Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(2): 051
http://doi.org/10.31083/j.rcm2302051

Original Research

Elevated red cell distribution width and cardiovascular mortality in ASCVD risk cohorts: National Health and Nutrition Examination Survey (NHANES III)

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Academic Editors: Ichiro Wakabayashi and Klaus Groschner
Submitted: 21 July 2021 Revised: 19 August 2021 Accepted: 6 September 2021 Published: 9 February 2022

Abstract

Background: Although red cell distribution width (RDW) is associated with increased cardiovascular mortality, the relationship between an elevated RDW and cardiovascular mortality among various ASCVD risk groups is unknown. **Methods**: We utilized the National Health and Nutrition Examination Survey (NHANES) III, which uses a complex, multistage, clustered design to represent the civilian, community-based US population. Out of 30,818 subjects whose data were entered during the 1988–1994 period, 8884 subjects over 40 years of age, representing a weighted sample of 85,323,902 patients, were selected after excluding missing variables. The ACC/AHA pooled cohort equation (PCE) was used to calculate atherosclerotic cardiovascular disease (ASCVD) risk, and low (<7.5%), intermediate (7.5–20%), and high (>20%) risk groups were created. The primary endpoint was cardiovascular mortality. A multivariate proportional hazard regression was performed using the Fine and Gray (sub-distribution) method. Red cell distribution (RDW), C-reactive protein (CRP), age, sex, race, diabetes, smoking status, high-density lipoprotein (HDL), and chronic kidney disease (CKD) were used as covariates in each of the ACC/AHA pooled cohort risk groups. **Results**: The adjusted hazard ratios for RDW >14 (Normal range 12.5–14.5 %) as compared to <13 were 2.79 (95% confidence intervals (95% CI) 2.77–2.81, $p < 0.01$), 2.02 (95% CI 2.01–2.02, $p < 0.01$), 1.18 (95% CI 1.18–1.18, $p < 0.01$) in the low, intermediate and high-risk groups respectively. The 20-year cumulative cardiovascular mortality (RDW >14 vs. <13) was 4% vs. 1.3% low, 17.7% vs. 7.7% in intermediate and 28.1% vs. 24.6% in high ASCVD risk groups respectively. **Conclusion**: Our findings support that measurement of RDW in the intermediate ASCVD group may be clinically valuable for further risk stratification and prognostication in the general population of people aged more than 40 years of age with regards to identifying those at an increased risk for cardiovascular mortality.

Keywords: Red cell distribution width; Atherosclerotic cardiovascular disease (ASCVD); Cardiovascular prognosis; Cardiovascular mortality

1. Introduction

Red cell distribution width (RDW), a marker of red cell size variation, was described as a prognostic marker in heart failure patients using the data from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program and the Duke Databank approximately one decade ago [1]. Additionally, prior observational studies have shown that increased RDW is associated with all-cause, cardiovascular mortality [2], post-procedure outcomes [3,4] and atrial fibrillation [5–8]. Inflammation and oxidative stress are proposed mechanisms that are known to be associated with both abnormally increased RDW and increased cardiovascular disease risk [9,10].

The 2019 American College of Cardiology/American Heart Association (ACC/AHA) prevention guidelines recommend using ACC/AHA pooled cohort equation to determine atherosclerotic cardiovascular disease risk (ASCVD) and guide management [11]. The widely used ACC/AHA pooled cohort equation uses traditional cardiovascular risk factors including age, sex, smoking status, diabetes mellitus (DM), hypertension (HTN), and serum cholesterol values to determine cardiovascular (CV) disease risk. Evidence from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial [12], the Canakinumab Antiinflammatory Thrombosis Outcome Study(CANTOS) trial [13] and the Colchicine Cardiovascular Outcomes Trial (COLCOT) [14] support the role of inflammation in CV disease pathogenesis in addition to traditional risk factors as described above. High-sensitivity C-reactive protein (hs-CRP) level ≥2 mg/L is included as an atherosclerotic cardiovascular disease risk

enhancer in the current prevention guidelines [11]. However, hs-CRP is not routinely performed in the primary care setting [15]. On the other hand, RDW, which is known to be increased with inflammation (as is hs-CRP), is widely available since it is included in the results each time a complete blood count is ordered. In a large multiethnic community-based population representing the United States general population [16], we aimed to study the utility of RDW to stratify the risk of cardiovascular mortality in ASCVD risk categories of Low (<7.5% 10-year CVD outcomes), Intermediate (7.5–20% 10-year CVD outcomes) and High-ASCVD risk cohorts (≥20% 10-year CVD outcomes).

