


RESEARCH ARTICLE

Red blood cell distribution width as a predictor of atrial fibrillation

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Background: Current evidence suggests that a higher red blood cell distribution width (RDW) may be associated with increased risk of atrial fibrillation (AF) development. Given that some controversial results have been published, we conducted a systematic review of the current literature along with a comprehensive meta-analysis to evaluate the association between RDW and AF development.

Methods: We performed a systematic search of the literature using electronic databases (PubMed, Ovid, Embase, and Web of Science) to identify studies reporting on the association between RDW and AF development published until June 2016. We used both fix-effects and random-effects models to calculate the overall effect estimate. An $I^2 > 50\%$ indicates at least moderate statistical heterogeneity. A sensitivity analysis and subgroup analysis were performed to find the origin of heterogeneity.

Results: A total of 12 studies involving 2721 participants were included in this meta-analysis. The standardized mean difference in the RDW levels between patients with and those without AF development was 0.66 units ($P < .05$; 95% confidence interval 0.44-0.88). A significant heterogeneity between the individual studies was observed ($P < .05$; $I^2 = 80.4\%$). A significant association between the baseline RDW levels and AF occurrence or recurrence following cardiac procedure or surgery was evident (SMD: 0.61; 95% confidence interval 0.33-0.88; $P < .05$) with significant heterogeneity across the studies ($I^2 = 80.7\%$; $P < .01$).

Conclusions: Our comprehensive meta-analysis suggests that higher levels of RDW are associated with an increased risk of AF in different populations.

KEYWORDS

atrial fibrillation, inflammation, marker, meta-analysis, red blood cell distribution width

1 | INTRODUCTION

Atrial fibrillation (AF) is one of the commonest cardiac arrhythmias encountered in clinical practice, related to considerable cardiovascular morbidity and mortality. The association between inflammation and the development of AF is well recognized. Thus, different inflammatory biomarkers have been implicated in AF while anti-inflammatory upstream

therapies may reduce AF burden. In this context, high sensitivity C-reactive protein (hs-CRP) levels have been associated with a higher risk of AF recurrence after electrical cardioversion^{1,2} as well as after catheter ablation.³ Red blood cell distribution width (RDW) is a quantitative measure of variability of the size of circulating red blood cells. It can aid clinicians in the differential diagnosis of anemia.⁴ This is now routinely reported in complete blood count (CBC) tests and is readily available

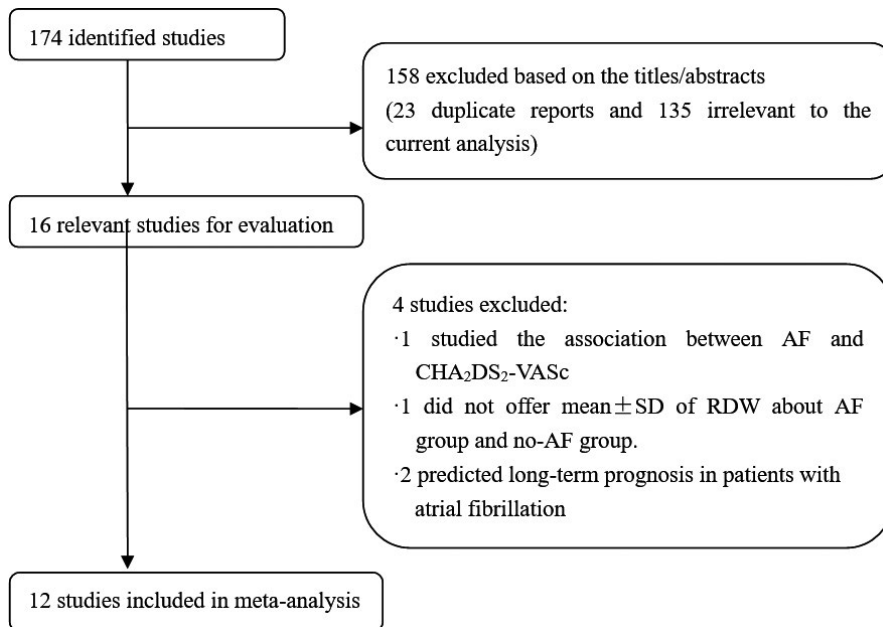


FIGURE 1 Flow diagram of the selection process. SD, standard deviation; RDW, red blood cell distribution width; AF, atrial fibrillation

