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Original Article

Red cell distribution width and all-cause mortality in patients with atrial fibrillation: A cohort study

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ABSTRACT

Background: Increased red cell distribution width (RDW), a measure of red cell size variability, has been associated with increased mortality in multiple cardiovascular diseases. However, whether RDW is associated with increased mortality in patients with atrial fibrillation remains unknown.
Methods: Using the computerized database of the largest health maintenance organization in Israel, we identified a cohort of adults with atrial fibrillation diagnosed before January 1, 2012. Cardiovascular risk factors and comorbidities were ascertained using an electronic medical record–based algorithm. Mortality was established using the National Death Index through December 31, 2013.
Results: Of 69,412 patients, 12,104 (17.4%) participants died during follow-up. The crude, two-year cumulative all-cause mortality rate increased across RDW quartiles; 9.8%, 13.6%, 18.8%, and 28.5%, respectively. After adjustment for age, sex, anemia, cardiovascular risk factors, comorbidities, and medication use, compared to the lowest RDW quartile, the hazard ratio (HR) for mortality was 1.20 (95% CI, 1.13–1.27) in the second quartile, 1.44 (1.36–1.53) in the third quartile, and 1.90 (1.79–2.00) in the highest RDW quartile. The results were similar after further adjustment for smoking, socioeconomic status, renal function, low and high density lipoprotein cholesterol levels, with HR=1.82 (1.71–1.93) in the highest RDW quartile compared to the lowest quartile. Changes in RDW over time were strongly associated with mortality; increased RDW was associated with higher risk of mortality and decline in RDW was associated with decreased mortality.
Conclusions: RDW and changes in RDW are independently associated with the risk of all-cause mortality in patients with atrial fibrillation.

1. Introduction

Red cell distribution width (RDW) is a measure of red cell size variability, with higher RDW values reflecting greater heterogeneity (anisocytosis), and its use in the clinical setting has been confined to the differentiation between several etiologies of anemia [1]. However, in recent years, RDW has emerged as a novel predictor of all-cause mortality in multiple cardiovascular settings including congestive heart failure (CHF), and ischemic heart disease (IHD) [2–8].

Atrial fibrillation is a common cardiac arrhythmia among older adults that is likely to increase 2.5-fold during the next 50 years [9]. Frequent hospitalization, hemodynamic abnormalities, and thromboembolic events related to atrial fibrillation can result in significant morbidity and mortality [10]. Identification of new prognostic risk factors like RDW would be valuable for adverse outcome prediction in patients with atrial fibrillation, especially if obtained routinely and inexpensively. Recently, we showed that RDW is an independent predictor of stroke in patients with atrial fibrillation [11]. However, whether RDW is also associated with increased risk of mortality in patients with atrial fibrillation remains unknown. In this study we aimed to assess the association of RDW and changes in RDW over time with all-cause mortality in patients with atrial fibrillation, using data from a population-based electronic medical registry (EMR) database of the largest health maintenance organization (HMO) in Israel.

2. Materials and methods

2.1. Data source

Clalit Health Services (CHS) is a not-for-profit health care provider covering more than half of the Israeli population [11,12]. The EMR database of the CHS includes data from multiple sources:

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Table 1
Baseline distribution of demographic and clinical characteristics of participants according to red blood cell distribution width (RDW) quartiles; CHS cohort, Israel 2012.