2. Methods

2.1 Study population

The National Health and Nutrition Examination Survey (NHANES) III is a survey designed by the National Center of Health Statistics (NCHS) conducted between 1988–1994 using a complex, multistage, clustered design to represent the civilian, community-based United States population [17]. More information on survey methods is available at https://wwwn.cdc.gov/nchs/nhanes/nhanes3/default.aspx. In brief, a comprehensive home interview was conducted using predesigned questionnaires, followed by physical examination and collection of blood samples at the mobile examination centers by trained professionals. In total, data for 30,818 were available in the original sample that included all subjects ages two months and above. For the present analysis, subjects with age less than 40 years (n = 20,637) were excluded, and those with missing pooled cohort equation variables, RDW, CRP, and mortality data (n = 1297) were excluded. In addition, we excluded patients younger than 40 years as these patients were not included in the derivation and validation of the AHA/ACC pooled cohort equation [18]. A final sample of 8884 was analyzed in this study. Analytical guidelines published by NCHS were followed, and appropriate sample weights were used in the final analysis. The final weighted sample analyzed represented 85,323,902 subjects. NHANES III data was used for follow-up.

2.2 Variables

Age, race, and sex were self-reported and included in the household screening questionnaire of the NHANES III survey. DM was defined as serum hemoglobin A1c ≥6.5% or answering yes to "Have you ever been told by a doctor that you have diabetes or sugar diabetes?" on the questionnaire. Total cholesterol, HDL cholesterol, systolic blood pressure were also recorded. Smoking status was defined as active smoking at the time of the questionnaire for subjects who have smoked at least 100 cigarettes in their lifetime. RDW was measured using the Coulter Counter Model S-PLUS JR (Normal range: 12.5–14.5%). The range for RDW used in clinical practice is variable. In our study cohort, the median, 75th percentile, 85th percentile and 95th percentile values for RDW were 12.95%, 13.55%, 14% and 15.15% respectively. We divided RDW into three groups, <13%, 13–14% and >14%. This division would ensure that RDW is divided into groups around the median first (less than 13%) and then we chose a cutoff of 85th percentile for RDW to assess if a progressive increase in RDW is associated with progressively increased mortality. We did not use a single cutoff value for this reason. No specific cutoff's for RDW are widely accepted, and 85th percentile has been used to define other parameters such as body mass index [19]. CRP was measured using latex enhanced nephelometry, while hs-CRP values were not available. CRP values were divided into <2 mg/dL and ≥2 mg/dL. Glomerular filtration rate (GFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation instead of the Modification of Diet in Renal Disease (MDRD) equation due to better chronic kidney disease (CKD) predication [20]. ASCVD 10-year risk was estimated using the ACC/AHA pooled cohort equations. Three risk groups were made based on the ASCVD Risk score: low (<7.5%), intermediate (7.5–20%), and high risk (>20%). The cutoffs for ASCVD were chosen based on 2019 ACC/AHA prevention guidelines [11].

2.3 Outcomes

The primary endpoint was cardiovascular mortality. NCHS obtained mortality data of NHANES III subjects through multiple sources, including the national death index, centers for Medicaid and Medicare, United States renal data system, and social security administration data. Cause of death was extracted from death certificates, and all underlying causes of death were converted into ICD-10 codes. ICD-10 codes (I00-I09, I11, I13, I20-I51) were used for cardiovascular mortality. This mortality data was available in the NCHS data linkage file. Follow-up data were available until December 31, 2015. The analytic guidelines published by NCHS were used for data linkage and analysis [21].

2.4 Statistical analyses

Baseline characteristics of the study population were described using means ± SD or median [25th–75th percentiles] for continuous variables and were compared with the Kruskal-Wallis test [22]. Percentages were used to describe categorical variables, and comparisons were performed using the chi-square test. Prospective analysis was performed on the weighted sample with three proportional hazard models with the Fine and Gray (sub-distribution hazards) method for competing risk analysis, whereby other causes of mortality were considered as competing events [23]. Competing risks model was chosen as it provided more accurate estimates for the incidence of cardiovascular mortality by taking other causes of mortality into account [24].

Table 1. Baseline characteristics.

