

## COMPARATIVE ANALYSIS OF C-REACTIVE PROTEIN AND RED BLOOD CELLS DISTRIBUTION WIDTH LEVELS IN SUBGROUPS DEPENDING ON THE SEVERITY OF HYPERLIPIDEMIA ACCORDING TO LABORATORY REGISTRY DATA

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**Objective:** To identify patients with severe hyperlipidemia and to analyze red cells distribution width (RDW) and C-reactive protein (CRP) levels in subgroups depending on the severity of hyperlipidemia.

**Methods:** All patients who underwent complete blood count, total cholesterol (TC) and LDL tests in our hospital from January to December 2016 were included in the study. CRP data were added to the database, if available. Criteria for severe hyperlipidemia were accepted LDL values of 5.0 mmol/L and more in this study.

**Results:** 8056 patient records were included in the final analysis. Detection of severe hyperlipidemia in this population by this criteria was 8.0%. A comparative analysis of RDW and CRP depending on the presence of severe hyperlipidemia was carried out for the whole study group and for patients with circulatory system diseases (CSD). Differences in the level of CRP and RDW were obtained depending on the presence of severe hyperlipidemia for both groups of patients. But statistically significant differences were obtained only in RDW level in patients with CSD. Among them, the RDW level in patients with severe hyperlipidemia was lower:  $12.9 \pm 0.8$  (n=173) vs  $13.2 \pm 0.8$  (n=2119),  $p=0.007$ .

**Conclusions:** Statistically significant differences were found in the level of RDW in patients with severe hyperlipidemia only in the group of patients with CSD (but not for the whole group). RDW should be considered as an additional biomarker in patients with cardiovascular diseases.

**Keywords:** C-reactive protein, red blood cells distribution width, LDL, screening, severe hyperlipidemia.

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## СРАВНИТЕЛЬНЫЙ АНАЛИЗ УРОВНЕЙ С-РЕАКТИВНОГО БЕЛКА И ИНДЕКСА ГЕТЕРОГЕННОСТИ ЭРИТРОЦИТОВ В ПОДГРУППАХ В ЗАВИСИМОСТИ ОТ ВЫРАЖЕННОСТИ ГИПЕРЛИПИДЕМИИ ПО ДАННЫМ ЛАБОРАТОРНОГО РЕГИСТРА

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**Цель:** выявление пациентов с выраженной гиперлипидемией и анализ уровней индекса гетерогенности эритроцитов (ИГЭ) и С-реактивного белка (СРБ) в подгруппах в зависимости от выраженности гиперлипидемии.

**Материал и методы:** в исследование были включены все пациенты, которым были выполнены общий анализ крови, анализ крови на общий холестерин и ЛПНП в нашей больнице с января по декабрь 2016 года. Результаты анализа СРБ добавлялись в базу данных, если они были выполнены. За критерии выраженной гиперлипидемии в настоящем исследовании были приняты значения ЛПНП 5,0 ммоль/л и более.

**Результаты:** 8056 записей пациентов были включены в окончательный анализ. Выявление выраженной гиперлипидемии в этой популяции по этим критериям составило 8,0%. Сравнительный анализ ИГЭ и СРБ в зависимости от наличия выраженной гиперлипидемии был проведён для всей исследуемой группы и для пациентов с заболеваниями системы кровообращения (БСК). Различия в уровне СРБ и ИГЭ в зависимости от наличия выраженной гиперлипидемии были получены для обеих групп пациентов. Однако статистически значимые различия были получены только по уровню ИГЭ у пациентов с БСК. В этой группе уровень ИГЭ у пациентов с выраженной гиперлипидемией был ниже:  $12,9 \pm 0,8$  (n=173) против  $13,2 \pm 0,8$  (n=2119),  $p=0,007$ .

**Заключение:** статистически значимые различия по показателю ИГЭ были обнаружены у пациентов с выраженной гиперлипидемией только в группе пациентов с заболеваниями системы кровообращения (но не для всей группы исследования). ИГЭ можно рассматривать в качестве дополнительного биомаркера у пациентов с сердечно-сосудистыми заболеваниями.

**Ключевые слова:** С-реактивный белок, индекс гетерогенности эритроцитов, ЛПНП, скрининг, гиперлипидемия.

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## INTRODUCTION

Recently, much attention in the field of preventive medicine is given to the study of various biomarkers [1]. These are common indicators, such as total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol. They are included in major risk stratification models such as Framingham, PROCAM and SCORE [2-4]. Lipid markers are used to make a decision on the timely initiation of lipid-lowering therapy, to assess its effectiveness, and to screen for familial hypercholesterolemia. At the same time, much attention is paid to markers of inflammation and indicators of complete blood count (CBC) as early precursors of changes in the homeostasis of the human body from infectious and inflammatory diseases, atherosclerosis and cancer [5-8].