Variable	All	Red cell distribution width (RDW) quartiles			
		Quartile-1	Quartile-2	Quartile-3	Quartile-4
	$n=69,412$	($\leq 13.6\%$) $n=19,061$	(13.6–14.3%) $n=17,186$	(14.3–15.2%) $n=16,013$	($>15.2\%$) $n=17,152$
Age* (years)	74.8 ± 12.0	71.8 ± 13.2	74.9 ± 11.8	76.4 ± 11.0	76.6 ± 10.9
Age*					
< 65 years	13,094 (18.9%)	5520 (27.4%)	3205 (18.6%)	2315 (14.5%)	2354 (13.7%)
65–75 years	16,178 (23.3%)	4756 (25.0%)	4077 (23.7%)	3538 (22.1%)	3807 (22.2%)
≥ 75 years	40,140 (57.8%)	9085 (47.7%)	9904 (57.6%)	10,160 (63.4%)	10,991 (64.1%)
Gender*					
Males	33,415 (48.1%)	9809 (51.5%)	8385 (48.8%)	7461 (46.6%)	7760 (45.2%)
Females	35,997 (51.9%)	9252 (48.5%)	8801 (51.2%)	8552 (53.4%)	9392 (54.8%)
Ethnicity*					
Arabic	7123 (10.3%)	1778 (9.3%)	1637 (9.5%)	1624 (10.1%)	2084 (12.2%)
Jewish	62,289 (89.7%)	17,283 (90.7%)	15,549 (90.5%)	14,389 (89.9%)	15,068 (87.8%)
Socioeconomic status*,†					
Low	23,660 (34.2%)	6194 (32.6%)	5668 (33.1%)	5480 (34.4%)	6318 (37.0%)
Middle	29,775 (43.1%)	8014 (42.2%)	7253 (42.4%)	6929 (43.5%)	7579 (44.4%)
High	15,660 (22.7%)	4781 (25.2%)	4181 (24.4%)	3529 (22.1%)	3169 (18.6%)
Smoking status*,†					
Never	43,990 (64.4%)	12,098 (64.3%)	10,998 (65.0%)	10,228 (65.1%)	10,666 (63.3%)
Ever	24,303 (35.6%)	6706 (35.7%)	5932 (35.0%)	5477 (34.9%)	6188 (36.7%)
$CHADS_2$	2.5 ± 1.5	2.1 ± 1.5	2.4 ± 1.4	2.7 ± 1.4	2.9 ± 1.4
CHA_2DS_2-VASc	4.4 ± 1.9	3.7 ± 2.0	4.3 ± 1.9	4.7 ± 1.8	5.0 ± 1.8
Comorbidities					
Hypertension*	56,232 (81.0%)	13,913 (73.0%)	13,827 (80.5%)	13,552 (84.6%)	14,940 (87.1%)
Diabetes*	26,047 (37.5%)	5663 (29.7%)	6039 (35.1%)	6394 (39.9%)	7951 (46.4%)
CHF*	18,854 (27.2%)	3197 (16.8%)	3805 (22.1%)	4790 (29.9%)	7062 (41.2%)
IHD*	37,961 (54.7%)	8774 (46.0%)	8997 (52.4%)	9351 (58.4%)	10,839 (63.2%)
PVD*	5791 (8.3%)	1134 (5.9%)	1299 (7.6%)	1430 (8.9%)	1928 (11.2%)
Stroke/TIA*	16,415 (23.6%)	3664 (19.2%)	3923 (22.8%)	4076 (25.5%)	4752 (27.7%)
Malignancy*	14,040 (20.2%)	3147 (16.5%)	3301 (19.2%)	3362 (21.0%)	4230 (24.7%)
COPD*	9930 (14.3%)	1982 (10.4%)	2190 (12.7%)	2404 (15.0%)	3354 (19.6%)
Medications use in the prior 120 days					
Anticoagulants*	28,272 (40.7%)	5696 (29.9%)	6953 (40.5%)	7275 (45.4%)	8348 (48.7%)
Antiplatelet	37,173 (53.6%)	10,163 (53.3%)	9212 (53.6%)	8649 (54.0%)	9149 (53.3%)
Statins*	44,945 (64.8%)	12,064 (63.3%)	11,380 (66.2%)	10,636 (66.4%)	10,865 (63.3%)
ACE-inh and ARBs*	43,205 (62.2%)	10,846 (56.9%)	10,773 (62.7%)	10,517 (65.7%)	11,069 (64.5%)
Beta-blockers*	41,949 (60.4%)	10,612 (55.7%)	10,312 (60.0%)	9,987 (62.4%)	11,038 (64.4%)
Laboratory tests					
Anemia‡,*	27,932 (40.2%)	4698 (24.6%)	5494 (32.0%)	6867 (42.9%)	10,873 (63.4%)
Hemoglobin* (g/dL)	12.8 ± 1.6	13.4 ± 1.4	13.1 ± 1.5	12.7 ± 1.5	11.9 ± 1.6
LDL*,† (mg/dL)	94.6 ± 30.6	98.8 ± 30.4	95.7 ± 30.3	93.7 ± 30.2	89.7 ± 30.5
HDL*,† (mg/dL)	48.3 ± 13.6	49.7 ± 13.3	49.1 ± 13.3	48.4 ± 13.7	46.1 ± 13.8
RDW* (%)	14.6 ± 1.60	13.1 ± 0.44	14.0 ± 0.20	14.8 ± 0.25	16.6 ± 1.55
Creatinine*,† (mg/dL)	1.08 ± 0.72	0.96 ± 0.42	1.02 ± 0.52	1.09 ± 0.69	1.25 ± 1.07
eGFR*,† (mL/min/1.73 cm^2)	74.2 ± 29.5	79.8 ± 26.2	75.3 ± 26.6	72.0 ± 28.0	69.0 ± 35.3

Abbreviations: CHF=congestive heart failure, IHD=ischemic heart disease, PVD=peripheral vascular disease, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, ACE-inh=angiotensin converting enzyme inhibitor, ARBs=angiotensin receptors blockers, LDL=low density lipoprotein, HDL=high density lipoprotein, RDW=red cell distribution width, eGFR=estimated glomerular filtration rate.