		Risk groups based on 10-year ASCVD risk			*p*-value
		<7.5 (51.3%)	**7.5–20% (25.5%)**	**>20% (23.20%)**	
Age (yrs)	Median [IQR]	47.33 [43.08–53.67]	61.50 [55–67.08]	74 [68.33–79.42]	<0.001
Sex	Female n (%)	27652603 (63.23%)	8798623 (40.38%)	8786393 (44.37%)	<0.001
Race	White n (%)	38362982 (87.72%)	18821174 (86.38%)	17458398 (88.16%)	<0.001
	Black n (%)	3589330 (8.20%)	2436824 (11.18%)	1919149 (9.69%)	
	Others n (%)	1780880 (4.07%)	530001 (2.44%)	425164 (2.15%)	
Diabetes n (%)		1430517 (3.27%)	2624252 (12.04%)	5829079 (29.44%)	<0.001
Hemoglobin g/dL	Mean ± SD	13.92 ± 1.34	14.41 ± 1.32	14.11 ± 1.45	<0.001
RDW	Mean ± SD	12.96 ± 0.99	13.16 ± 0.99	13.42 ± 1.15	<0.001
Total cholesterol mg/dL	Median [IQR]	206 [183–234]	224 [199–252]	223 [194–251]	<0.001
HDL Cholesterol mg/dL	Median [IQR]	51 [43–63]	45 [37–55]	45 [36–57]	<0.001
Systolic blood pressure mmHg	Median [IQR]	119 [111–128]	132 [121–143]	145 [133–158]	<0.001
Hemoglobin	<7 n (%)	13153 (0.03%)	0	902 (0.005%)	<0.001
	7.1–13 n (%)	260612 (0.59%)	72598 (0.33%)	131516 (0.66%)	
	>13 n (%)	43459426 (99.37%)	21715402 (99.67%)	19670292 (99.33%)	
CRP	≥2 n (%)	579144 (1.32%)	840706 (3.86%)	859139 (4.34%)	<0.001
Smoker n (%)		8741595 (19.98%)	7406220 (33.99%)	4158321 (21%)	<0.001
Event	Alive/censored n (%)	37473967 (85.69%)	11805312 (54.18%)	2865528 (14.47%)	<0.001
	Cardiovascular n (%)	932658 (2.13%)	2114952 (9.7%)	5022520 (25.36%)	
	Others n (%)	5326566 (12.18%)	7867735 (36.11%)	11914663 (60.17%)	
RDW	>14 n (%)	3570331 (8.16%)	2938791 (13.49%)	3973997 (20.07%)	<0.001
	13–14 n (%)	12221866 (27.94%)	7638467 (35.05%)	7487279 (37.81%)	
	<13 n (%)	27940994 (63.89%)	11210741 (51.45%)	8341435 (42.12%)	
Follow up in years	Median [IQR]	19.58 [18.17–21.17]	18.25 [13.5–20.25]	10.5 [5.833–16]	<0.001

Univariate sub-distribution hazards for cardiovascular mortality were calculated in each of the ASCVD risk groups for age, blood pressure, HDL, total cholesterol, BMI, vitamin B12, serum iron as continuous variables, and DM, smoking status, sex, CKD stage, serum CRP and race as categorical variables. Variables with a significant cardiovascular mortality subdistribution hazard in at least one of the ASCVD risk groups were age, diabetes, smoker, HDL, sex, serum CRP, CKD stage, and race. All these variables were included in the final multivariate model. The cumulative incidence function (CIF) provides incidences in the presence of competing events [24]. Cumulative incidence function and estimates were calculated in all the ASCVD risk groups for cardiovascular mortality. Further, CIF was plotted. All analyses were completed in SAS version 9 (Cary, NC), and all plots were obtained using R version 3.6.1.

3. Results

The total NHANES weighted sample of 85,323,902 subjects was analyzed. These subjects were divided into three groups based on the ASCVD 10-year risk. The low-risk group (<7.5%) contained 51.3% of the subjects, the intermediate (7.5–20%) risk group contained 25.5% of the subjects, while the high (>20%) risk group had 23.2% of the individuals. Baseline characteristics are described in Table 1. The median age was 47.33, 61.05, and 74 years ($p < 0.001$) among the low, intermediate, and high ASCVD risk groups. Females represented 63.23%, 40.38%, and 44.37% ($p < 0.001$) in these groups, respectively. Cardiovascular mortality in the low-risk group was 2.13% over a median follow-up of 19.6 years, 10.5% over a median follow-up of 18.2 years in the intermediate-risk group, and 21.4% over a median follow-up of 9.7 years in the high-risk group.

