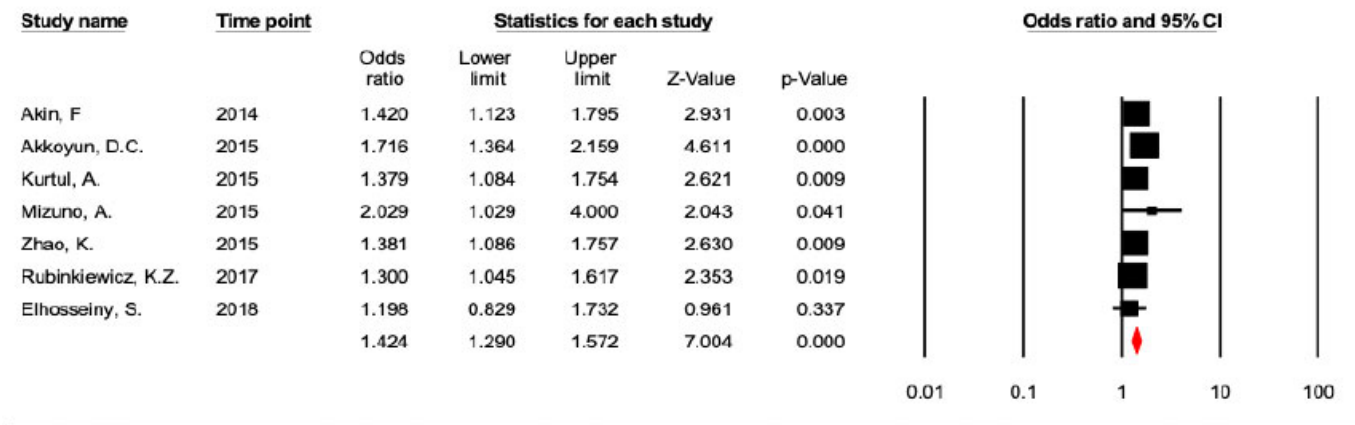

Fig. (6). Forest plot showing the risk of contrast-induced nephropathy in patients with high red cell distribution width.

4. DISCUSSION

The potential mechanism that links high RDW with adverse overall clinical outcomes is still not clear. Several mechanisms have been hypothesized to explain the association. One possible explanation is chronic inflammation since inflammation plays a key role in atherogenesis and possibly platelet activation. Previous studies correlate RDW with interleukin-1, interleukin-6, tumor necrosis factor I and II receptors, and fibrinogen levels. These inflammatory cytokines desensitize the red blood cell production from hematopoietic stem cells and inhibit their maturation leading to anisocytosis [27]. Moreover, chronic inflammation disrupts normal iron metabolism and reduces bone marrow responsiveness to erythropoietin leading to impaired hematopoiesis and high RDW values. Additionally, low vitamin D3 levels which is a well-known CAD risk factor, can affect RDW levels by deranging the bone marrow erythropoiesis. High oxidative stress can shorten the lifespan of red blood cells, intensifying the production as well as the release of immature red blood cells into the circulation, which is reflected by high RDW. Likewise, oxidative stress generates oxidized forms of low-density lipoproteins, playing a crucial role in atherogenesis [28]. Wen *et al.* observed increased ultrasound detection of advanced subclinical atherosclerosis in patients with high RDW. Lipid disorders reduce the fluidity of red cell membranes, and high total erythrocyte membrane levels deform the red cell membrane affecting the life span of red cells and therefore resulting in high RDW levels [28]. Sánchez-Chaparro *et al.* reported that high RDW levels are associated with metabolic syndrome, which is a well-studied condition encompassing risk factors for cardiovascular diseases [29]. Finally, activation of the neuroendocrine system disturbs the red blood cell membrane, thereby increasing RDW in patients with CAD.

Similar to the results of our analysis, various clinical studies have shown that the relationship between RDW and mortality is not dependent on the association of RDW and anemia. Borzorgi *et al.* [7] showed that high values of RDW were independent predictors of 6-month mortality in non-anemic STEMI patients undergoing primary PCI (HR:

2.703; 95% CI: 1.208-6.048; P = 0.016) after performing multivariable analysis of the non-anemic subgroup of patients. Isik *et al.* observed RDW as an independent risk factor for intermediate-term mortality after adjustment for hemoglobin (HR: 2.98; 95% CI: 1.42-6.23; P = 0.004) [30]. Likewise, a recent meta-analysis by Bao *et al.*, including 12 studies, showed that high values of RDW in non-anemia subgroups of patients are associated with a higher risk of all-cause (RR: 1.77; 95% CI: 1.32-2.37), cardiovascular (RR: 1.70; 95% CI: 1.25-2.32) mortality, and MACE (R: 1.62; 95% CI: 1.21-2.18) in patients with CAD undergoing PCI [31]. A retrospective study by Xiao *et al.* (N=331) demonstrated that erythrocyte count ratio and RDW correlate with adverse cardiovascular outcomes during hospitalization in patients with STEMI undergoing PCI [32].