* $P<0.05$.

† Variables with missing data: socioeconomic status 0.5%, smoking status 1.6%, LDL 6.0%, HDL 4.7%, creatinine 0.8%).

‡ Anemia was defined as hemoglobin levels < 13.0 g/dL in males and < 12.0 g/dL in females in accordance with the World Health Organization (WHO) classification criteria.

primary care physicians, specialty clinics in the community, hospitals, laboratories, and pharmacies. A chronic disease registry is compiled from these data sources. Diagnoses are captured in the registry by diagnosis-specific algorithms, employing code reading (e.g., ICD-9 and ICPC), text reading, laboratory test results, and disease-specific drug usage. A record is kept of the sources and dates of diagnosis used to establish the diagnosis, with the earliest recorded date being considered the starting date of the diagnosis.

2.2. Study population

The CHS computerized database was retrospectively searched for all adult patients (age, ≥ 20 years) in whom atrial fibrillation was diagnosed before January 1, 2012 (77,297 subjects). We included only subjects who had at least one complete blood cell count test result performed during the year prior to study entry (69,412 subjects).

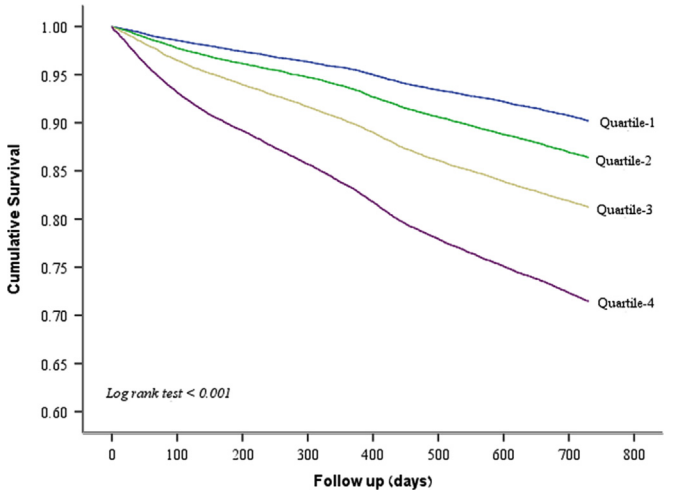

Fig. 1. Kaplan–Meier curves for the distribution of time to death according to red cell distribution width quartiles in patients with atrial fibrillation; CHS cohort, Israel 2012 ($n=69,412$).

2.3. Follow-up

The cohort of subjects with atrial fibrillation was retrospectively followed for the outcome of all-cause mortality from January 1, 2012 until December 31, 2013. Mortality was established by matching our data with the National Death Index.

2.4. Study variables and definition of terms

The most recent RDW test performed in the year prior to study entry (2011) was used to examine the association of RDW with all-cause mortality. For this purpose, RDW was classified into quartiles ($\leq 13.6\%$, 13.6–14.3%, 14.3–15.2%, $>15.2\%$). In addition, RDW was classified into two categories based on the upper bound of the normal RDW: normal (RDW $\leq 14.5\%$) and elevated (RDW $>14.5\%$). RDW was also tested as a continuous variable. To examine the association of the changes in RDW over time with all-cause mortality, we included subjects with at least two RDW tests performed during the year prior to study entry ($n=50,597$). The first and last (most recent) tests were selected and each classified into the aforementioned categories. The combinations of the first and second test categories yielded four different combinations: normal-normal (both first and second test were normal), normal-elevated, elevated-normal, and elevated-elevated.

