

## Red Blood Cell Distribution Width (RDW) in Chronic Heart Failure: Does it have a Prognostic Value in Every Population?

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### ABSTRACT

**Objectives:** Chronic heart failure (CHF) is a global health issue with notable morbidity and mortality. Currently, red cell distribution width (RDW) has appeared to be potential prognostic marker in patients with CHF. This study aims to assess the prognostic value of RDW in Saudi population with CHF.

**Methods:** This study was a retrospective cohort study that included 233 CHF patients treated with standard anti-failure drugs. RDW were ascertained at baseline with 2-D echocardiographic assessments of left ventricular mass and function. The follow up period was 24 months. Primary endpoint was the relationship between RDW and all-cause mortality (ACM). Secondary endpoints included the potential association with major adverse cardiovascular events (classical 3-point MACE).

**Results:** The mean age of patients was  $60.15 \pm 12.24$  years, and 64.8% were males. Baseline RDW was 14.40 (13.50, 15.80) % (median, and interquartile ranges); 43 deaths occurred during the follow-up period. RDW was found to be the most significant and independent predictor of ACM, with a hazard ratio (HR) of 1.238 (95% CI; 1.090, 1.407) ( $P=0.001$ ). While RDW change over 12 months had similar predictive value for ACM with HR 1.226 (95% CI; 1.117, 1.346) ( $P<0.0001$ ). RDW was also found to be a significant and independent predictor for secondary endpoints.

**Conclusion:** Our study supports the usefulness of RDW as an independent prognostic indicator for ACM and other CV outcomes in Saudi population with CHF.

**Keywords:** red blood cell distribution width, anemia, heart failure, left ventricular mass index, all-cause mortality

## INTRODUCTION

One of the most prevalent diseases worldwide is chronic heart failure [CHF]. It is linked with low quality of life and notable morbidity/mortality [1]. In Saudi Arabia, the Heart function Assessment Registry Trial in Saudi Arabia (HEARTS) reported that CHF occurs in mostly younger age, with much higher rates of diabetes mellitus (DM), and predominant left ventricular (LV) systolic dysfunction [2]. Considering the age factor, the established adverse effects of DM on patients with CHF [3], and the strong predictive value of reduced LV ejection fraction (EF) on cardiovascular outcomes in such patient population [4], indicates the obvious need to identify new risk factors/biological markers that could guide the treatment strategy and/or identify inadequate management. RDW determines the variation in red blood cell (RBC) sizes in peripheral blood smear. A rise in RDW is often, directly or indirectly, results from more than one factor, e.g., advancing age [5], inflammatory cascades [6], oxidative stress [7], anemia-subtypes [8], and reduced kidney function [9]. Fortunately, RDW assessment is now a routine test in the complete blood count. The prognostic value of RDW was first established in CHF by the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, which involved

2,679 patients, where RDW was the most powerful predictor of all-cause mortality amongst 36 laboratory tests [10]. Such results were supported later by other studies [11-13]. Against this background, the present cohort study was planned to evaluate the RDW prognostic value in Saudi population with CHF.

## SUBJECTS

The target population was CHF above 18 years of age, who are treated in King Fahd Hospital of the University (KFHU), Al Khobar, Saudi Arabia, with standard anti-failure drugs (irrespective of LV ejection fraction or New York Heart Association NYHA functional class).

### Exclusion Criteria

- Acute heart failure
- Serum Hb < 9 gr/dl/ hematocrit < 30%
- Known inherited hemoglobinopathy (sickle cell disease, thalassemia) with documented hemoglobin electrophoresis
- Iron deficiency anemia/megaloblastic anemia (with documented serum ferritin, transferrin saturation, or macrocytosis on peripheral blood smear)

- Severe reduction of kidney function (eGFR < 30 mL/min/1.73 m<sup>2</sup>)
- ESR > 20 mm/hr/ CRP > 0.3 mg/dl (suggestive of chronic inflammatory conditions)
- Malignancy/myelodysplastic syndrome
- Recent hemorrhage/transfusion (within 3 months)

## METHODS

This study was an observational, with a retrospective cohort design, to evaluate the relationship between RDW and ACM, during a follow up period of 24 months (from RDW measurements) as the primary endpoint. Secondary endpoints included the association of RDW with classical 3-point major adverse cardiovascular events (classical 3-point MACE), defined as a composite of nonfatal stroke, nonfatal myocardial infarction (MI), and cardiovascular death.

