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Elevated red blood cell distribution width predicts mortality in persons with known stroke

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ABSTRACT

Background: Red cell distribution width (RDW) is a hematological parameter routinely obtained as part of the complete blood count. Recently, RDW has emerged as a potential independent predictor of clinical outcome in patients with established cardiovascular disease. However, little is known about the role of RDW as a prognosticator among persons with stroke, especially with regard to an incontrovertible endpoint like mortality. We assessed the association of RDW with stroke, and its effect on mortality among persons with stroke.

Methods: Data from the National Health and Nutrition Examination Survey (NHANES) a nationally representative sample of United States adults were analyzed. The study population consisted of 480 individuals aged ≥25 years with a baseline history of stroke followed-up from survey participation (1988–1994) through mortality assessment in 2000. Proportional hazard regression (Cox) was utilized to explore the independent relationship between RDW and mortality after adjusting for potential confounders.

Results: Among the cohort, 52.4% were female, 64% aged ≥65 years. Mean RDW was significantly higher among persons with stroke compared to individuals without a stroke (13.7% vs.13.2%,$p<0.001$). Baseline RDW was higher among persons with known stroke who later died vs. remained alive (13.9% vs.13.4%, $p<0.001$). After adjusting for confounders, those with elevated RDW (fourth vs. first quartile) were more likely to have experienced a stroke (OR 1.71, CI = 1.20–2.45). Higher RDW level (fourth vs. first quartile) among those with known stroke independently predicted subsequent cardiovascular deaths (HR = 2.38 and CI = 1.41–4.01) and all-cause deaths (HR = 2.0, CI = 1.25–3.20).

Conclusions: Elevated RDW is associated with stroke occurrence and strongly predicts both cardiovascular and all-cause deaths in persons with known stroke.

1. Introduction

The red blood cell distribution width, or RDW, is a measure of the variation of red blood cell volume that is reported as part of a standard complete blood count (CBC). Higher RDW values indicate greater variation in size. Increased RDW has been associated with several medical disorders and nutritional deficiencies and recently hospital admission was shown to be a prognosticator of early outcomes following hospitalization for general medical conditions [1]. Furthermore, RDW was noted to be a strong independent predictor of morbidity and mortality in patients with prior myocardial infarction, heart failure and end stage renal disease [2–4]. Several have speculated that higher levels of RDW may reflect an underlying inflammatory state, which is associated with adverse clinical outcomes and leads to impaired erythrocyte maturation.

We are unaware of any studies that have looked at the prognostic value of RDW among stroke patients. Since RDW is widely available to clinicians as part of the complete blood count and therefore incurs no additional costs, (in contrast to other novel markers of cardiovascular risk) if found to be an independent prognosticator of stroke outcomes, this might be of immense clinical relevance. In this study we aimed to assess the association of stroke with RDW and the ability of baseline RDW to predict cardiovascular and all-cause mortality among individuals with a known history of stroke.

2. Methods

2.1. Subjects and methods

This study utilized data from a nationally representative sample of the civilian, non-institutionalized US population. This data was

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collected by the Centers for Disease Control and Prevention's third National Health and Nutrition Examination Surveys [NHANES III] conducted at 89 survey locations between January 1, 1988, and December 31 1994. This survey utilized a complex multistage cluster design and over-sampled persons 60 years and older, non-Hispanic black individuals, and Mexican American individuals to enhance the precision of prevalence estimates in these groups. [5–11] In-person interviews were conducted in sampled households, and all subjects were invited to participate in medical examinations conducted at a nearby NHANES III mobile examination center. Interviews collected demographic, socioeconomic, dietary, as well as health-related questions, and the mobile examination component consisted of medical and dental examinations, physiological measurements, and laboratory tests. The prevalence of common chronic conditions and associated risk factors was also determined during this survey. Details of the survey design and examination procedures have been previously published [12,13].

The primary study outcomes, cardiovascular and all-cause mortality were recorded from the NHANES III mortality follow-up data. These mortality follow-up data relied on a probabilistic match between NHANES III and National Death Index [National Center for Health Statistics (NCHS) 2006] death certificate records available for a total of 18,149 participants of the total of 30,818 individuals (59%) completing the initial interviews and physical examination and laboratory assessment at a mobile examination center and included only adult participants (those 17 years and older) [14]. Mortality assessments were conducted from the baseline interview in 1988–1994 through the end of the follow-up period in December 31, 2000. These mortality data included cause specific mortality and mortality dates. Cause specific mortality was coded using the International Classification of Diseases Ninth Revision (ICD-9) Clinical Modification for deaths occurring between 1988 and 1998 and the International Classification of Diseases Tenth Revision for deaths occurring between 1999 and 2000 [14]. Cardiovascular deaths included deaths from heart disease, cerebrovascular disease, atherosclerosis, and hypertension. We selected the total sample of individuals self-reporting a physician diagnosis of a stroke(n=559). Of these we excluded participants who were pregnant (0.001%) and were aged less than 25 years of age (13.4%) to get a total sample size of 480 participants self-reporting a history of stroke.

