Original Article

Associations of Increased Red Cell Distribution Width Levels with the Severity of Carotid Artery Stenosis: Cross-sectional Study Results

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Abstract

Background: Red blood cell distribution width (RDW) is being actively studied as a biomarker in various cardiovascular diseases (CVDs). The aim of this study was to conduct a comparative analysis of RDW in patients with carotid atherosclerosis, comparing it with an assessment of the severity of carotid artery stenosis (CAS). **Methods:** The Duplex registry database was used to conduct this retrospective cross-sectional study. The study participants underwent a complete blood count test, analysis for lipid profile, and carotid ultrasound. The patients were divided into 5 groups depending on CAS degree: none; 20%–49%; 50%–69%; 70%–99%; and occlusion. **Results:** Data from 2548 patients were included in the final analysis (mean age: 57.9 ± 12.3 years; 51% males [n = 1301]). The analysis confirmed the relationship between the increase in the RDW index and CAS gradation increase in men (Kr-W H = 16.43; P = 0.0009), but was not confirmed in women (Kr-W H = 4.32; P = 0.22). Significantly higher levels of high-density lipoprotein cholesterol and platelets and lower levels of red blood cell and white blood cells were registered in female patients without CAS and with CAS < 50% compared with men (P < 0.001). **Conclusion:** The results of the present study showed that RDW is an indicator whose increase is associated with an increase in the degree of carotid atherosclerosis in men, but not in women. This allows to discuss the role of the RDW index as a possible new laboratory biomarker of inflammation and progression of atherosclerosis, which can make an additional contribution to the formation of increased morbidity and mortality in men from atherosclerotic CVD.

Keywords: Gender differences, red cell distribution width, severity of carotid artery stenosis

Introduction

Simple and accessible laboratory markers can be used to diagnose and assess the severity of various diseases. It has been shown that an increase in red blood cell distribution width (RDW) is associated with development, more severe course, and worse prognosis in patients with cardiovascular diseases (CVD), such as acute coronary syndrome, coronary artery disease, heart failure, atrial fibrillation, and stroke.[1-5] RDW is a measure of size heterogeneity of circulating red blood cells (RBCs), which is routinely determined by an automatic analyzer in the complete blood count test. Since previous studies have demonstrated that RDW is a promising biomarker in various CVD, we decided to investigate this indicator in patients with carotid atherosclerosis, comparing it with an assessment of the severity of carotid artery stenosis (CAS).

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Analysis of publications in peer-reviewed medical journals on this issue was carried out to understand the relevance of studying this topic. PubMed database query for the combination of the search words "RDW and carotid atherosclerosis" dated January 03, 2023 provided a sample of only 18 studies conducted between 2003 and 2023. Their analysis showed that 16 of them were actually related to the study of this topic.[6-21]

The aim of this study was to conduct a comparative analysis of RDW and other standard laboratory markers in patients with carotid atherosclerosis, comparing it with an assessment of the severity of CAS.

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Materials and Methods

We conducted a retrospective cross-sectional study with an analysis of the Duplex registry database. The registry's protocol conforms to the ethical guidelines of the Helsinki Declaration. The detailed characteristics of this registry have been described in previous publications.[22,23] This study was approved by the Ethics Committee of the United Hospital with Outpatient Clinic (№7 of 02/09/2021). The complete blood count test was performed using an automatic Sysmex XS 1000I analyzer (Roche Diagnostics Rus). The normal reference range for RDW was 11.5%–14.5% in our laboratory. Analysis for lipid profile was performed on a UniCel DxC 600 PRO analyzer (Beckman Coulter).

Duplex scanning was performed on GE devices (Vivid 7) according to the standard technique. Both common carotid arteries, their bifurcations, and internal carotid arteries were examined in longitudinal and transverse projections to determine the section where the atherosclerotic plaque (AP) had the largest size. The percentage of stenosis was determined at the site of the maximum narrowing of the arterial lumen in % by the diameter and area of the vessel lumen according to the ECST criteria.[24] The absence of blood flow in the lumen of the artery was considered occlusion. All patients of the registry were divided into 5 gradations depending on the degree of detected carotid atherosclerosis: 0 – no AP was detected in the carotid arteries; 1 – AP, stenosing the lumen from 20% to 49%; 2 – AP, stenosing the lumen from 50% to 69%; 3 – AP, stenosing the lumen from 70% to 99%; and 4 – revealed occlusion of the carotid artery. All patients initially signed informed consent for the examination and processing of personal data. Additional written consent from the participants was not required, given the retrospective nature of this study. All patient data were anonymized prior to final analysis.

