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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).

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