It has been found that elevated levels of C-reactive protein (CRP) are associated with an increased risk of coronary artery disease (CAD) (risk ratio [RR] 1.6, 95% confidence interval 1.6-2.9) [9]. At the same time, in later studies, it was shown that the red cells distribution width (RDW), rather than CRP, was associated with the mortality of CAD, regardless of the traditional risk factors in the cohort without a previously existing cardiovascular disease [10]. RDW is calculated as the standard deviation (SD) of the red blood cell volume divided by the mean corpuscular volume (MCV). The number of medical studies devoted to the analysis of this indicator began to increase every year over the past decade [11].

The important prognostic value of RDW for survival of various categories of patients was studied and confirmed: in patients with chronic and acute forms of CAD, in patients with trauma and stroke, in patients with chronic renal failure, cancer, both elderly and young patients [12-19].

Early studies showed that RDW is a promising biomarker, so we decided to use it as an additional marker to the C-reactive protein in screening for severe hyperlipidemia.

The aim of the study was to analyze the lipid profile in patients of the local laboratory registry data, to identify among them patients with severe hyperlipidemia and to conduct a comparative analysis of CRP and RDW levels depending on the presence or absence of severe hyperlipidemia.

## METHODS

We conducted a retrospective study using computer data and electronic medical records in our medical center for 2016. All patients who underwent complete blood count, blood tests for TC and LDL in the period from January to December 2016 were included in the study. In addition, the CRP data for each patient were added to the research database, if available. CBC measurements (including RDW) were performed using a Sysmex XS 1000I automatic hematology analyzer (Roche Diagnostics). The normal range for RDW was 11.5%-14.5% in our laboratory. Blood tests for TC, LDL and CRP were performed on a UniCelDxC 600 PRO analyzer (Beckman Coulter).

Basic characteristics of the patients included age, gender, the code of the main diagnosis when referring to a blood test (circulatory system diseases (CSD) or others) and the type of treatment at the time of the analysis (outpatient or inpatient).

The criteria for severe hyperlipidemia were accepted LDL values of 5.0 mmol/L and more, which corresponded to the Dutch Lipid Clinic Network Criteria (DCLN) with a rating of 3 or more [20].

All patients initially signed a written consent to blood tests and informed consent to the processing of personal data. Additional

written informed consent for each participant was not required for such a retrospective study. All patient records or information were anonymized and de-identified before analysis.

## STATISTICAL ANALYSIS

Statistical analysis was performed using statistical software package Statistica 10.0 (StatSoft Inc., USA). All data represented as the mean  $\pm$  standard deviation (SD) for continuous variables or the number (n) and percentage (%) for categorical variables. The Spearman rank correlation test was used to determine the relationship between investigated features. Intergroup comparisons of continuous variables was carried out using the Mann-Whitney test. The results were considered significant at a p-value  $<$  0.05.

## RESULTS

The research database included 8056 patient records. The basic characteristics of patients included in this study presented in Table 1.

The Spearman rank correlation analysis showed the presence of significant interrelations between the following variables: the type of treatment (inpatient vs outpatient) correlated with age ( $r=0.24$ ,  $p<0.001$ ), CRP level ( $r=0.14$ ,  $p<0.0001$ ), ESR ( $r=0.17$ ,  $p<0.0001$ ) and RDW ( $r=0.13$ ,  $p<0.0001$ ). TC level correlated with age ( $r=0.12$ ,  $p<0.001$ ), gender ( $r=0.2$ ,  $p<0.0001$ ), LDL level ( $r=0.94$ ,  $p<0.0001$ ) and platelets ( $r=0.13$ ,  $p<0.0001$ ). CRP correlated with ESR ( $r=0.5$ ,  $p<0.001$ ), WBC ( $r=0.2$ ,  $p<0.0001$ ) and RDW ( $r=0.16$ ,  $p<0.0001$ ). HB correlated with ESR ( $r=0.5$ ,  $p<0.001$ ), WBC ( $r=0.2$ ,  $p<0.0001$ ) and RDW ( $r=0.16$ ,  $p<0.0001$ ). ESR level showed the presence of correlations with the type of treatment (inpatient vs outpatient) ( $r=0.17$ ,  $p<0.0001$ ), age ( $r=0.25$ ,  $p<0.001$ ), gender ( $r=0.14$ ,  $p<0.0001$ ), CRP ( $r=0.5$ ,  $p<0.001$ ), HB ( $r=0.44$ ,  $p<0.001$ ), RBC ( $r=0.39$ ,  $p<0.001$ ), platelets ( $r=0.21$ ,  $p<0.001$ ), WBC ( $r=0.13$ ,  $p<0.0001$ ) and RDW ( $r=0.2$ ,  $p<0.0001$ ). Correlations of various variables with RDW presented in Table 2.

Based on LDL criteria of 5.0 mmol/L and more, all patients were divided into groups according to the presence or absence of severe hyperlipidemia. The detection of severe hyperlipidemia according to this criteria for the whole study group was 8.0%, for patients with CSD – 7.5%.