In the low ASCVD risk cohort (10-year ASCVD risk cohort <7.5%), the subdistribution hazard ratio (HR) for cardiovascular mortality was 3.05 (95% CI: 3.03–3.07, $p < 0.001$) for the highest RDW group (RDW >14) compared to the lowest (RDW <13) in the unadjusted model. In the fully adjusted model, the HR was 2.79 (95% CI: 2.77–2.81, $p < 0.001$), while the adjusted HR for RDW (13–14 vs. <13) was 2.38 (95% CI: 2.37–2.39, $p < 0.001$) (Table 2). The cumulative incidence for cardiovascular mortality at 10 years increased from 0.4% in the low RDW (RDW <13) to 1.2% and 1.3% in the intermediate (RDW 13–14) and the high (RDW >14), respectively. For 20-year cardiovascular mortality, the rates were 1.3%, 3.6%, and 4% in the low, intermediate, and high-risk groups, respectively (log-rank $p < 0.01$) (Table 3 and Fig. 1A).

Table 2. Proportional hazard regression with competing risk analysis using fine and gray subdistribution hazard model for cardiovascular mortality.

Parameter	ASCVD risk <7.5		ASCVD risk 7.5–20		ASCVD risk >20	
	Hazard Ratio (95% Hazard Ratio Confidence Limits)	Pr > ChiSq	Hazard Ratio (95% Hazard Ratio Confidence Limits)	Pr > ChiSq	Hazard Ratio (95% Hazard Ratio Confidence Limits)	Pr > ChiSq
Univariable analysis						
RDW >14	3.048 (3.029–3.067)	<0.0001	2.417 (2.409–2.426)	<0.0001	1.166 (1.164–1.169)	<0.0001
RDW 13–14	2.740 (2.728–2.752)	<0.0001	1.258 (1.254–1.262)	<0.0001	1.029 (1.027–1.031)	<0.0001
Multivariable analysis[#$@]						
RDW >14	2.794 (2.775–2.812)	<0.0001	2.016 (2.008–2.024)	<0.0001	1.180 (1.177–1.183)	<0.0001
RDW 13–14	2.381 (2.370–2.392)	<0.0001	1.152 (1.149–1.156)	<0.0001	1.043 (1.041–1.045)	<0.0001
CRP ≥2 mg/dL	0.181 (0.175–0.187)	<0.0001	1.399 (1.390–1.407)	<0.0001	1.124 (1.119–1.129)	<0.0001
CKD5	0.000 (0.000–0.000)	<0.0001	0.725 (0.713–0.736)	<0.0001	0.138 (0.135–0.141)	<0.0001
CKD4	0.000 (0.000–0.000)	<0.0001	2.019 (1.992–2.046)	<0.0001	0.827 (0.819–0.835)	<0.0001
CKD3	1.486 (1.473–1.498)	<0.0001	0.815 (0.810–0.820)	<0.0001	0.715 (0.709–0.720)	<0.0001
CKD2	1.109 (1.101–1.117)	<0.0001	0.656 (0.652–0.660)	<0.0001	0.652 (0.647–0.657)	<0.0001
Male	1.156 (1.149–1.162)	<0.0001	1.316 (1.312–1.320)	<0.0001	1.346 (1.344–1.349)	<0.0001
Non-diabetic	0.168 (0.167–0.169)	<0.0001	0.514 (0.512–0.516)	<0.0001	0.898 (0.896–0.900)	<0.0001
Non-smoker	0.246 (0.245–0.247)	<0.0001	0.578 (0.576–0.580)	<0.0001	1.582 (1.578–1.587)	<0.0001
White	0.164 (0.163–0.165)	<0.0001	17.862 (17.174–18.577)	<0.0001	1.819 (1.805–1.833)	<0.0001
Black	0.243 (0.241–0.245)	<0.0001	13.804 (13.268–14.361)	<0.0001	1.523 (1.510–1.536)	<0.0001
Age in yrs	1.095 (1.095–1.096)	<0.0001	1.075 (1.075–1.075)	<0.0001	1.019 (1.019–1.019)	<0.0001
HDL	0.995 (0.995–0.995)	<0.0001	1.002 (1.002–1.002)	<0.0001	0.999 (0.999–0.999)	<0.0001

[@]Red Cell distribution width (RDW) <13; [#]C-Reactive Protein (CRP) <2 mg/dL; [$]Chronic Kidney Disease (CKD) 1 were used to compare the groups.

