Letter to the Editor

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Red blood cell distribution width is significantly associated with aging and gender

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To the Editor,

The red blood cell distribution width (RDW) is an easy and inexpensive laboratory parameter, which reflects the burden of anysocytosis by means of a simple equation where the standard deviation (SD) of erythrocyte volume is divided by the mean corpuscular volume (MCV). The final results are multiplied by 100 to express them as a percentage [1]. Several lines of evidence now attest that an increased RDW value – typically above 14.6% – should be regarded as an important biomarker of morbidity and mortality in the general population [2], as well as in selected categories of patients with either acute [3] or chronic disorders [4]. This correlation is particularly evident in patients with ischemic and thrombotic conditions [5, 6], and is substantially independent from the hemoglobin level.

The leading causes of an increased RDW include iron deficiency anemia, megaloblastic anemia, immune hemolytic anemia, myelodysplastic syndrome, liver disease and sickle cell disease, among others [1]. As regards to additional physiological determinants, the impact of aging seems less clear. Although the current reference range of RDW is univocal and virtually independent from patients' age, in a recent article Qiao et al. calculated age- and sex-related reference intervals for the complete blood count [7], and showed a consistent trend towards increased RDW from the lowest (18–29 years) to the highest (>70 years) age groups.

As such, in order to establish whether age may be a significant determinant of RDW, we carried out a retrospective analysis in the database of the laboratory information system of the Verona University Hospital to retrieve results of hematological testing performed on a cohort of ostensibly healthy, current and former blood donors aged >20 years, and referred to the local transfusion service for routine check-up over a 1-year period (from January to December 2013). Routine hematological testing was performed on the entire study population using identical laboratory instrumentation (Sysmex XE-2100, Sysmex Inc, Mundelein, IL, USA). The quality of data was validated throughout the study period by regular internal quality control (IQC) procedures and participation to External Quality Assessment Scheme (EQAS). Correlation between variables was assessed by Pearson's correlation coefficient (r) and multiple linear regression, where RDW was included as the dependent variable and age, gender, hemoglobin, MCV and mean corpuscular hemoglobin (MCH) as independent variables. The significance of differences between age groups was assessed by one-way analysis of variance (ANOVA) and Pearson's χ^2-test. Statistical analysis was performed using Analyse-it (Analyse-it Software Ltd, Leeds, UK). Data were finally reported as median and interquartile range (IQR).

Cumulative results could be retrieved for 1907 blood donors (562 females and 1345 males). The value of RDW consistently increased across different age groups ($p<0.001$ for trend) (Figure 1). Interestingly the median RDW value was approximately 11% higher in subjects aged 60 years or older than in those aged <60 years (14.6% vs. 13.2%; $p<0.001$), and nearly 20% higher in the highest age group (>90 years; RDW 15.7%) compared to the lowest (<41 years; RDW 13.1%; $p<0.001$). The percentage of subjects with RDW value above the conventional upper limit of the reference range (i.e., 14.6%) increased from 6% in patients aged <41 years, to 8%

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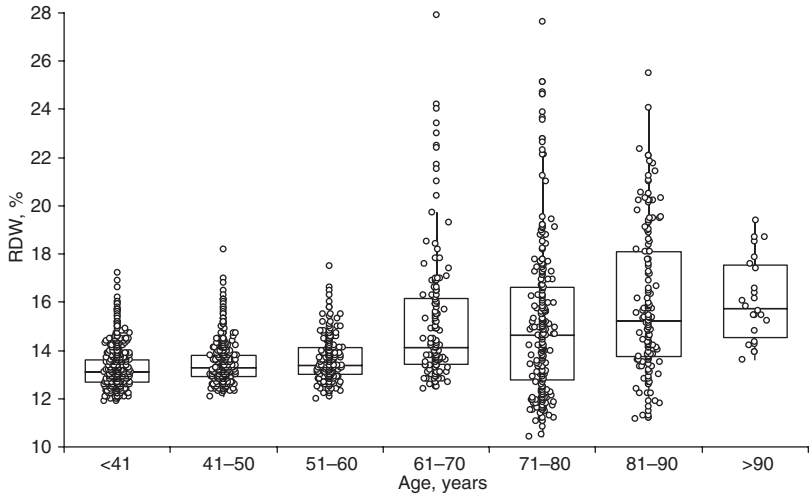