in hospital care settings. Elevated RDW has been observed in pro-inflammatory conditions.^{5,6} Of note, several studies have reported higher RDW levels as a strong independent predictor of morbidity and mortality in various cardiovascular disease states.⁷⁻¹⁴ Interestingly, several studies have reported on the association between RDW and the development of AF.¹⁵⁻¹⁷ Given that some controversial results have been published, we aimed to conduct a systematic review and meta-analysis to further elucidate the relationship between RDW and AF development.

2 | METHODS

2.1 | Search strategies and selection criteria

PubMed, Ovid, Embase, and Web of Science were systematically and independently searched by two reviewers (Q. S. and T.L.) up to June 2016 to identify relevant articles evaluating the association between RDW and AF development. The search items were “red blood cell distribution width,” “RDW,” and “atrial fibrillation.” Additionally, a manual search was conducted in Abstract books of the scientific sessions of the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) over the past 5 years.

The inclusion criteria were as follows: (1) a prospective cohort study, retrospective cohort study, or case-control study; (2) RDW levels and clinical outcomes during follow-up were documented; (3) the potential association between RDW levels and AF development was examined; (4) diagnosis of AF was clearly defined in accordance with current guideline-based definitions. Published studies without language restriction were included.

2.2 | Data extraction

All entries were independently reviewed by two reviewers (Q. S. and T.L.) for compliance with the inclusion criteria. Potentially

relevant reports were then retrieved as complete manuscripts and assessed for compliance with the inclusion criteria using a standardized form. A third reviewer (G.L.) was consulted for uncertainties or discrepancies between the two reviewers. These were then resolved by majority opinion among three reviewers. The mean and standard deviation (SD) of RDW in AF group and no-AF group were extracted. If the study provided medians and interquartile ranges instead of means and SDs, we computed the means and SDs as previously described.¹⁸ The lower end of the range was calculated by (upper quartile – lower quartile)/2 – median, whereas the upper end of the range was calculated by (upper quartile – lower quartile)/2 + median. The following data were extracted from studies that met the inclusion criteria: first author’s last name, publication year, study design, study population, sample size, gender, age, follow-up duration, methods for AF detection, and postoperative AF rates.

2.3 | Quality assessment

To reduce the heterogeneity due to different study designs, the quality of each study was evaluated based on the United States Preventive Task Force¹⁹ and the Evidence-Based Medicine Working Group²⁰ guidelines. Quality was assessed based on (1) clear inclusion and exclusion criteria; (2) study sample representative for mentioned population; (3) sample selection is clearly described; (4) full specification of clinical and demographic variables; (5) sufficient period of follow-up; (6) reporting loss of follow-up; (7) clear definition of AF; (8) clear definition of outcomes and outcome assessment; (9) confounders and prognostic factors were mentioned. Studies meeting <5 criteria were graded as poor, those meeting 5-7 criteria were regarded as fair, and those meeting ≥8 criteria were graded as good.