Statistical analysis

Descriptive statistics data for categorical variables were presented as number of observations (n) and percentage of total (%). Data for continuous variables were presented as median, 25% and 75% quartile. Comparison of two groups by quantitative sign was carried out using the Mann–Whitney test. Kruskal–Wallis rank analysis was applied for multiple group comparisons by quantitative sign. Analysis of variance (ANOVA) was additionally applied for RDW score. The results were considered significant at $P < 0.05$. Statistical analysis was carried out using the Statistica 10.0 software package (StatSoft Inc, USA).

Results

Data from 2548 patients were included in the final analysis (15–97 years old; mean age: 57.9 ± 12.3 years; 51% males [n = 1301]). The distribution of patients into 5 gradation groups among the entire study group and separately for men and women is summarized in Table 1. The incidence of CAS was higher in men than in women (58.6% (n = 763) versus 45.5% (n = 568), $P < 0.0001$). Statistically significant differences among the sexes on this sign were noted in all gradation categories ($P < 0.05$).

Table 1: Distribution of study patients by groups of carotid atherosclerosis gradations

Gradation	Male, *n* (%)	Female, *n* (%)	Total, *n* (%)
0 (abs)	538 (41.4)	679 (54.5)	1217 (47.8)
1 (20–49)	652 (50.1)	500 (40.1)	1152 (45.2)
2 (50–69)	79 (6.1)	55 (4.4)	134 (5.3)
3 (70–99)	25 (1.9)	13 (1.0)	38 (1.5)
4 (occlusion)	7 (0.5)	0	7 (0.3)
Total	1301 (100)	1247 (100)	2548 (100)

Analysis of the entire study group

Comparison of patient's characteristics from different groups by age, lipid profile, levels of RBCs, white blood cells (WBC), platelets (PLT), RBC (erythrocytes) sedimentation rate (ESR), and RDW is presented in Table 2.

Significant intergroup differences according to the results of statistical analysis were noted for the following signs: age, high-density lipoprotein cholesterol (HDL-C), WBC, PLT, and RDW [Table 2]. Interestingly, there were no statistically significant differences between groups for total cholesterol (TC), low-density lipoprotein, RBC, and ESR. An association of RDW increase with an increase in CAS gradation was revealed, independent of RBC level and not associated with concomitant anemia [Figure 1].

The forecasting model equation obtained in the analysis: $RDW = 12.788 + 0.2214*x - 0.005*x^2$, where x is the degree of CAS gradation.

Comparative analysis of sex differences between different carotid artery stenosis gradations groups

The subsequent analysis of intergroup differences in RDW in groups of different CAS gradations was carried out separately for male and female patients, taking into account the presence of distinct gender differences, confirmed in a previous study based on this registry[22] and in review articles.[25,26] Due to the absence of female patients in the group of the 4th level of CAS gradation (occlusion), this group was removed from subsequent analysis to avoid bias in the analysis results. The results of the analysis are presented in Figures 2 and 3.

The performed analysis confirmed the relationship between an increase in the RDW index and an increase in CAS gradation in males as when using Kruskal–Wallis rank analysis (Kr-W H (3;475) =16.431; P = 0.0009) and ANOVA (F = 5.283; P = 0.0014). At the same time, these data were not confirmed in females (Kr-W H = 4.3278; P = 0.2282; F = 0.5108; P = 0.6750).

Interesting data were also obtained on HDL-C in this study. There were no significant intergroup differences in men in all CAS categories (P = 0.46). Significant differences were registered in women: a lower level of HDL-C was registered

Table 2: Comparison of baseline characteristics of patients from 5 groups by age and laboratory parameters