Figure 1 Median value (and interquartile range) of red blood cell distribution width (RDW) in a cohort of ostensibly healthy blood donors (n=707).

in those aged 41–50 years, to 13% in those aged 51–60 years, to 41% in those aged 61–70 years, to 50% in those aged 71–80 years, to 59% in those aged 81–90 years, up to 75% in those aged more than 90 years (Pearson's χ^2-test statistic 473.2; DF 7; p<0.001 for trend). The median RDW value was also found to be slightly but significantly higher in females (13.8%; IQR 13.1%–15.0%) than in males (13.3%; IQR 12.9%–14.1%; p=0.001). In univariate regression analysis, RDW values were found to be significantly associated with age (r=0.44; 95% CI 0.40–0.47; p<0.001) (Figure 2). In multiple regression analysis, the RDW remained significantly associated with increasing age (β coefficient, 0.58; 95% CI 0.17–0.99; p=0.005) and female gender (β coefficient, 9.2; 95% CI 7.7–10.8; p<0.001), even after adjustment for hemoglobin, MCV and MCH values.

The results of this retrospective investigation based on a population of ostensibly healthy subjects confirm that RDW is strongly dependent upon age and gender, and this finding carries at least two meaningful clinical implications. First, cross-sectional and perspective studies aimed to establish whether this parameter is a

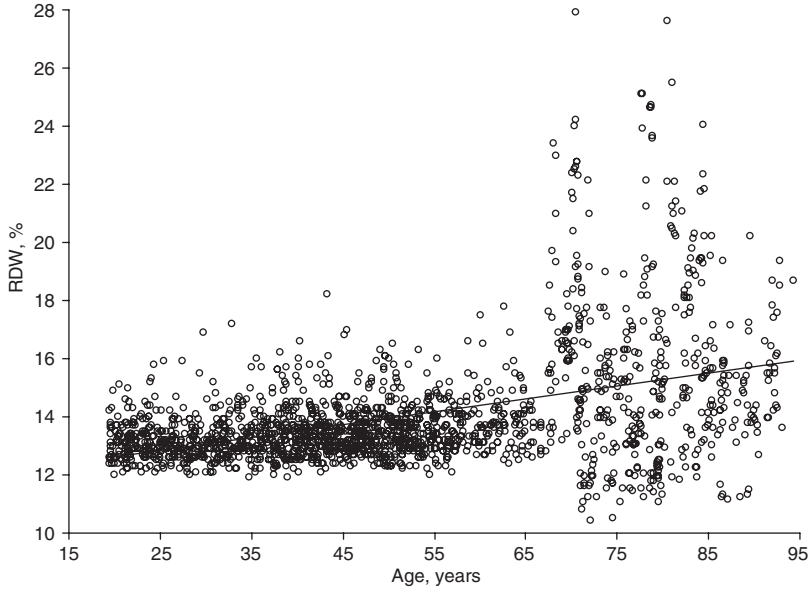

Figure 2 Pearson's correlation (r=0.44; 95% CI 0.40–0.47; p<0.001) between red blood cell distribution width (RDW) and age in a cohort of ostensibly healthy blood donors (n=707).

risk factor for disease vulnerability and overall mortality should always entail data adjustment for age and sex, so that flawed or biased associations can be prevented. However, a strong, graded increase of inflammatory biomarkers has been described by comparing the fourth vs. the first quartiles of RDW in a large cohort of unselected adult outpatients [8]. Since the concentration of inflammatory biomarkers also increases during physiological aging along with the prevalence of folate and vitamin B deficiencies, even at a subclinical level [9], the observation of increased RDW in the elderly is hence not really unpredictable. Accordingly, the progressive increase of anysocytosis in the aged population may be regarded as a risk factor rather than a simple biomarker of both frailty and greater burden of disease in the elderly. In support of this hypothesis, it was shown that larger variation of red blood cell volume is strictly associated with decreased erythrocyte deformability, which in turn impairs blood flow through microcirculation [10]. The following hypoxia may hence help explain the well-established increased risk of thrombotic disorders and mortality associated with elevated RDW [1].

Conflict of interest statement

Authors' conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article.
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