TABLE 1 Characteristics of the 12 studies included in the meta-analysis

Author	Year	Study design	Study population	Patients (n)	Men (n)	Mean age, years	Follow-up	Rates of postoperative AF	Methods of AF detection	Quality score
Ertas et al ²⁴	2013	Retrospective cohort	After CABG	132	99 (75)	61	Until discharge	25%	Heart rate and rhythm were continuously monitored for the first 48-72 h, and daily, ECG was performed until discharge.	8
Gungor et al ¹⁴	2014	Case-control	AF patients and controls	177	104 (58.8)	48	NM	NM	Medical records and patient-reported episodes of arrhythmias lasting >30 s compatible with AF	8
Liu et al ³⁰	2014	Case-control	AF patients and controls	234	114 (48.7)	65	NM	NM	NM	7
Sarikaya et al ³¹	2014	Case-control	Patients with hypertensive	126	50 (50)	71	NM	NM	NM	7
Korantzopoulos et al ²⁸	2015	Prospective cohort	After cardiac surgery	109	79 (72.5)	67	During hospitalization	40.1	NM	8
Gurses et al ²⁵	2015	Prospective cohort	Patients with AF After cryoballoon ablation	299	152 (50.8)	55.4	26 mo	23.4%	48 h in the telemetry unit and then ECG, Holter	9
Aksu et al ²³	2015	Prospective cohort	Patients with AF After cryoballoon ablation	49	25 (51.02)	55.8	10.2 mo	14.3%	ECG, Holter after Discharge	9
Korantzopoulos et al ²⁷	2016	Case-control	Patients with SSS	101	47 (46.5)	77	NM	NM	NM	7
Yanagisawa et al ¹⁵	2016	Retrospective cohort	Patients with AF After RFCA	678	507 (74.78)	61.4	22.3 mo	39.7%	Continuous rhythm monitoring for 3 d and ECG, Holter after discharge	9
Li et al ²⁹	2016	Retrospective cohort	Patients with AF After RFCA	104	47 (45.2)	62.7	30 mo	33.7%	The symptoms and ECG of the patients were followed up	9
Akar et al ¹³	2016	Prospective cohort	Patients with AF After CABG	91	78 (86)	64	Until discharge	27.5%	NM	8
Karatas et al ²⁶	2016	Retrospective cohort	Patients with STEMI After PCI	621	464 (74.7)	57	22 mo	6.4%	Medical records	9

AF, atrial fibrillation; CABG, coronary artery bypass grafting; RFCA, radiofrequency catheter ablation; ECG, electrocardiograph; PCI, percutaneous coronary stent implantation; SSS, sick sinus syndrome; STEMI, ST-segment elevation myocardial infarction; NM, not mentioned.