2.2. Study variables

2.2.1. Primary predictor variable

Red cell distribution of width (%) was measured using the using the Coulter analyzer, [12] (normal range11.5%–14.5%), and investigated as a continuous and categorical variable in quartile (Q1=0–12.75%, Q2=>12.75%–13.30%, Q3=>13.30%–13.90%, Q4=>13.9%).

2.2.2. Primary outcome variable

The primary study outcome variables were cardiovascular and all-cause mortality recorded from the NHANES III mortality follow-up data for baseline surveys conducted between 1988–1994 and followed-up through December 31, 2000. These variables were utilized as dichotomized categorical variables (deceased vs. alive). Secondary study outcome was prevalence of stroke (yes vs. no).

2.2.3. Covariates

Covariates included known cardiovascular, hematological, lifestyle and socio-demographic variables demonstrated to be associated with stroke incidence and mortality [15–23]. Hypertension status was established by triangulating variables recording a) history of physician diagnosis b) hypertension medication taking history and c) examination blood pressure (BP) levels (systolic pressure of greater than or 140 mm Hg or diastolic pressure of 90 mm Hg or greater. The best three of four blood pressure readings were averaged for the examination blood pressure (BP) levels measure. These readings were collected using a mercury sphygmomanometer were recorded by certified technicians using standardized procedures [17].

To determine the presence of Diabetes mellitus, participants who reported either a) self report of physician diagnosis of diabetes and b) fasting blood glucose levels of greater than 125 mg/dL were recorded as having diabetes or no diabetes. Myocardial Infarction and congestive heart failure were recorded using patient self-report of a physician diagnosis. Dyslipidemia was defined as self-reported physician diagnosis of high cholesterol, total serum cholesterol ≥240 mg/dL, serum triglycerides>200 mg/dL, Low-density Lipoprotein-C ≥160 mg/dL, or High-Density Lipoprotein-C<40 mg/dL. White blood cell count and Hematocrit levels (%) were also assessed to adjust for indices of infection and to see if RDW had an effect beyond the often-checked hematocrit level.

Smoking status utilized three categories: non-smokers, ex-smokers and current smokers. Body mass index (BMI) was calculated from height and weight (kg/m^2) measured using standardized examination protocols and measurements of height and weight. Demographic characteristics of participants including age, gender, race-ethnicity and poverty income ration were also recorded. We included the duration since stroke occurrence, to control for any temporal influences of time of stroke on the outcome mortality event.

2.3. Statistical analysis

Sample weighted descriptive analyses of all the variables to be utilized in the analysis were conducted. Weighted estimates were applied to the descriptive prevalence analysis using NHANES mobile examination center-examined sample weight values. These weights adjust for the differential probabilities of selection and no-response in the survey sample and also post-stratified to the 1990 U.S. Census total population estimates. Next, using one-way Analysis of variance (ANOVA) techniques, the mean distribution of RDW was explored for the outcome variable and all covariates. Univariate regression analysis techniques were utilized to examine the association between the mortality for each of the predictors separately. The time to event was considered the time from the baseline RDW measurement to the time of death for participants. To account for the effect of the NHANES clustering design on the Cox hazard model the Primary Sampling Unit (PSU) variable was included as a stratification variable. Tests were conducted to rule out collinearity prior to running the final multivariable regression analysis model including all the covariates noted above. All data analyses were conducted using SAS (version 8.0; SAS Institute Inc, Cary, NC) and SPSS (version 15.0). Statistical hypotheses were tested using<0.05 as the level of statistical significance.

3. Results

3.1. Sample characteristics

The socio-demographic and clinical characteristics of the study sample can be found in Table 1. Among the sample of individuals with a known stroke, 52.4% were female and persons aged 65 years or older accounted for 64.0% of the sample. Mean duration since stroke occurrence among those with a stroke was 8.1 years. The analysis of mean RDW demonstrated higher mean RDW values among individuals with a stroke compared to individuals without a stroke (13.69% vs.13.24%, p<0.001).

3.2. RDW and stroke prevalence

Bivariate analysis demonstrated a graded increase in stroke prevalence from the first to fourth quartile for RDW. Specifically individuals at the fourth quartile for RDW had a statistically significant