Table 3. Cumulative incidence functions for cardiovascular mortality by pooled cohort equation risk group.

	Cumulative incidence function					
	Cardiovascular mortality					
	ASCVD risk <7.5%		ASCVD risk 7.5–20%		ASCVD risk >20%	
RDW	10 year	20 year	10 year	20 year	10 year	20 year
>14	1.3%	4%	7.7%	17.7%	16.8%	28.1%
13–14	1.2%	3.6%	4.1%	9.6%	15%	25.2%
<13	0.4%	1.3%	3.3%	7.7%	14.6%	24.6%

In the intermediate ASCVD risk cohort (10-year ASCVD risk cohort 7.5–20%), the subdistribution hazard ratio (HR) for cardiovascular mortality was 2.41 (95% CI: 2.41–2.42, $p < 0.001$) for the highest RDW group (RDW >14) compared to the lowest (RDW <13) in the unadjusted model. In the fully adjusted model, the HR was 2.02 (95% CI: 2.01–2.02, $p < 0.001$), while the adjusted HR for RDW (13–14 vs. <13) was 1.15 (95% CI: 1.15–1.16, $p < 0.001$) (Table 2). The cumulative incidence for cardiovascular mortality at 10 years increased from 3.3% in the low RDW group (RDW <13) to 4.1% and 7.7% in the intermediate and high RDW groups, respectively. At 20 years, cardiovascular mortality was 7.7%, 9.6%, and 17.7% in the three groups (log-rank $p < 0.01$) (Table 3 and Fig. 1B).

In the high ASCVD risk cohort (10-year ASCVD risk cohort >20%), the subdistribution hazard ratio (HR) for cardiovascular mortality was 1.67 (95% CI: 1.16–1.17, $p < 0.001$) for the highest RDW group (RDW >14) compared to the lowest (RDW <13) in the unadjusted model. In the fully adjusted model, the HR was 1.18 (95% CI: 1.18–1.18, $p < 0.001$), while the adjusted HR for RDW (13–14 vs. <13) was 1.04 (1.04–1.04; $p < 0.0001$) (Table 2). The cumulative incidence for cardiovascular mortality at 10 years increased from 14.6% in the low RDW (RDW <13) to 15% and 16.8% in the intermediate (RDW 13–14) and the high (RDW >14) RDW groups. In the three groups, cardiovascular mortality was 24.6%, 25.2%, and 28.1%, respectively (log-rank $p < 0.01$) (Table 3 and Fig. 1C).

4. Discussion

Our study shows that an RDW greater than 14 is associated with higher cardiovascular mortality in all ASCVD risk cohorts. However, it was the intermediate-risk group, where we found a remarkable difference in cardiovascular mortality for patients with RDW >14 vs. RDW <13 HR: 2.41 (95% CI: 2.41–2.42, $p < 0.001$). The cumulative incidence for cardiovascular mortality was 7.7% vs. 3.3% at 10 years and 17.7% vs. 7.7% at 20 years. Our study also showed that adults aged over 40 years with low ASCVD risk (<7.5%) and RDW < 13 had a very low risk of 20-year cardiovascular mortality (1.3%), which was significantly lower compared to RDW >14 (4%). The effect of RDW on cardiovascular mortality in various ASCVD risk groups was maintained even after adjusting for age, gender, race, renal dysfunction, diabetes, C-reactive protein, smoking, and HDL cholesterol.

The pooled cohort equation is derived from multiple historical cohorts. This equation utilizes age, sex, blood pressure, DM, smoking status, and cholesterol. It is internally validated [18]. Even after taking all the risk factors into account, an elevated RDW greater than 14 was still associated with cardiovascular mortality. The working group behind the AHA/ACC pooled equation noted that several novel markers were not included in the equation due to insufficient evidence or lack of additional benefit [18]. CRP,