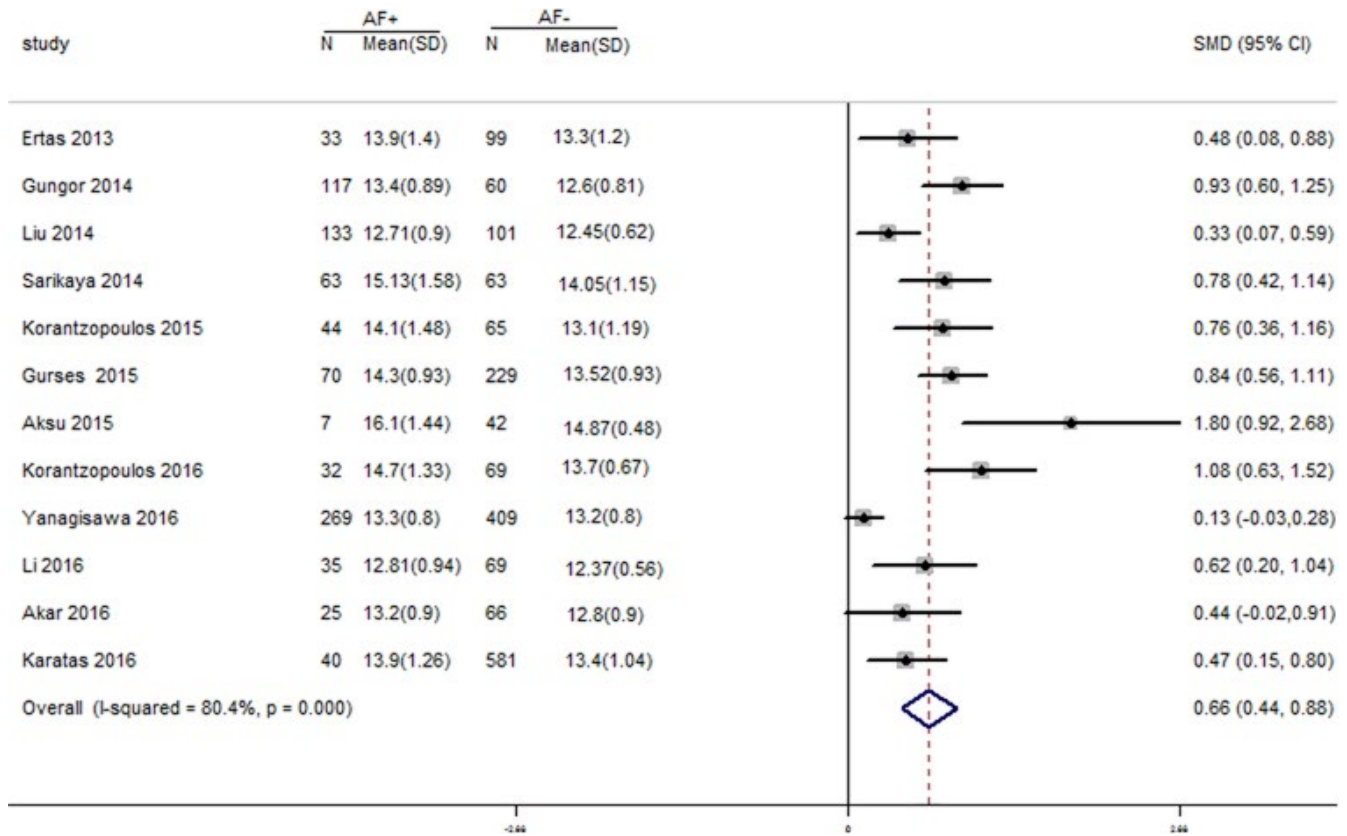


FIGURE 2 Forest plot demonstrating the association between baseline RDW and AF risk. AF, atrial fibrillation; SD, standard deviation; CI, confidence interval; SMD, standardized mean difference

2.4 | Statistical analysis

Standardized effect sizes were derived by dividing the mean difference of RDW levels between AF and no-AF groups of each study by its SD. Heterogeneity was measured by Cochran's Q statistic and the inconsistency index (I^2). $P < .05$ for the Cochran's Q and an $I^2 > 50\%$ indicate the presence of moderate statistical heterogeneity. A fixed-effects model was used when $I^2 < 50\%$, otherwise the random-effects model was used. Sensitivity analysis that performed in a random, predefined manner was used to investigate the influence of a single study on the overall risk estimate and was carried out by sequentially excluding one study at a time. Subgroup analysis was performed on the study design (cohort study or case-control study), duration of follow-up (≥ 3 months or < 3 months), study population (postoperative AF or other AF), and sample size (< 200 or ≥ 200). Publication bias was assessed by funnel plot analysis. A two-tailed P -value $< .05$ was considered statistically significant. All statistical analyses were performed using STATA 11 (Stata Corp LP, College Station, TX, USA).

3 | RESULTS

3.1 | Literature search

The search strategy and study selection process are detailed in Figure 1. A total of 174 studies were initially found using our search

criteria while 23 duplicate studies were identified and subsequently excluded. The remaining 151 studies were further screened, and 135 studies were excluded, because they were either unrelated, irrelevant, review articles, or editorials. Then full-text studies were retrieved for detailed evaluation. Of the remaining 16 articles, one study²¹ examined the association between AF and CHA2DS2-VASc, two^{22,23} predicted long-term prognosis in patients with AF, and one²⁴ did not offer mean \pm SD of RDW in AF group and no-AF group, and therefore were excluded. The remaining 12 studies^{15-17,25-33} were finally included in our meta-analysis.