Variables studied as possible confounders were: socio-demographic variables, cardiovascular risk factors and comorbidities reflecting leading causes of death, smoking status, use of selected medications, and selected laboratory tests. Socio-demographic variables included sex, age at the time of study entry, and socioeconomic status (SES) defined based on the SES score of the clinic neighborhood as defined by the Israeli Central Bureau of Statistics and classified into three categories (low, middle, and high). Diagnosis of cardiovascular risk factors and comorbidities included hypertension, diabetes mellitus (DM), CHF, IHD, peripheral vascular disease (PVD), prior stroke or transient ischemic attack (TIA), chronic obstructive pulmonary disease (COPD), and any malignancy not including non-melanoma skin cancer. Medication use was established by searching the pharmacy database, and defined as any prescription filled during the 120 days prior to study entry. The use of the following medications was considered: anticoagulants, antiplatelet, statins, angiotensin converting enzyme inhibitors (ACE-inh), angiotensin receptor blockers (ARBs), and beta-blockers. Smoking status was classified into ever-smoking and never-smoking. In addition to RDW, the following test results were retrieved from the CHS laboratory database: hemoglobin, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and creatinine level. Only blood tests from the year prior to study entry were selected; if more than one test result was available, the blood test conducted near to the time of study entry was selected. Anemia was defined as hemoglobin levels <13.0 g/dL in men and <12.0 g/dL in women in accordance with the World Health Organization (WHO) classification criteria [13]. Estimated glomerular filtration rate (eGFR) was calculated based on the formula from the Modification of Diet in Renal Disease Study [14].

Table 2
Two-year crude cumulative all-cause mortality rate and crude hazard ratios (HRs) for the association between red cell distribution width (RDW) and all-cause mortality in patients with atrial fibrillation, examined separately for three different RDW classification categories (RDW quartiles, dichotomous variable, and continuous variable); CHS cohort, Israel 2012 ($n=69,412$).

Type of RDW variable	Number at risk	Number of deaths	Cumulative mortality rate	Crude HR (95% CI)
RDW Quartiles				
Quartile-1 ($\leq 13.6\%$)	19,061	1866	9.8%	Reference
Quartile-2 (13.6–14.3%)	17,186	2341	13.6%	1.42 (1.34–1.51)
Quartile-3 (14.3–15.2%)	16,013	3003	18.8%	2.02 (1.91–2.14)
Quartile-4 ($>15.2\%$)	17,152	4894	28.5%	3.31 (3.13–3.49)
RDW dichotomous variable				
Normal ($\leq 14.5\%$)	40,466	4930	12.2%	Reference
Elevated ($>14.5\%$)	28,946	7174	24.8%	2.21 (2.13–2.30)
RDW continuous variable				
HR for each 1% increase in RDW	–	–	–	1.23 (1.22–1.24)

Abbreviations: RDW=red cell distribution width, HR=hazard ratio, CI=confidence interval.

2.5. Statistical methods

Continuous variables are summarized with mean $\pm$ SD, and categorical variables are presented as numbers and proportions. Analysis of variance (ANOVA) was used to compare continuous variables, and the chi-square test to compare categorical variable between RDW quartiles. Kaplan-Meier method was used to plot the distribution of time to death by RDW quartiles, and the log rank test was used to compare curves. Cox proportional hazard regression models were used to assess the association between time to death and RDW. Two models were tested; Model I included variables with complete data and was adjusted for age, sex, anemia, cardiovascular risk factors and comorbidities (hypertension, DM, CHF, IHD, PVD, stroke or TIA, malignancy, COPD), and selected medication use (anticoagulants, antiplatelet, statins, beta-blockers, ACE-inh and ARBs). In addition to the variables included for Model I, Model II included variables with a missing value (socioeconomic and smoking status, renal function, LDL and HDL levels), with 91.9% of subjects included in Model II overall. Included in both models, all covariates were checked against one another for collinearity. *P*-values less than 0.05 for the two-tailed tests were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 21.0, and forest plots were constructed using WinPepi version 11.15.

Table 3
Cox proportional hazard models for the association between red cell distribution width (RDW) quartiles and all-cause mortality in patients with atrial fibrillation; CHS cohort, Israel 2012.