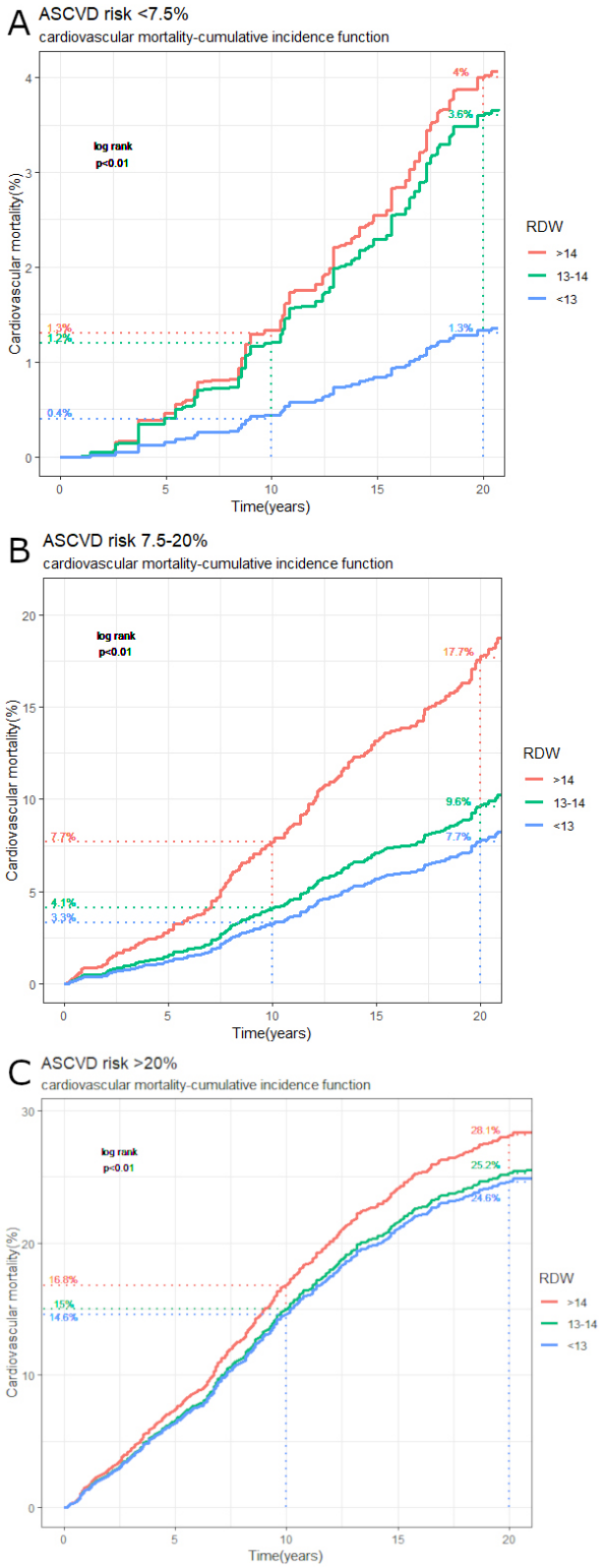

Fig. 1. Cumulative incidence function (CIF) plot with 10-year and 20-year CIF estimates for cardiovascular mortality. (A) Low-risk ASCVD cohort (10-year ASCVD risk <7.5%). (B) Intermediate risk ASCVD cohort (10-year ASCVD risk 7.5%–20%). (C) High-risk ASCVD cohort (10-year ASCVD risk >20%).

a marker of inflammation, and CKD stage were included in our model to further account for this limitation of the pooled cohort equation and to see if their addition would decrease RDW impact on the outcomes. Even with the addition of these variables to the multivariate regression model, RDW greater than 14 had a significant association with an increase in cardiovascular mortality among the various subgroups.

Compared to the NHANES 2007-10 sample, our study population contains a more significant proportion of high-risk subjects (23.2% vs. 10.2%) but has a comparable number of intermediate-risk subjects (25.5% vs. 24.6%) [18]. This difference is likely due to better risk factor management in newer NHANES samples and inclusion of adults younger than 70 years.

To our knowledge, RDW association with cardiovascular mortality has not been studied previously within the different ASCVD risk categories. However, RDW has been studied in the same dataset previously and has been shown to be associated with increased cardiovascular and all-cause mortality when tested in the NHANES sample as a whole [2]. This finding is replicated in our study (Fig. 1), but it is also expanded to the different subgroups. RDW has been shown to be associated with increased coronary artery disease risk and can increase the predictive value of the Framingham risk score [25,26]. However, these analyses did not account for competing risks posed by other causes of death and were unweighted [24]. In addition, RDW has been shown to be associated with poor cardiovascular fitness, increased mortality in peripheral arterial disease patients, and macrovascular complications in diabetes, and all of those are known to be associated with increased cardiovascular mortality [18,27–31]. With the increasing use of PCE in clinical practice to estimate cardiovascular risk, the additional utility of using RDW to estimate the risk for cardiovascular mortality in patients where PCE can be used was unknown. The results of our study add to the increasing evidence of the prognostic importance of RDW as a marker of inflammation and oxidative stress in cardiovascular disease and specifically to cardiovascular mortality and therefore may help identify individuals at high cardiovascular mortality risk within the PCE calculated ASCVD subgroups.