Signs	Gradations of carotid atherosclerosis (groups), median (25%–75%)					*P*
	0	1	2	3	4	
Age (all)	53.0 (44.0–60.0)	62.0 (56.0–68.0)	66.5 61.0–76.0)	72.0 (62.0–78.0)	74.0 (60.0–77.0)	0.000
Age (men)	52.0 (43.0–60.0)	61.0 (54.0–66.0)	65.0 (60.0–72.0)	70.0 (62.0–73.0)	74.0 (60.0–77.0)	0.000
Age (women)	54.0 (46.0–61.0)	64.0 (58.0–71.0)	73.0 (62.0–77.0)	79.0 (71.0–85.0)	-	0.000
TC (all)	5.80 (5.08–6.51)	5.75 (5.05–6.55)	5.70 (4.70–6.51)	5.22 (4.28–5.84)	4.28 (4.24–4.32)	0.27
TC (men)	5.70 (4.97–6.46)	5.63 (4.78–6.41)	5.85 (3.93–6.57)	4.28 (3.25–6.15)	4.28 (4.24–4.32)	0.29
TC (women)	5.89 (5.14–6.58)	5.95 (5.32–6.75)	5.65 (5.40–6.28)	5.53 (5.22–5.84)	-	0.56
HDL-C (all)	1.49 (1.20–1.89)	1.36 (1.12–1.68)	1.23 (1.07–1.47)	1.18 (1.08–1.44)	0.85 (0.80–0.90)	0.000
HDL-C (men)	1.27 (1.09–1.52)	1.27 (1.08–1.51)	1.21 (1.01–1.46)	1.27 (1.09–1.62)	0.85 (0.80–0.90)	0.46
HDL-C (women)	1.74 (1.44–2.14)	1.59 (1.33–1.91)	1.27 (1.07–1.48)	1.08 (1.02–1.16)	-	0.000
LDL-C (all)	3.55 (2.94–4.15)	3.56 (2.80–4.26)	3.51 (2.44–4.38)	2.93 (1.96–3.48)	2.60 (2.40–2.80)	0.38
LDL-C (men)	3.58 (2.95–4.16)	3.52 (2.56–4.17)	3.58 (2.20–4.32)	2.65 (1.27–3.22)	2.60 (2.40–2.80)	0.11
LDL-C (women)	3.54 (2.93–4.13)	3.70 (3.11–4.39)	3.44 (3.13–4.44)	3.75 (3.22–4.42)	-	0.48
RBC (all)	4.60 (4.30–4.90)	4.63 (4.31–4.95)	4.57 (4.08–4.85)	4.46 (4.13–4.90)	4.46 (4.18–4.74)	0.38
RBC (men)	4.83 (4.60–5.12)	4.76 (4.50–5.06)	4.68 (4.27–5.02)	4.52 (4.04–4.89)	4.46 (4.18–4.74)	0.04
RBC (women)	4.41 (4.16–4.64)	4.44 (4.16–4.74)	4.18 (3.90–4.56)	4.46 (4.23–4.91)	-	0.22
WBC (all)	5.80 (4.90–7.00)	6.10 (5.20–7.40)	6.75 (5.55–7.40)	6.55 (5.50–8.00)	5.30 (5.20–5.40)	0.002
WBC (men)	6.00 (5.20–7.10)	6.30 (5.50–7.70)	6.90 (5.80–7.90)	6.05 (5.50–7.90)	5.30 (5.20–5.40)	0.033
WBC (women)	5.50 (4.70–6.80)	5.80 (4.90–7.00)	6.50 (4.70–7.10)	7.15 (5.80–8.20)	-	0.21
ESR (all)	10.0 (6.0–16.0)	10.0 (6.0–18.0)	12.5 (6.0–22.0)	12.0 (5.5–18.0)	4.0 (2.0–6.0)	0.17
ESR (men)	6.0 (4.0–10.0)	8.0 (4.0–16.0)	10.0 (4.0–20.0)	12.0 (7.0–16.0)	4.0 (2.0–6.0)	0.013
ESR (women)	12.0 (8.0–20.0)	12.0 (8.0–22.0)	14.5 (10.0–26.0)	10.0 (4.0–25.0)	-	0.66
PLT (all)	226.0 (195.0–259.0)	212.5 (188.0–251.0)	206.0 (181.0–233.5)	190.5 (163.0–220.0)	202.5 (200.0–205.0)	0.002
PLT (men)	214.0 (187.0–247.0)	210.0 (185.0–237.5)	209.0 (178.0–233.0)	187.5 (159.0–224.0)	202.5 (200.0–205.0)	0.422
PLT (women)	235.0 (205.0–268.0)	222.0 (196.5–268.0)	205.5 (190.0–236.0)	194.0 (180.0–209.0)	-	0.017
RDW (all)	12.9 (12.4–13.4)	12.9 (12.5–13.6)	13.25 (12.8–13.8)	13.50 (13.05–14.25)	13.75 (13.6–13.9)	0.001
RDW (men)	12.8 (12.4–13.4)	12.9 (12.5–13.6)	13.2 (12.7–13.8)	13.90 (13.40–14.40)	13.75 (13.6–13.9)	0.001
RDW (women)	12.9 (12.4–13.5)	13.0 (12.5–13.7)	13.2 (13.0–13.8)	13.15 (12.40–13.40)	-	0.22