### Ethical Approval

The protocol was approved by the Institutional Review Board (IRB Number IRB-2019-05-009), Deanship of Scientific Research, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. The study was carried out in accordance with the Declaration of Helsinki (2013). Verbal consents from the patients/next of kin was taken by the investigators, through telephone conversations to check for study endpoints.

### Data Collection

Data collected by the investigators; MAA, MHA, and AAA at study entry included: demographic information, NYHA functional class, and co-morbidities. Using 2-D images of echocardiograms, left ventricular mass index (LVMI), and ejection fraction (EF) were calculated [14]. The primary/secondary endpoints were extracted from the electronic records, and the patients/next of kin were contacted to confirm. Cardiovascular deaths were classified as in the CHARM program [4].

### Red Blood Cell Distribution Width (RDW) Assessment

Complete blood count parameters were examined with an automated hematology analyzer DxH 800 (Beckman Coulter (UK) Ltd, High Wycombe, UK). RDW was calculated as the coefficient of variation (CV) of the red blood cell volume distribution (%).

$$\text{RDW} = [1 \text{ standard deviation of RBC volumes/MCV}] \times 100$$

Where MCV is the average volume (size) of the patient's RBC (in femtoliters, fL). The normal range of RDW obtained from our laboratory was 11.5-14.5%.

### Statistical Analysis

Data are reported as mean  $\pm$  SD, or median and ranges of values for non-normally distributed data. Patients were compared through unmatched Student's t-test, Mann-Whitney U test, or the chi-square test, based on the kind of data collected. The relationship between RDW values (as a continuous variable) and the primary endpoint (ACM) was assessed using Cox proportional hazards model (within 24 month). The model included variables the number of which was based on events occurred [15]. These variables were; age, sex, RDW, eGFR, LVMI, and EF. RDW association with secondary endpoints (classical 3-point MACE) was assessed using binary logistic regression, with goodness-of-fit tests. All statistical

analyses were done by MedCalc statistical software (version 19.1.13, MedCalc software, Ostend, Belgium). Statistical significance was defined with  $p < 0.05$ .

## RESULTS

### Baseline Characteristics

The initial search for heart failure/cardiac failure patients (Jan 2005- Dec 2016) revealed 876 patients. A total of 233 eligible patients were enrolled, after excluding 643 patients according to the pre-determined exclusion criteria. The participant's clinical characteristics and anti-failure medications are demonstrated in **Table 1**. Their hematological, biochemical, and echocardiographic characteristics are demonstrated in **Table 2**.

### Study Population as per their Baseline RDW Values

Dividing the study population based on a cut limit of RDW of 14.5% showed that patients with higher RDW had worse heart failure severity, higher prevalence of hypertension and bronchial asthma, and their medications showed less number of patients maintained on aspirin and sulphonylureas, and more maintained on loop diuretics and warfarin (**Table 1**).

### Study Endpoints

#### Primary endpoint

Within 24 months from baseline RDW measurements, 43 deaths occurred (18.5%), 39 of which (16.7%) were considered cardiovascular deaths. The average time from baseline RDW values till death was  $14.92 \pm 6.61$  (95% CI; 12.89, 16.95) months. The predictive value of RDW of ACM in the univariate analysis as well as the multivariate analysis is shown (**Table 3**).