Cardiovascular risk reduction strategies in subjects with high cardiovascular disease risk are clear and involve risk factor optimization and management of chronic conditions, including lipid lowering with statins prescriptions [11]. However, in the intermediate-risk group, statin initiation is usually a shared decision since benefits are unclear [32]. It is essential to identify patients at higher risk of having major adverse cardiovascular outcomes among this intermediate-risk population [11]. Concerning that, the most striking finding of our analysis probably was our results for the intermediate-risk group, which represented 25.5% of the study population. The cardiovascular mortality was significantly higher when RDW $>$14 was compared to $<$13, with cardiovascular mortality being 7.7% vs. 3.3% at 10 years and 17.7% vs. 7.7% at 20 years, respectively. The increased mortality in this group can be potentially explained by the fact that higher RDW as an indicator of the inflammatory burden and oxidative stress may act as a prodromal finding for the development of coronary artery disease, atrial fibrillation, PAD, stroke or heart failure, as it is known that an increase in oxidative/inflammatory states may lead to worsening LV function and decrease in LV function may further worsen oxidative/inflammatory stress [33].

Current guidelines recommend evaluating for risk-enhancing factors when the 10-year ASCVD risk calculated by pooled cohort equations is 7.5–20%, which should be followed by shared decision-making about risk and the benefits of starting statins [11]. Currently, red cell distribution is not included in the list of risk-enhancing factors.

Given the increasing evidence regarding the role of the red cell distribution width in cardiovascular disease [34] and our results, we think that future studies should try to examine whether they can confirm our findings regarding RDW utility in prognostication and risk stratification for cardiovascular mortality and if therapies such as the use of statin medications significantly decrease risk in those patients with elevated RDW values which are believed to be related to inflammatory/oxidative stress.

NHANES survey follows a complex multistage design to represent the non-institutionalized population of the United States. Therefore, we believe that our results have high generalizability and may have potential clinical value.

5. Limitations

Our study has a number of limitations. First, we looked only at cardiovascular mortality and not other outcomes. Second, subjects may have developed various additional cardiovascular risk factors during the follow-up period, which may have influenced the mortality rates. Third, CRP values were not high sensitivity CRP values which makes them suboptimal. Fourth, single RDW values were taken since serial measurements were not available. Fifth, LDL cholesterol values were not available for a large number of patients in the study population and could not be included in the analysis. Finally, socioeconomic status and ethnicity have not been adjusted for in the current analysis.

6. Conclusions

Our study demonstrated that an increase in RDW greater than 14 was associated with significantly increased cardiovascular mortality in all ASCVD risk groups using the NHANES III database between 1988–1994, especially in the low and the intermediate-ASCVD risk cohort where RDW had the highest impact. Therefore, RDW may be a potential risk enhancer, similar to hs-CRP and in lieu of hs-CRP, especially for the intermediate-ASCVD risk population of people in the United States. An elevated RDW

believed to be related to inflammatory and oxidative stress factors may become clinically helpful to further risk stratify individuals for cardiovascular mortality in conjunction with the use of the ASCVD risk assessment. Further validation of our study results is required.

Author contributions

AK, RTF—Conceptualization; AK, DGK, JM, RTF—Methodology; AK, DGK—Statistical analysis; AK, DKG—Investigation; AK, DGK, GG, JM, RTF, GS—Writing original draft and revision; AK—Visualization; RTF—Supervision.

Ethics approval and consent to participate

Appropriate consent was taken from all subjects by NHANES III surveyors. Institutional Review Board of the Centers for Disease Control and Prevention approved the NHANES survey. Our study is a secondary data analysis of the initial data collected following the Declaration of Helsinki, and the protocol was approved by the NCHS Research Ethics Review Board (ERB). More information can be found at https://www.cdc.gov/nchs/nhanes/irba98.htm.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

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