Age: Age at the time of inclusion in the registry, TC: Total cholesterol, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, RBC: Red blood cells, WBC: White blood cells, PLT: Platelets, ESR: Red blood cell sedimentation rate, RDW: Red blood cell distribution width

with a higher CAS gradation ($P < 0.001$). A comparative analysis of the 0th and 1st CAS gradation groups (absence of CAS and CAS <50%) showed significant differences between the sexes in HDL-C: it was significantly higher in women (1.74 [1.44–2.14] vs. 1.27 [1.09–1.52], $P < 0.001$; and 1.59 [1.33–1.91] vs. 1.27 [1.08–1.51], $P < 0.001$). These intersex differences in HDL-C disappeared in the 2nd and 3rd CAS gradation groups (>50%).

Intersex differences between 0th and 1st CAS gradation groups in addition to HDL-C were also noted in TC, RBC, WBC, PLT, and ESR. Significantly lower levels of RBC (4.41 [4.16–4.64] vs. 4.83 [4.60–5.12], $P < 0.001$; 4.44 [4.16–4.74] vs. 4.76 [4.50–5.06], $P < 0.001$) and WBC (5.50 [4.70–6.80] vs. 6.00 [5.20–7.10), $P = 0.002$; 5.80 [4.90–7.00] vs. 6.30 [5.50–7.70], $P < 0.001$) were recorded in women.

Higher levels of TC (5.89 [5.14–6.58] vs. 5.70 [4.97–6.46], $P = 0.069$; 5.95 [5.32–6.75] vs. 5.63 [4.78–6.41], $P = 0.003$), PLT (235.0 [205.0–268.0] vs. 214.0 [187.0–247.0], $P < 0.001$; 222.0 [196.5–268.0] vs. 210.0 [185.0–237.5], $P < 0.001$), and ESR (12.0 [8.0–20.0] vs. 6.0 [4.0–10.0], $P < 0.001$; 12.0 [8.0–22.0] vs. 8.0 [4.0–16.0], $P < 0.001$) were recorded in women of the 0th and 1st CAS gradation groups compared to men. At the same time, a significant trend in ESR level increase with CAS gradation increase was registered in men ($P = 0.013$), which was not registered in women ($P = 0.66$).

Discussion

In the present study, CAS >50% was found in 7.1% of study participants ($n = 179$), which is comparable to the results obtained in similar and larger population-based studies.[27,28] Poorthuis *et al*. on a large population sample ($n = 112,117$) obtained a prevalence of CAS >50% equal to 5.7% ($n = 6354$).[28]

Statistically significant differences between the sexes were noted for all CAS gradations in this study. The pathophysiology of atherosclerosis in men and women is different. The obvious prerequisites for this are hidden in hormonal and behavioral differences between the sexes. The protective effect of female sex hormones and the reverse effect of menopause explains the later development of atherosclerosis in women.[29,30] At the same time, the behavioral features of the greater prevalence of smoking and alcohol consumption among men compared to women contribute to the development of atherosclerosis.[31,32]

If previously the protective role of HDL-C in relation to atherosclerosis was not questioned, in recent years, the role of HDL-C has been significantly revised.[33]

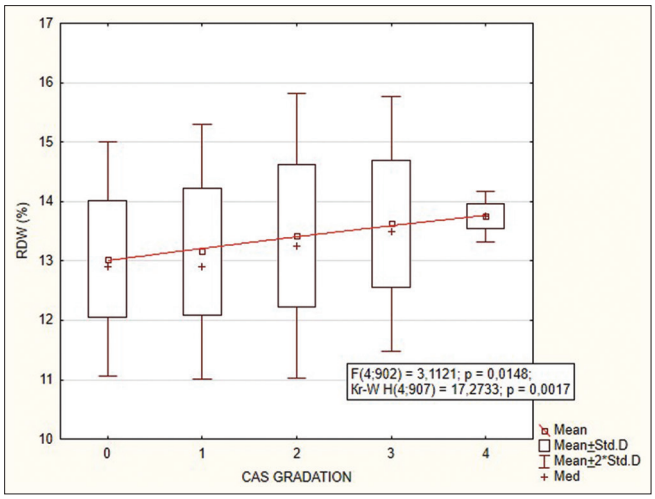

Figure 1: Intergroup differences in red blood cell distribution width depending on carotid artery stenosis gradation