#### The change of RDW over 12 months period and all-cause mortality

Data related to the change in RDW values from baseline was available for 215 patients over a mean duration of  $12.46 \pm 5.21$  (SD) months. The recorded change was 0.20 (-0.40, 0.90) % (median, and interquartile ranges). Univariate cox proportional hazard model showed that the change in RDW over 12 months has a significant predictive value for all-cause mortality, with HR 1.241 (95% CI; 1.159, 1.329) ( $P < 0.0001$ ). The change in RDW (when replaced baseline RDW values) was the strongest predictor of ACM in the multivariate model, HR 1.226 (95% CI; 1.117, 1.346) ( $P < 0.0001$ ) (model not shown). **Figure 2** shows the survival analysis of those classified patients (91 patients had a decrease/ no change, and 124 patients had an increase). Classifying the patients as per their baseline RDW and the trend of change reveals; 120 patients had a normal baseline RDW (in 40, it decreased, while in 80, it increased) and; 95 patients had high RDW at baseline (in 51, it decreased, while in 44, it increased). The four group's survival analyses are displayed in **Figure 3**.

#### Secondary endpoints

The same predictors were utilized in order to assess the relationship of RDW with stroke (22 events), MI (39 events), CV death (39 events), and MACE (84 events). Such analysis has showed that RDW has significant and independent association with stroke; HR 1.330 (95% CI; 1.047, 1.689) ( $P = 0.017$ ), CV death; HR 1.236 (95% CI; 1.029, 1.484) ( $P = 0.020$ ), and MACE; HR 1.162 (95% CI; 1.001, 1.349) ( $P = 0.043$ ) (models not shown).

**Table 1.** Baseline clinical and pharmacologic characteristics of study patients as one group and divided based on RDW values

Characteristic	All patients N=233	Patients with RDW ≤ 14.5% N= 127	Patients with RDW > 14.5% N= 106	P value
Age (years)	60.15 ± 12.2	59.37 ± 12.35	61.08 ± 12.11	0.29
Male sex	151 (64.8%)	90 (70.9%)	61 (57.6%)	0.034
BMI (kg/m <sup>2</sup> )*	29.05 (25.10, 33.30)	28.9 (25.40, 33.20)	29.4 (24.80, 33.70)	0.61
NYHA class**				<0.001
1	29 (12.4%)	25 (19.7%)	4 (3.8%)	
2	89 (38.2%)	49 (38.6%)	40 (37.7%)	
3	75 (32.2%)	40 (31.5%)	35 (33.0%)	
4	35 (15.0%)	11 (8.7%)	24 (22.6%)	
Ischemic etiology of CHF	156 (67.0%)	92 (72.4%)	64 (60.4%)	0.051
<i>Co-morbidities</i>				
Hypertension	180 (77.3%)	90 (70.9%)	90 (84.9%)	0.011
Diabetes mellitus (type 2)	166 (71.2%)	92 (72.4%)	74 (69.8%)	0.66
Dyslipidaemia	131 (56.2%)	65 (51.2%)	66 (62.3%)	0.089
Arrhythmias***/AF	51 (21.9%)/ 45 (19.3%)	24 (18.9%)/ 20 (15.7%)	27 (25.5%)/ 25 (23.6%)	0.23/0.13
Bronchial asthma	21 (9.0%)	7 (5.5%)	14 (13.2%)	0.041
<i>Cardiac medication</i>				
ACEIs/ARBs	133 (57.1%)/69 (29.6%)	74 (58.3%)/35 (27.6%)	59 (55.7%)/34 (32.1%)	0.69/0.45
Beta blockers	192 (82.4%)	110 (86.6%)	82 (77.4%)	0.065
CCBs	53 (22.8%)	30 (23.6%)	23 (21.7%)	0.73
Aspirin/Clopidogrel	194 (83.3%)/90 (38.6%)	114 (89.8%)/47 (37.0%)	80 (75.5%)/43 (40.6%)	0.004/0.58
Warfarin	35 (15.0%)	13 (10.2%)	22 (20.8%)	0.025
Thiazide diuretics	39 (16.7%)	25 (19.7%)	14 (13.2%)	0.19
Loop diuretics	157 (67.4%)	74 (58.3%)	83 (78.3%)	0.001
Spirolactone	89 (38.2%)	43 (33.9%)	46 (43.4%)	0.14
<i>Antidiabetic medication</i>				
Insulin	70 (30.0%)	36 (28.3%)	34 (32.1%)	0.54
Sulphonylureas	53 (22.8%)	41 (32.3%)	12 (11.3%)	<0.001
Metformin	99 (42.5%)	59 (46.5%)	40 (37.7%)	0.18