Variables	Model I $n=69,412$		Model II $n=63,820$	
	HR (95% CI)	***P value***	***HR (95% CI)***	***P value***
RDW Quartiles				
Quartile-1 (≤ 13.6%)	Reference		Reference	
Quartile-2 (13.6–14.3%)	1.20 (1.13–1.27)	< 0.001	1.16 (1.08–1.24)	< 0.001
Quartile-3 (14.3–15.2%)	1.44 (1.36–1.53)	< 0.001	1.40 (1.31–1.49)	< 0.001
Quartile-4 (> 15.2%)	1.90 (1.79–2.00)	< 0.001	1.82 (1.71–1.93)	< 0.001
Age				
< 65 years	Reference		Reference	
65–75 years	1.69 (1.54–1.87)	< 0.001	1.68 (1.52–1.86)	< 0.001
≥ 75 years	3.97 (3.65–4.32)	< 0.001	3.98 (3.64–4.36)	< 0.001
Gender				
Males	Reference		Reference	
Females	1,02 (0.99–1.06)	0.221	1.10 (1.06–1.15)	< 0.001
Ethnicity				
Arabs	1.01 (0.95–1.08)	0.761	0.98 (0.91–1.06)	0.646
Jews	Reference		Reference	
Comorbidities				
Hypertension	1.27 (1.19–1.35)	< 0.001	1.19 (1.11–1.28)	< 0.001
Diabetes	1.18 (1.14–1.23)	< 0.001	1.14 (1.10–1.19)	< 0.001
CHF	2.14 (2.05–2.22)	< 0.001	2.11 (2.02–2.20)	< 0.001
IHD	1.16 (1.11–1.20)	< 0.001	1.12 (1.07–1.17)	< 0.001
PVD	1.23 (1.17–1.30)	< 0.001	1.21 (1.14–1.28)	< 0.001
Stroke or TIA	1.43 (1.38–1.49)	< 0.001	1.42 (1.36–1.48)	< 0.001
Malignancy	1.28 (1.23–1.33)	< 0.001	1.33 (1.27–1.39)	< 0.001
COPD	1.37 (1.31–1.43)	< 0.001	1.38 (1.32–1.45)	< 0.001
Medications use in the prior 120 days				
Anticoagulants	0.72 (0.70–0.75)	< 0.001	0.75 (0.72–0.78)	< 0.001
Antiplatelet	0.92 (0.88–0.96)	< 0.001	0.94 (0.90–0.99)	0.008
Statins	0.60 (0.58–0.62)	< 0.001	0.63 (0.60–0.66)	< 0.001
ACE-inh & ARBs	0.75 (0.72–0.77)	< 0.001	0.78 (0.75–0.82)	< 0.001
Beta-blockers	0.96 (0.92–0.99)	0.026	0.94 (0.90–0.98)	0.003
Laboratory tests				
Anemia	1.63 (1.57–1.69)	< 0.001	1.60 (1.54–1.67)	< 0.001
Creatinine†	–	–	1.13 (1.11–1.15)	< 0.001
LDL†	–	–	1.00 (1.00–1.00)	0.034
HDL†	–	–	0.99 (0.99–0.99)	< 0.001
Socioeconomic status				
Low	–	–	Reference	
Middle	–	–	0.99 (0.94–1.03)	0.499
High	–	–	0.90 (0.86–0.95)	< 0.001
Smoking status				
Never	–	–	Reference	
Ever	–	–	1.01 (0.97–1.06)	0.646

Abbreviations: CHF=congestive heart failure, IHD=ischemic heart disease, PVD=peripheral vascular disease, TIA=transient ischemic attack, COPD=chronic obstructive pulmonary disease, ACE-inh=angiotensin converting enzyme inhibitor, ARBs=angiotensin receptors blockers, LDL=low density lipoprotein, HDL=high density lipoprotein, RDW=red cell distribution width, HR=hazard ratio, CI=confidence interval.
Model I: adjusted for age, gender, ethnicity, cardiovascular risk factors and comorbidities (hypertension, diabetes mellitus, CHF, IHD, PVD, stroke or TIA, malignancy, COPD), anemia, and selected medications use (anticoagulants, antiplatelet, statins, beta-blockers, ACE-inh & ARBs).
Model II: adjusted for socioeconomic status, smoking status, creatinine, LDL and HDL cholesterol levels in addition to covariates in Model I.
† HR for each 1 mg/dL increase.

3. Results

A total of 69,412 adult subjects with atrial fibrillation were included in the study. The mean age was 74.8 (± 12.0) years, and 35,415 (51.9%) were women. A previous history of stroke or TIA was detected in 16,415 (23.6%) subjects, and overall 28,272 (40.7%) patients with atrial fibrillation were treated with anticoagulants at baseline (Table 1). Compared to those in the lowest quartile, subjects in the highest quartile were older, and were more likely to be women. The proportion of subjects with cardiovascular risk factors, and comorbidities along with the average $CHADS_2$ and CHA_2DS_2-VASc scores increased across RDW quartiles (Table 1). The baseline socio-demographic, clinical, medication use, and laboratory characteristics of the study participants are presented by RDW quartiles as shown in Table 1.