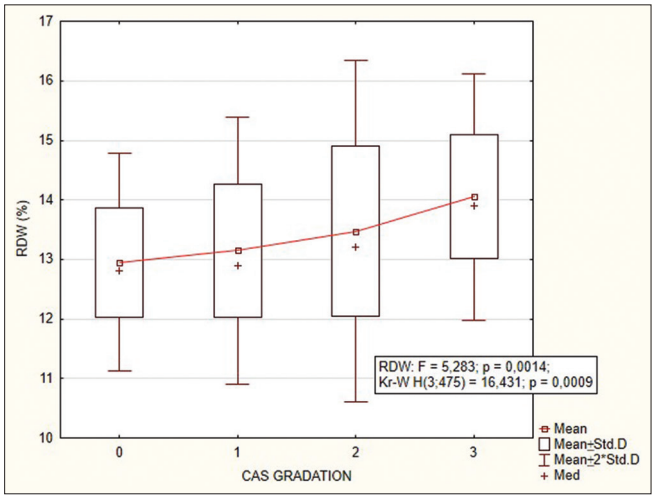

Figure 2: Red blood cell distribution width intergroup differences depending on carotid artery stenosis gradation in males

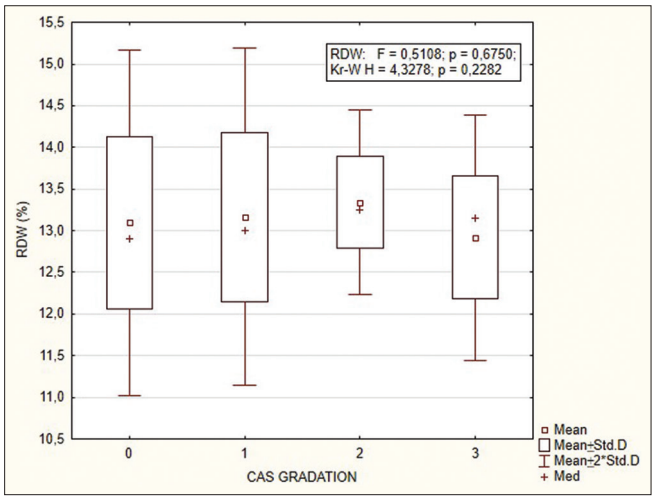

Figure 3: Red blood cell distribution width intergroup differences depending on carotid artery stenosis gradation in females

However, in this study, significant differences in the level of HDL-C were noted: (1) between the sexes; it was significantly higher in women (for gradation 0: 1.74 [1.44–2.14] vs. 1.27 [1.09–1.52], $P < 0.001$); (2) depending on the CAS gradation in women, lower HDL-C levels were recorded at a higher CAS gradation. At the same time, it was stated that at CAS >50%, these intersex differences in HDL-C leveled out.

Furthermore, interesting data were obtained regarding WBC and ESR in this study. Higher WBC levels in men compared to women in all CAS gradations and ESR increase with CAS gradation increase in men, indirectly confirm the role of pro-inflammatory factors in the development of atherosclerosis.[34]

In the present study, we obtained significant differences in the RDW level with an increase in the gradation of carotid atherosclerosis independent of the RBC level and not associated with concomitant anemia. This circumstance indirectly indicates the independent role of the influence of this sign on the progression of carotid atherosclerosis. This agrees with the results obtained by Furer *et al*. in their study ($n = 522$; mean age 66 ± 11 years). RDW was associated with significant carotid stenosis (odds ratio [OR] =1.77, 95% confidence interval [CI]: 1.12–2.82, $P = 0.015$).[9] Patients with higher RDW (RDW above 14.1%) were significantly older, which was also noted in our study (group 0 vs. group 4: 53.0 [44.0–60.0] vs. 74.0 [60.0–77.0]).