Values are expressed as mean ± SD or number (percentage of patients). Median with interquartile ranges are used for non-normally distributed data.

Abbreviations: BMI, body mass index; NYHA, New York Heart Association; AF, atrial fibrillation (paroxysmal and permanent); ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

Missing data from medical records: \*13 patients did not have their heights recorded, \*\* 5 patients did not have their NYHA class recorded, \*\*\* Other 6 arrhythmias (premature ventricular contractions, atrial flutter, 2 supraventricular tachycardia, and 2 ventricular tachycardia)

**Table 2.** Hematological, biochemical, and echocardiographic characteristics of patients, overall and by RDW group

Characteristic	All patients N=233	Patients with RDW ≤ 14.5% N= 127	Patients with RDW >14.5% N= 106	P value
<i>Hematological</i>				
Hb (g/dl)	13.15 ± 1.84	13.77 ± 1.64	12.41 ± 1.81	<0.001
Hematocrit (%)	39.46 ± 5.34	40.83 ± 4.94	37.81 ± 5.36	<0.001
RDW (%)	14.40 (13.50, 15.80)	13.50 (13.00, 14.00)	15.95 (15.30, 17.30)	<0.001
<i>Biochemical</i>				
Serum creatinine (mg/dL)	1.00 (0.90, 1.30)	1.00 (0.80, 1.20)	1.10 (0.90, 1.30)	0.019
eGFR (ml/min/1.73m <sup>2</sup> )	72.00 (57.00, 89.00)	76.00 (62.00, 93.00)	66.00 (54.00, 81.00)	<0.001
<i>Echocardiographic</i>				
Left ventricular mass index (g/m <sup>2</sup> )*	107.00 (82.00, 131.00)	108.00 (85.00, 136.00)	104.50 (78.00, 127.75)	0.28
Ejection fraction (EF)**	41.00 (30.00, 55.00)	43.00 (33.00, 55.00)	40.00 (28.00, 55.00)	0.20

Values are expressed as mean ± SD or number (percentage of patients). Median with interquartile ranges are used for non-normally distributed data.