3.1. Association between RDW and all-cause mortality

Overall, 12,104 (17.4%) of 69,412 participants died during follow up. The distribution of time to death according to RDW quartiles is depicted in Fig. 1. The two-year crude cumulative all-cause

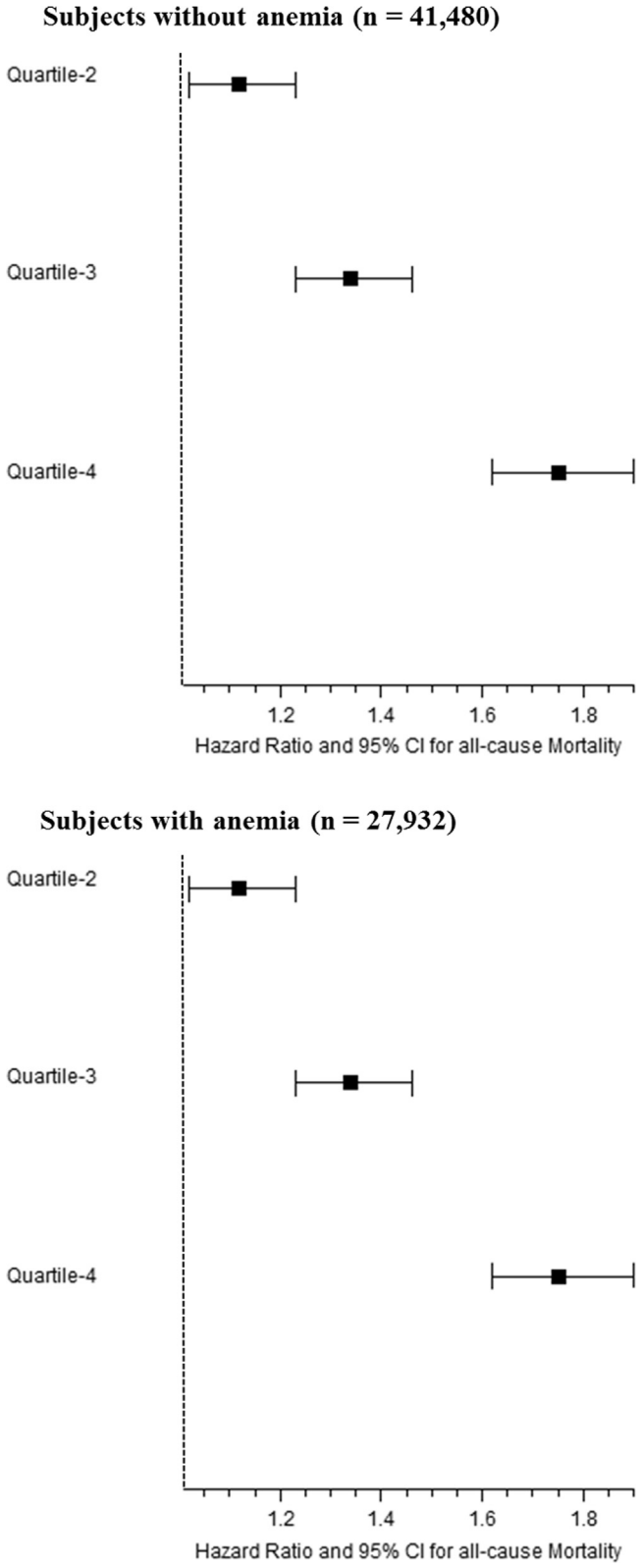

Fig. 2. Adjusted hazard ratios, stratified by anemia status, for the association between red cell distribution width (RDW) quartiles and all-cause mortality in patients with atrial fibrillation (the lowest RDW quartile represents the reference category); CHS cohort, Israel 2012 ($n=69,412$).

mortality rate increased across RDW quartiles (9.8%, 13.6%, 18.8%, and 28.5%, respectively) (Table 2).

Multivariate Cox proportional hazard regression analysis showed that RDW was independently associated with all-cause mortality after adjustment for age, sex, anemia, cardiovascular risk factors, comorbidities, and medication use (Model I, Table 3). Compared to subjects in the lowest RDW quartile, the risk of mortality increased with increasing RDW quartiles; adjusted HR was 1.20 (95% CI, 1.13–1.27) for the second RDW quartile, 1.44 (1.36–1.53) for the third quartile, and 1.90 (1.79–2.00) for the highest quartile (P for trend <0.001) (Model I, Table 3). We reached similar results after further adjusting for smoking, socioeconomic status, renal function, and LDL and HDL levels (Model II, Table 3). Stratified analysis by anemia status of the fully adjusted model showed that the results were similar both for patients with and without anemia (P for interaction $=0.162$) (Fig. 2).