3.2 | Description of included studies

A total of 12 studies involving 2721 patients were finally included in the analysis. The main features of the studies are presented in Table 1. The age of patients ranged from 48 to 77 years old. The proportion of male in the studies ranged between 46.5% and 86%. Four studies (16, 29, 32, and 33) were case-control studies, and the remaining eight studies (15, 17, 25-28, 30, and 31) were cohort studies. Eight studies (15, 17, 25-28, 30, and 31) indicated an association between RDW and occurrence/recurrence of AF following cardiac procedure or surgery, including coronary artery bypass grafting (CABG), radiofrequency catheter ablation (RFCA), cryoballoon ablation, percutaneous coronary intervention (PCI), and valvular surgery.

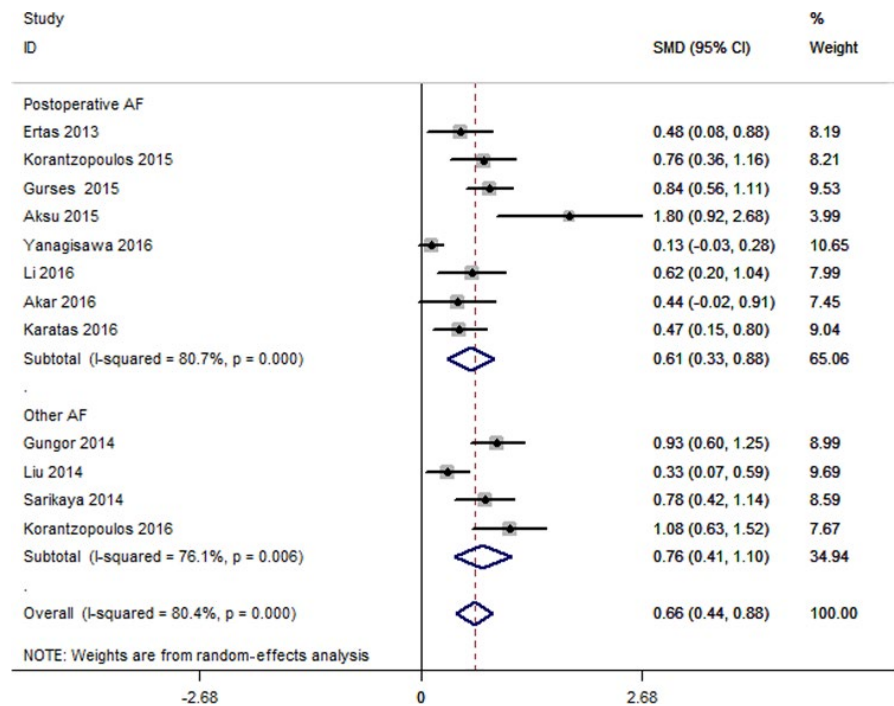


FIGURE 3 Forest plot demonstrating the association between baseline RDW and AF risk dependent on the different study population. SMD, standardized mean difference; CI, confidence interval

3.3 | Main analysis

Red blood cell distribution width levels were higher in patients with AF compared to those without AF with a standardized mean difference [SMD] of 0.66 units ($P < .05$; 95% confidence interval 0.44-0.88) (Figure 2). The heterogeneity test showed that there were significant differences among individual studies ($P < .05$; $I^2 = 80.4%$). The baseline RDW levels predicted the AF occurrence or recurrence following any of the following procedures of CABG, RFCA, cryoballoon ablation, PCI, or valvular surgery (SMD: 0.61; 95% confidence interval 0.33-0.88; $P < .05$) with significant heterogeneity across studies ($P < .01$; $I^2 = 80.7%$) (Figure 3 and Table 2).