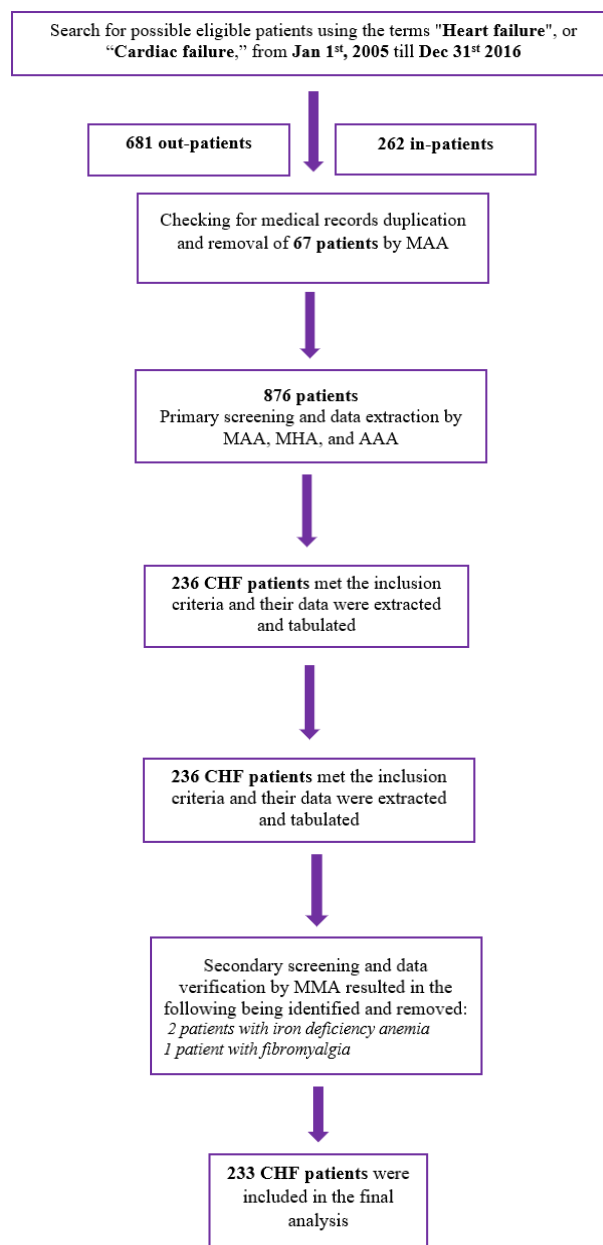
Abbreviations: Hb, hemoglobin; eGFR, estimated glomerular filtration rate

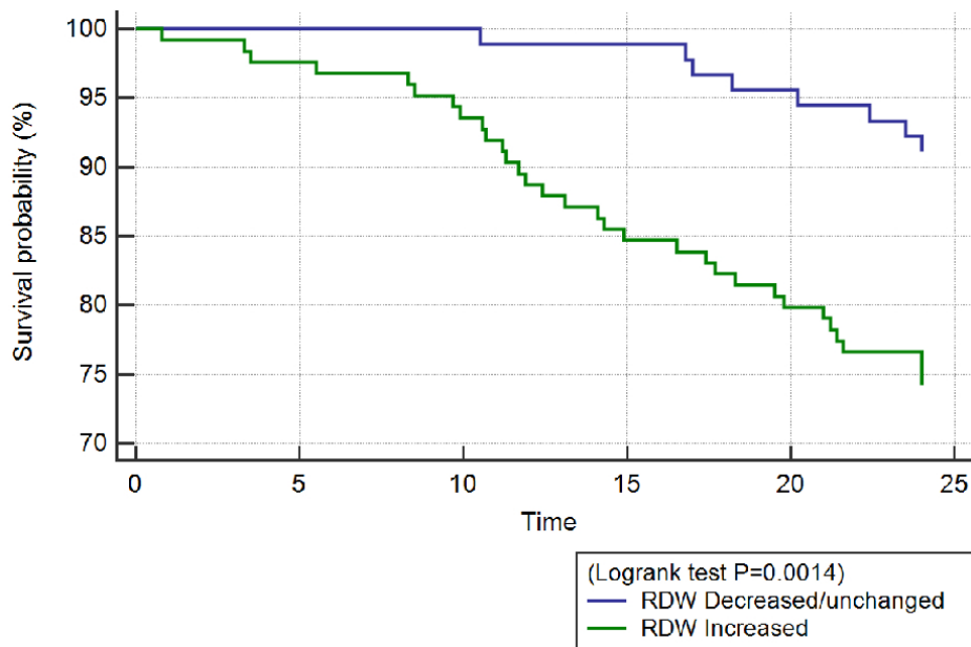
Missing data from medical records; \*data from 211 patients (10 patients had no matching echocardiograms, 3 had echocardiograms for EF estimation only, and 9 had no height recorder to calculate LVMI), \*\* data from 223 patients