A distinctive feature of our study was that it described for the first time the gender differences in RDW depending on the CAS gradations, which concerned men but not women, which was not noted by previous researchers in their studies.[6,7,9,11,12,16]

Lappegård *et al*. in The Tromsø Study showed that the association between RDW and cardiovascular morbidity and mortality could be explained by atherosclerosis.[6] A 1% increase in RDW was associated with an increase in total carotid AP area of 0.6 mm^2 (0.1–1.2) on multivariate analysis ($P = 0.03$). RDW was associated with progression of atherosclerosis after adjusting for traditional risk factors. However, the Swedish study did not separately conduct a gender analysis on this sign, so it is impossible to draw parallels with our study.[6]

Jia *et al*. in their study found an independent relationship between RDW and CAS in patients aged 60–70 years with primary ischemic stroke.[7] The sex ratio was comparable between the groups. The CAS group was dominated by smokers, hypertensives, and had higher levels of body mass index (BMI), blood pressure (BP), TC, triglycerides, and uric acid compared to the control group.[7] What is more typical for the "male patient portrait" of this group, which is confirmed by population studies that indicate a greater prevalence of smoking and arterial hypertension among men.[35]

Söderholm *et al*. found that RDW was associated with carotid intima-media thickness (CIMT) but not with carotid plaques.[11] A high level of RDW was associated with an

increased incidence of stroke in this study. The relationship between RDW and stroke rate was influenced by smoking status, but not by gender. At the same time, participants with a high RDW were more likely to be smokers and high alcohol consumers and had higher age,[11] which is again more typical for men.[27] It is worth noting that there were 1.5 times more women than men in this study.[11]

A lot of works devoted to the study of the associations of RDW and carotid atherosclerosis were concerned selective categories of patients, namely patients with metabolic syndrome, diabetes mellitus, arterial hypertension, and coronary artery disease.[12,13,16,17] Moreover, in most of them, the CIMT was used as a criterion for atherosclerosis but not the presence of an AP in the carotid artery.

Ren *et al*. conducted a study among Chinese patients with metabolic syndrome aged 24–54 years (mean age 48.9 years; males: 65.3%). Compared with the first quartile, people from the third and fourth quartiles had a higher risk of CAS developing (OR = 1.41, 95% CI: 1.01–197; OR = 2.10, 95% CI: 1. 30–3.40). Ren *et al*. did not conduct a separate analysis of RDW among men and women.[12]

In another Chinese study, Wen Y. noted a close relationship between a high level of RDW, CIMT, and the incidence of carotid plaque formation in patients with arterial hypertension (n = 156, men: 87.2%).[16]

In a Korean study, Nam *et al*. confirmed that RDW is associated with subclinical atherosclerosis as assessed by CIMT in patients with type 2 diabetes without CVD or cerebrovascular disease (more than half of them were men: 65%). Study participants with the highest RDW tertile were older, more likely to be smokers, obese, have higher BP levels, and longer duration of diabetes compared to those with the lowest RDW tertile. Correlation analysis showed that CIMT significantly correlated with age, male sex, BMI, BP, smoking status, and RDW.[13]

Chang *et al*. in their study did not confirm statistically significant differences in RDW between groups of patients with and without atheroma in the carotid artery. The small and selective cohort of this study was a possible reason for these results (50 study and control patients; all males), and an unreliable imaging modality for carotid atheroma (panoramic X-ray not carotid duplex scanning), which biased the results of this study.[21]

Thus, the analysis of the data of the present study and previous research works indicate an important prognostic role of RDW in the development and progression of carotid atherosclerosis along with other more well-studied lipid and pro-inflammatory factors.

Moreover, it should be taken into account that RDW is significantly and independently associated with death from all causes and from CVD in patients with asymptomatic CAS.[8] This is probably based on the concept proposed by Ananthaseshan *et al*., who studied the mechanism of RDW influence on the development of atherosclerosis in their experimental research. The authors of the study concluded that RDW, being a marker of inflammation, directly affects intravascular hemodynamics, the interaction of circulating cells and the vessel wall, causing local changes that predispose to atherothrombosis.[15]

Limitations of the study

This study was performed on a representative sample of patients (n = 2548), but some limitations may arise when translating its results to the population level.

This study did not take into account the influence of traditional risk factors, conditions, and diseases (such as arterial hypertension, diabetes mellitus, coronary artery disease, peripheral artery disease, and previous stroke) on RDW level, as this was not originally included in the goals of this study. At the same time, it should be noted that the influence of these factors on CAS detection is reflected in previous publications.[22,23]

Conclusion

The results of the present study show that RDW is an indicator whose increase is associated with an increase in the degree of carotid atherosclerosis. It is important to note that these findings are registered only in men, but not in women. The latter allows us to discuss the role of the RDW index as a possible new laboratory biomarker of inflammation and atherosclerosis progression, which can make an additional contribution to the formation of higher morbidity and mortality in men from atherosclerotic CVD.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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