3.4 | Sensitivity and subgroup analysis

Sensitivity and subgroup analyses were performed to identify the origin of heterogeneity. After removing one study²⁵ with a sample size of <50 cases, the analysis did not find a significant influence on the pooled effect estimates. A predefined subgroup analyses were performed according to study design (prospective or retrospective cohort and case-control), study population, follow-up period, geographic area, and sample size (Table 2). The likely origin of the observed heterogeneity is geographic area and follow-up period.

3.5 | Publication bias

The findings of the funnel plot for the association baseline RDW and AF development were symmetrical, indicating the potential for no publication bias ($P = .193$) (Figure 4).

4 | DISCUSSION

Red blood cell distribution width (RDW) is a quantitative measure of variability in the size of circulating red blood cells. Its assessment has been used to aid clinicians in the differential diagnosis of anemia. In complete blood count (CBC) tests, RDW is routinely provided and it is convenient for use in clinical practice. Previous studies have reported that higher RDW levels as a strong independent predictor of increased morbidity and mortality in patients with acute and chronic heart failure,⁷⁻¹⁰ myocardial infarction,^{11,12} and after coronary artery bypass grafting¹³ or coronary angiography¹⁴

The mechanisms between elevated RDW levels and poor clinical outcomes in cardiovascular diseases have not yet been fully understood.³⁴ First, recent studies indicate that high levels of RDW may reflect a pro-inflammatory state^{5,6} Indeed, the release of pro-inflammatory cytokines can suppress erythropoietin-induced red cell maturation, and then, higher numbers of immature red cells can produce higher RDW levels.³⁵ Secondly, Patel et al³⁶ proposed that increased erythrocyte life span, with lower MCV and higher RDW, could be a fundamental response to disease. Another possible explanation could be that erythrocytes that have been circulating for a long time (old erythrocytes are smaller, which increased RDW) has deteriorated enzyme systems, which lost some of their anti-oxidative functions. Several pathophysiological processes, such as oxidative stress and pro-inflammatory environment, can increase RDW levels through reducing red blood cell survival, thereby producing a more mixed population of erythrocytes in the circulation.

Atrial fibrillation is a prevalent medical condition affecting a significant percentage of the population, with an increasing prevalence with age. It increases the risk of stroke and death. An increasing

TABLE 2 Subgroup analyses of the association between RDW and incidence of AF

Subgroup	Study	Number of studies	Heterogeneity		Meta-analysis	
			I^2	<i>P</i> -value	SMD	95% CI
Study design	Prospective cohort	4	59.2%	.061	0.83	0.48-1.18
	Retrospective cohort	4	65.5%	.034	0.38	0.12-0.64
	Case-control	4	76.1%	.006	0.76	0.41-1.10
Study population	Postoperative AF	8	80.7%	.000	0.61	0.33-0.88
	Other AF	4	76.1%	.006	0.76	0.41-1.10
Follow-up	<3 mo	3	0.0%	.504	0.57	0.33-0.81
	≥3 mo	5	87.8%	.000	0.65	0.25-1.06
Geographic area	Asian	10	80.7%	.000	0.45	0.35-0.54
	Non-Asian	2	7.5%	.299	0.90	0.60-1.20
Sample size	<200	8	43.7%	.087	0.78	0.58-0.98
	≥200	4	85.4%	.000	0.43	0.11-0.75

AF, atrial fibrillation; SMD, standardized mean difference; CI, confidence interval.

body of evidence suggests a link between inflammation or oxidative stress and AF.^{1,2} Thus, there appears to be an association between RDW and AF. In this comprehensive meta-analysis that involved 12 studies (2721 patients), baseline RDW levels were a consistent and strong predictor of incidence of AF. However, it is a pity that the study by Adamson Eryd which did not offer mean ± SD of RDW in AF group and no-AF group was excluded.²⁴ That study included 27 124 participants and 1 894 AF events during a mean follow-up time of 13.6 years. The incidence of AF was significantly associated with RDW (hazard ratio (HR) 1.33, 95% confidence interval (CI) 1.16-1.53 for fourth vs first quartile of RDW; HR per 1 SD 1.08, 95% CI 1.04-1.12). The adjusted HR (per 1 SD) was 1.08 (95% CI 1.02-1.14) for men and 1.12 (95% CI 1.05-1.21) for women, and the adjusted HR (per 1 SD) was 1.14 (95% CI 1.02-1.27) for subjects below the median age (57.5 years) and 1.08 (95% CI 1.03-1.13) for subjects above 57.5 years at baseline. No matter how the research results by Adamson Eryd are consistent with our meta-analysis results.