**Table 3.** Univariate and multivariate Cox proportional hazard models of RDW and ACM

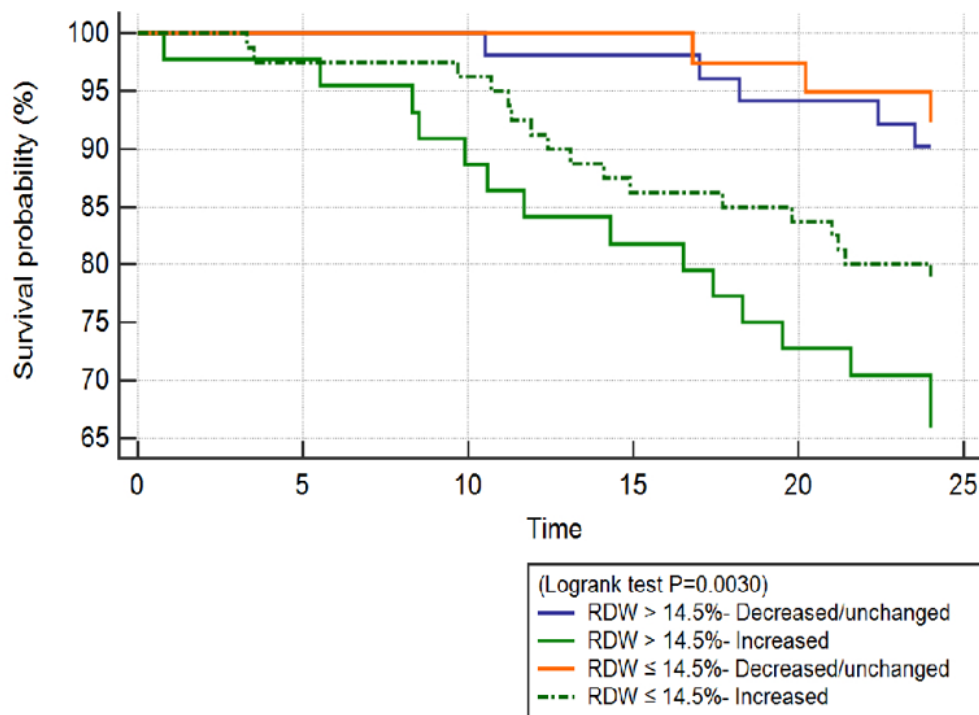
Univariate analysis		
Variable	HR (95% CI)	P-value
Age	1.083 (1.050, 1.118)	< 0.001
RDW	1.213 (1.075, 1.368)	0.002
eGFR	0.982 (0.968, 0.997)	0.017
LVMl	1.006 (1.000, 1.013)	0.049
EF	0.994 (0.971, 1.017)	0.607
Sex (female)	1.489 (0.816, 2.727)	0.195
Multivariate analysis		
Variable	HR (95% CI)	P-value
Age	1.078 (1.043, 1.114)	<0.001
RDW	1.238 (1.090, 1.407)	0.001
eGFR	0.990 (0.975, 1.005)	0.184
LVMl	1.010 (1.002, 1.018)	0.016
EF	1.010 (0.984, 1.036)	0.46
Sex (female)	1.002 (0.512, 1.962)	0.99

Abbreviations: RDW, red blood cell distribution width; eGFR, estimated glomerular filtration rate; LVMl, left ventricular mass index; EF, ejection fraction  
Overall Model Fit Null model -2 Log Likelihood 460.214; Full model -2 Log Likelihood 402.475; Chi-squared 57.739; Significance level  $P < 0.0001$

**Figure 1.** Study flow chart



**Figure 2.** Kaplan-Meier survival analysis in CHF patients based on RDW change over 12 months



**Figure 3.** Kaplan-Meier survival analysis in CHF patients based on baseline RDW value and its change over 12 months

## DISCUSSION

This study is the first to show that one-occasional assessment of RDW has a predictive value to ACM, stroke, CV death, and MACE in Saudi population with CHF. In addition, it appears that the trend of change (if it continues to rise) of such parameter with time is of equal importance. The magnitude of predictability found for ACM in our study is greater than other studies/meta-analyses in the literature [4,10,12,13]. In particular interest, the usefulness of RDW in predicting clinical outcomes in this study is superior to echocardiographic parameters, and such finding was reported in the literature [16,17].