The association of RDW with all-cause mortality persisted when tested as a continuous variable: for each 1% increment RDW, the fully adjusted HR $=1.13$ (1.12–1.14). When tested as a dichotomous variable, the fully adjusted HR $=1.49$ (1.43–1.55) for patients with elevated RDW ($\geq 14\%$) compared to those with normal RDW ($<14.5\%$) (Model II, Table 4).

Table 4
Adjusted hazard ratios for the association between red cell distribution width (RDW) and all-cause mortality in patients with atrial fibrillation, examined separately for three different RDW classification categories (RDW quartiles, dichotomous variable, and continuous variable); CHS cohort, Israel 2012.

Type of RDW variable	Model I $n=69,412$		Model II $n=63,820$	
	HR (95% CI)	***P value***	***HR (95% CI)***	***P value***
RDW Quartiles				
Quartile-1 ($\leq 13.6\%$)	Reference		Reference	
Quartile-2 (13.6–14.3%)	1.20 (1.13–1.27)	<0.001	1.16 (1.08–1.24)	<0.001
Quartile-3 (14.3–15.2%)	1.44 (1.36–1.53)	<0.001	1.40 (1.31–1.49)	<0.001
Quartile-4 ($>15.2\%$)	1.90 (1.79–2.00)	<0.001	1.82 (1.71–1.93)	<0.001
P for trend		<0.001		<0.001
RDW dichotomous variable				
Normal ($\leq 14.5\%$)	Reference		Reference	
Elevated ($>14.5\%$)	1.52 (1.46–1.58)	<0.001	1.49 (1.43–1.55)	<0.001
RDW continuous variable				
HR for each 1% increase in RDW	1.13 (1.12–1.14)	<0.001	1.13 (1.12–1.14)	<0.001

Abbreviations: RDW = red cell distribution width, HR = hazard ratio, CI = confidence interval.
Model I: adjusted for age, gender, ethnicity, cardiovascular risk factors and comorbidities (hypertension, diabetes mellitus, congestive heart failure, ischemic heart disease, peripheral vascular disease, stroke or TIA, malignancy, chronic obstructive pulmonary disease), anemia, and selected medications use (anticoagulants, antiplatelet, statins, beta-blockers, ACE-inh & ARBs).
Model II: adjusted for socioeconomic status, smoking status, renal function, LDL and HDL cholesterol levels in addition to covariates in Model I.

3.2. Association between the change in RDW and all-cause mortality

Overall, 50,597 (72.9%) subjects, with at least two RDW tests performed during the year prior to study entry, were included in this analysis. The average time between the first and last RDW tests was 213 ± 88 days. The average difference between the last and first RDW tests was $0.24\% \pm 1.42$. The average RDW difference within each of the four groups is shown in Table 5. Multivariate Cox proportional hazard regression analysis showed that the change in RDW in the year prior to study entry was independently associated with all-cause mortality after adjustment for age, sex, anemia, cardiovascular risk factors, comorbidities, and medication use (Model I, Table 5). Compared to subjects with persistently

Table 5
Adjusted hazard ratios for the association between change in red cell distribution width and all-cause mortality in patients with atrial fibrillation; CHS cohort, Israel, 2012.

RDW change category*	Mean ± SD difference in RDW tests**	Model I (*n=50,597*)		Model II (*n=46,989*)	
		Number (%)	*HR (95% CI)*	*Number (%)*	*HR (95% CI)*
Normal–normal	0.15 ± 0.71	22,443 (44.4%)	Reference	21,017 (44.7%)	Reference
Elevated–normal	−1.45 ± 1.24	4827 (9.5%)	1.35 (1.25–1.45)	4446 (9.5%)	1.35 (1.25–1.46)
Normal–elevated	1.65 ± 1.27	7926 (15.7%)	1.49 (1.40–1.59)	7365 (15.7%)	1.48 (1.39–1.58)
Elevated–elevated	0.18 ± 1.62	15,401 (30.4%)	1.73 (1.65–1.82)	14,161 (30.1%)	1.70 (1.61–1.79)
P for trend			< 0.001		< 0.001

Abbreviations: RDW = red cell distribution width, HR = hazard ratio, CI = confidence interval, SD = standard deviation.
Model I: adjusted for age, gender, ethnicity, cardiovascular risk factors and comorbidities (hypertension, diabetes mellitus, congestive heart failure, ischemic heart disease, peripheral vascular disease, stroke or TIA, malignancy, chronic obstructive pulmonary disease), and selected medications use (anticoagulants, antiplatelet, statins, beta-blockers, ACE-inh & ARBs).
Model II: adjusted for socioeconomic status, smoking status, renal function, LDL and HDL cholesterol levels in addition to covariates in Model I.