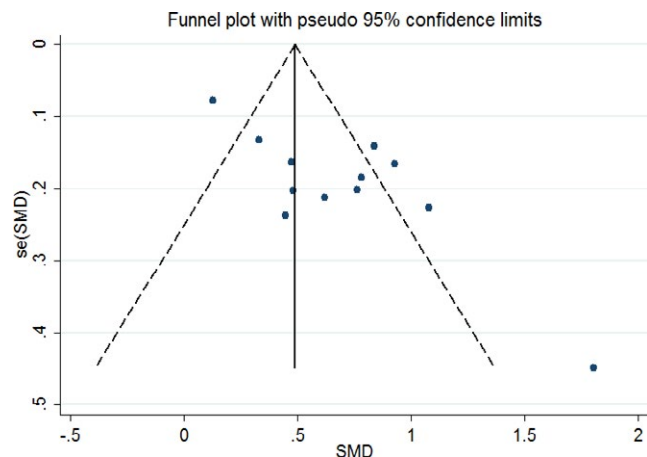


FIGURE 4 Funnel plot for the association between baseline RDW and AF risk. SE, standard error; SMD, standardized mean difference

It has also been suggested that elevated RDW is not only an independent predictor of incidence of AF, but also an independent predictor of long-term adverse clinical outcomes in patients with AF. Kurt et al²¹ indicated that RDW values were significantly correlated with CHA2DS2-VASc score in nonanemic patients with AF, while being an independent predictor of high CHA2DS2-VASc score. Moreover, a study that enrolled 567 patients who were newly diagnosed with paroxysmal AF showed that after a median follow-up of 4.8 years, RDW was a significant predictor for new-onset stroke [adjusted HR 1.32; 95% CI: 1.06-1.65, *P* = .015].²² In the same period, Wan et al²³ prospectively followed 300 consecutive patients with AF (50.3% males, mean age 62.6 ± 12.9 years) between February 2009 and October 2011. During a median follow-up period of 3.2 years, 60 deaths and 92 major adverse events (MAEs) that included death and nonfatal stroke, acute coronary syndrome (ACS) and major hemorrhage were recorded. Remarkably, RDW was independently associated with both all-cause mortality (HR: 1.024; 95% CI: 1.012-1.036, *P* < .001) and MAEs (HR: 1.012; 95% CI: 1.002-1.023, *P* = .023).

4.1 | Study limitations

The following limitations of this study should be noted. Firstly, RDW was assessed in different laboratories, and different interquartile range values used in each study were a possible cause of heterogeneity observed. Secondly, lack of repeated measurements of RDW was observed in some studies. Thirdly, the meta-analyses showed a significant association between baseline RDW and AF occurrence/recurrence after cardiac procedure or surgery. However, due to incomplete provided data, an association between levels of postoperative RDW and AF risk was not observed, and therefore, additional studies are needed to further clarify this issue. Finally, we did not evaluate the relative value of other inflammatory biomarkers along with RDW in the setting of AF.

5 | CONCLUSION

In this study, RDW represented a newly recognized and significant predictor of AF development. This easily assessable biomarker could assist in identifying patients at high risk of developing AF and can improve the strategies for prevention adverse cardiovascular events in this setting. Its widespread use may have significant clinical impact on this patient population and should be studied prospectively in larger studies in the future.

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