Another important association is the close relationship between high RDW value and inadequate tissue perfusion (no-reflow). Inadequate tissue perfusion has been demonstrated as an independent predictor of mortality after PCI. The predictive value of no-reflow following PCI is unknown, but potentially proposed mechanisms include high oxidative stress and underlying inflammatory processes. Karabulut *et al.* [33] studied the effect of RDW on inadequate reperfusion following PCI in STEMI patients, and they found that high RDW (>14.8%) was strongly associated with TIMI flow grades<3 with a P-value of < 0.001. Furthermore, in multivariable regression analysis, it was found to be a predictor of abnormal reperfusion (odds ratio: 2.20, 95% CI: 1.012-4.569; P = 0.05). In another study by Isik *et al.*, RDW of 14% was a predictor of no-reflow with 70% sensitivity and 64% specificity in 100 patients undergoing PCI (30). They also demonstrated that high levels of RDW were associated with intermediate-term mortality with an odds ratio of 2.93 (95% CI: 1.42-6.04; P = 0.004). Machado *et al.* [34] found a low RDW level (<13.4%) as an excellent negative predictive value (87.4%) for long-term all-cause mortality. This association between in-hospital mortality and long-term mortality is independent of multiple potential confounding factors such as old age, renal dysfunction, peripheral vascular disease, and diabetes prior to CAD and heart failure with reduced ejection fraction [8].

Lippi *et al.*, while investigating a large cohort of unselected adults in an outpatient setting, observed an inverse association between RDW and kidney function tests [35]. A National Health and Nutrition Examination Survey conducted in 1999-2006 reported a close association between RDW and microalbuminuria, which is a renal marker of vascular injury [36]. Impaired renal function increased in-hospital mortality by 20% [37]; therefore, the prediction of CIN and protection from it plays an important role in decreasing the overall mortality and morbidity in patients undergoing PCI. Mehran risk score (MRS) is widely used in clinical practice to predict CIN post-PCI. Mizuno *et al.* [22] demonstrated that RDW, when used with MRS, has additional predictive value for CIN in STEMI patients undergoing PCI. In patients with stable CAD, chronic inflammation associated with high RDW could lead to renal dysfunction after PCI. In STEMI patients with inflammation requiring urgent interven-

tion, a higher incidence of CIN can be explained by the fact that in an acute setting, these patients could not be hydrated properly, thus more at risk for renal hypoperfusion and contrast-induced acute kidney injury. The results of our meta-analysis also showed that patients who had higher baseline RDW values have higher odds of developing CIN, supporting the aforementioned proposed hypothesis of CIN development in CAD patients.

Current guidelines recommend the use of GRACE risk score in the assessment of prognosis in patients with ACS. However, this risk score system might have some limitations as it doesn't cover various pathologic processes, including inflammation and oxidative stress. Some studies have reported prognostic effects of inflammatory biomarkers such as erythrocyte sedimentation rate, C-reactive protein, nitrite/nitrate, and superoxide dismutase when combined with the GRACE risk score system that could enhance the predictive power of adverse outcomes in patients with STEMI undergoing primary PCI. Chang *et al.* [38] showed that combined value of RDW level and GRACE score were more valuable in predicting MACE at 36 months follow up in patients with STEMI who underwent PCI (AUC = 0.775, 95% CI: 0.727-0.824, P < 0.001) with 72.2% sensitivity and 73.5% specificity.

One interesting observation was that high RDW levels were found in older patients. One potential explanation would be a high inflammatory burden, a higher incidence of baseline hypertension, anemia, renal dysfunction, poor nutritional status, and age-associated co-morbidities. In our analysis, hypertension was observed more in patients with high RDW; however, the frequency of DM was not significantly different between the two groups.

Limitations of our meta-analysis include 1) potential for publication bias, 2) most of the included studies were retrospective, 3) unable to evaluate the effects of gender, race, and ethnic background on the measured outcomes.

CONCLUSION

In this comprehensive meta-analysis involving 56,425 patients with CAD undergoing PCI from a total of 21 studies, high values of RDW either at baseline or discharge proved to be a consistent and strong independent predictor of mortality and morbidity involving the development of CIN and major adverse cardiac events. Increased RDW is associated with poor prognosis in CAD patients post PCI. It should be measured when comprehensively assessing the prognosis of CAD patients undergoing primary PCI. Incorporating RDW in the predictive models for the development of CIN, MACE, and mortality can help in triage to improve the outcomes in CAD patients who undergo PCI. It would also prove beneficial to use RDW as a risk stratification index for treating patients with stable CAD.

AUTHORS' CONTRIBUTION

Azka Latif and Muhammad Junaid Ahsan contributed to conceptualization. The formal analysis was performed by Amjad Kabach. An investigation was done by Noman La-

teef and Vikas Kapoor. Methodology was selected by Ahmad Iftikhar and Faryal Razzaq. Software was selected by Azka Latif, Vikas Kapoor, and Amjad Kabach. Faiz Anwer, Amjad Kabach, Mohsin Mansur Mirza, and Muhammad Zubair Ashfaq supervised the research. Validation was performed by Azka Latif, Muhammad Junaid Ahsan, and Noman Lateef. Writing the original draft was done by Azka Latif and Vikas Kapoor. Writing, reviewing, and editing were done by Faiz Anwer, Amjad Kabach, and Mohsin Mansur Mirza.

CONSENT FOR PUBLICATION

Not applicable.

STANDARDS OF REPORTING

PRISMA guidelines have been followed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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