* The first and the last RDW tests performed during the year before the study entry were each classified into two categories (normal if RDW ≤ 14.5% and elevated if RDW > 14.5%). Each group is labeled by the first and second RDW test category. For example, the group with normal RDW at the first test and elevated RDW at the second test is labeled as "normal-elevated".

** Mean with standard deviation of the difference between the last and first RDW tests.

normal RDW (normal-normal), the adjusted HR for all-cause mortality was 1.35 (1.25–1.45), 1.49 (1.40–1.59), and 1.73 (1.65–1.82) for subjects in elevated-normal, normal-elevated, and persistently elevated (elevated-elevated) RDW categories, respectively (Model I, Table 5). The results were similar after further adjustments for smoking, socioeconomic status, renal function, and LDL and HDL levels (Model II, Table 5).

4. Discussion

This study shows that the risk of all-cause mortality in patients with atrial fibrillation is directly associated with RDW in a dose-response manner. This association was independent of known risk factors of mortality. Notably, RDW is associated with all-cause mortality regardless of anemia status. In addition, this study shows that the dynamic changes in RDW are strongly associated with the risk of all-cause mortality; in patients with elevated RDW, the risk of mortality decreased when RDW declined to normal levels, and in patients with normal RDW, the risk of mortality increased with RDW elevation. Changes in RDW over time were also found to be associated with all-cause mortality in patients with CHF [15].

RDW is well known as a marker associated with increased risk of mortality in multiple cardiovascular settings [2–8]. RDW was also found to be associated with increased mortality and poor clinical outcome in patients with stroke, regardless of atrial fibrillation [16,17]. Furthermore, we recently demonstrated that RDW is an independent risk factor for stroke in patients with atrial fibrillation [11]. Hence, it may be suggested that the increased risk of mortality associated with RDW in patients with atrial fibrillation may be attributed to stroke mortality. Unfortunately, we did not have data related to cause of death; therefore, we were not able to confirm this hypothesis or to assess the relationship of RDW with specific causes of mortality.

Few previous small studies have assessed the association between RDW and all-cause mortality in patients with atrial fibrillation, and these studies have presented conflicting results [18,19]. Wan et al. studied 300 patients with atrial fibrillation and showed that RDW was independently associated with all-cause mortality and major adverse events [18]. Lee et al. studied 567 patients with paroxysmal atrial fibrillation and showed that RDW was significantly associated with composite clinical outcomes of death, hospitalization due to heart failure, and new-onset stroke; however, RDW was not associated with mortality when death was considered as a single outcome [19]. Compared to previous studies, our work more accurately represents everyday real-life scenarios of patients with atrial fibrillation, as it includes a large number of patients from a population-based database. Furthermore, this study was able to examine the association of change in RDW over time and mortality.

The exact biological mechanisms underlying the association of RDW and mortality in patients with atrial fibrillation cannot be gleaned by this cohort study. Furthermore, this cohort study is observational in nature and residual confounding may still exist. Hence, whether RDW has a causal effect in leading to mortality or is simply a marker of other comorbidities or biological mechanisms cannot be proven from this study. In this regard, a potential role may be played by systemic factors that alter erythrocyte hemostasis leading to anisocytosis, such as inflammation and oxidative stress [20,21]. Both decreased serum antioxidant levels (selenium, carotenoids, and vitamin E), and increased inflammatory biomarkers (IL-6, CRP, soluble TNF receptor I and II) were correlated with increased RDW [22–25]. Although this explanation seems to be plausible, adjustment for CRP and antioxidant levels did not meaningfully attenuate the association between RDW and mortality [25,26].

Our study has other limitations, one of which is that it relies on a computerized database not specifically designed for the present study. In addition, we did not have data on the type of atrial fibrillation (paroxysmal, persistent or permanent). In this study, we included patients who performed a complete blood count test during the year prior to study entry. Hence, one may argue that our study is affected by selection bias because patients with more severe disease tend to perform more tests. However, of the 77,297 patients with atrial fibrillation, 69,412 (~90%) performed the RDW test and were included in the study. Additionally, we did not have data on iron store status and other nutritional deficiencies that may have caused anemia and affected RDW. However, our study shows that RDW is associated with increased risk of all-cause mortality regardless of anemia status.

5. Conclusion

RDW and change in RDW over time are associated with mortality in patients with atrial fibrillation. Accounting for this widely available inexpensive test may be valuable for the prediction of mortality in patients with atrial fibrillation. Future studies are needed to confirm our findings and to elucidate the underlying mechanism of this association.

Conflicts of interest

The authors report no competing interests.

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