To consolidate these findings and base future recommendations, additional studies are required to confirm the reliability and robustness of RDW for routine clinical practice. Four important considerations warrant early attention and investigation. First, a large population-based study identified that 29% of the variability in RDW is due to a genetic component that increases with age: this issue needs clarification [18]. In the future, exploration of ethnic/ genetic factors to establish reference ranges and the predictive value of RDW in different populations will almost certainly require large, comparative epidemiological studies. Secondly, there is technological heterogeneity amongst different hematological analysers [19]; to solve this issue, standardization of the methods of analysis is essential, in accordance with the

recommendations of the International Council for Standardization in Haematology (ICSH) [20]. Thirdly, it is still not clear which factors/clinical conditions contribute significantly to RDW and, in turn, to what extent these are genetically determined. These factors should be possibly explored in different patient's population by relating the summative results to the clinical co-morbidities, but this piece of information is beyond the scope of this study.

Finally, for a future perspective on whether different drug treatments might have influenced RDW measurements, our study does not have enough statistical support to draw definitive conclusions but it has shown that patients with high RDW values used less of aspirin and sulphonylureas as and more of warfarin and loop diuretics, but this trend could not be separated from the primary indications of these drugs –the ischemic etiology of CHF, type 2 DM, AF, and NYHA functional class III-IV respectively. Nevertheless, it remains possible that these drug classes might influence “at least partially” the general inflammatory state and the measured RDW values. The anti-inflammatory action of anti-platelet/low-dose aspirin has been reported in human subjects [21] and the anti-inflammatory activity of sulphonylureas as has been shown in diabetic patients [22]. Data on the effects of warfarin on parameters of inflammatory reactions are sparse in the literature, with both stimulatory and inhibitory [23]. The same contradictory findings apply to furosemide therapy as well [24,25].

In summary, RDW is an emerging essential biomarker which has an independent prognostic value in patients with CHF for ACM, stroke, and CV death during the specified follow-up period. Before definitive recommendations can be made with respect to clinical intervention, however, a number of clarifications are required: for example, the establishment of reference values in different populations, taking into consideration genetic differences, age, sex, and different co-morbidities. Further, the effects of different pharmacological agents need to be explored and incorporated into future predictive models.

### Study Limitations

There are two major limitations in this study. First; we did not include patients who presented before 2005, for lack of completeness of echocardiogram reports and we excluded those patients whose RDW might have been raised by hematological disorders. Second; our study did not include the comparison of RDW against that of brain natriuretic peptide (BNP), because it is not a routine test for heart failure patients in our hospital.

## CONCLUSION

This study has shown that RDW is an easy, widely available, routine blood test with significant predictive value for ACM and CV events in patients with CHF. These findings are consistent with other populations. However, reference values, standardized techniques, are a priority, and so are identifying established factors that could contribute to high RDW readings. For now, a closer look at RDW in CBC reports is worth considering.

**Author contributions: MMA:** Conceived and designed the study, contributed data or analysis tools, verified the date, performed the analysis, and wrote the paper. **AMA:** Conceived and designed the study,

collected the data, contributed data or analysis tools, and revised the paper. **MMA:** Conceived and designed the search process, collected the data, contributed data or analysis tools. **MHA:** Conceived and designed the search process, collected the data, contributed data or analysis tools. **AAA:** Conceived and designed the search process, collected the data, contributed data or analysis tools. **RTB:** Conceived and designed the study, performed the analysis, and revised the paper. All authors have sufficiently contributed to the study, and agreed with the results and conclusions.

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**Declaration of interest:** No conflict of interest is declared by authors.

**Availability of supporting data:** The data which support the findings of this study are available from the corresponding author upon request.

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