A comparative analysis of RDW and CRP depending on the presence of severe hyperlipidemia was conducted for the whole study group and separately for patients with CSD (Table 3). In the present analysis, differences in the level of CRP and RDW were obtained depending on the presence of severe hyperlipidemia for both groups of patients. But statistically significant differences were obtained only in RDW level in patients with CSD. Among them, the RDW level in patients with severe hyperlipidemia was lower:  $12.9\pm 0.8$  ( $n=173$ ) vs  $13.2\pm 0.8$  ( $n=2119$ ),  $p=0.007$ .

## DISCUSSION

The detection of the severe hyperlipidemia in the present study was 8.0% for the whole study group based on accepted criteria. It is worth noting the limitations of our study – it was a retrospective study of computer laboratory database from real clinical practice. The patient's distribution to the subgroups depending on the presence or absence of circulatory system diseases was conducted on the basis of the analysis of the ICD code, which could have some limitations, but it is a generally accepted approach used in clinical studies [21, 22].

**Table 1** Basic characteristics of patients included in the study

|        | N obs.                       | mean                       | min                        | max                            | SD                             |
|--------|------------------------------|----------------------------|----------------------------|--------------------------------|--------------------------------|
| Age    | 8056                         | 57.8261                    | 16.0000                    | 101.0000                       | 15.40910                       |
| HB     | 8056                         | 139.2247                   | 54.0000                    | 187.0000                       | 15.76855                       |
| WBC    | 8055                         | 6.7303                     | 1.8000                     | 202.8000                       | 4.27254                        |
| RBC    | 8056                         | 4.5416                     | 2.2000                     | 7.1300                         | 0.51280                        |
| RDW    | 8046                         | 13.1767                    | 10.8000                    | 30.6000                        | 1.29410                        |
| PLAT   | 8056                         | 235.6449                   | 14.0000                    | 938.0000                       | 63.01527                       |
| ESR    | 7948                         | 15.6012                    | 1.0000                     | 170.0000                       | 16.66702                       |
| TC     | 7658                         | 5.3618                     | 1.7000                     | 24.3100                        | 1.35355                        |
| LDL    | 5763                         | 3.2590                     | 0.4400                     | 9.7300                         | 1.15349                        |
| CRP    | 3149                         | 1.4770                     | 0.1000                     | 102.0000                       | 4.49883                        |
|        | <b>N obs. (total)</b>        | <b>N obs. (male)</b>       | <b>% obs. (male)</b>       | <b>N obs. (female)</b>         | <b>% obs. (female)</b>         |
| Gender | 8056                         | 3779                       | 46.9%                      | 4227                           | 53.1%                          |
|        | <b>N obs. (total)</b>        | <b>N obs. (outpatient)</b> | <b>% obs. (outpatient)</b> | <b>N obs. (inpatient)</b>      | <b>% obs. (inpatient)</b>      |
| TTR    | 8056                         | 5653                       | 70.2%                      | 2403                           | 29.8%                          |
|        | <b>N obs. (all diseases)</b> | <b>N obs. (CSD)</b>        | <b>% obs. (CSD)</b>        | <b>N obs. (other diseases)</b> | <b>% obs. (other diseases)</b> |
| ICD DS | 8056                         | 2917                       | 36.2%                      | 5139                           | 63.8%                          |

HB – hemoglobin, WBC – white blood cells, RBC – red blood cells (erythrocytes), RDW – red blood cells distribution width, TC – total cholesterol, LDL – low-density lipoprotein cholesterol, TTR – type of treatment (outpatient or inpatient), ICD DS – international classification of diseases code-based diagnosis

In our study, it was found that RDW had a statistically significant correlation with age, which can be considered as an indirect confirmation of the relationship of this indicator for mortality prediction. RDW had the strongest negative relationship with HB level, which is particularly important and points to the need to take this into account and adjust for the presence of anemia in patients.

Negative correlation between RDW with TC and LDL was obtained in our research as well as in the Korean study [16], but it was statistically unreliable in our study. At the same time, it was found that RDW levels were lower in people with higher LDL levels, although the opposite could be expected. This can probably be explained by the fact that there are suggestions that when examining a CBC test with various hematological analyzers in patients with severe hyperlipidemia, false basic CBC parameters can be obtained [23].

We established a weak but reliable association of RDW with CRP level in our study, as well as Lappe JM et al [12]. At the same time, we did not find statistically significant differences in CRP level in patients with the presence or absence of a severe hyperlipidemia in the whole study group and in CSD patient's group. It is interesting that Rasouli M et al in their work received evidence that patients who underwent coronary angiography to verify the diagnosis of CAD, had no difference in CRP level, with or without CAD groups [24]. Veeranna V et al in their study concluded that CRP (unlike RDW) was not associated with mortality from CAD, regardless of the traditional risk factors in the cohort without a previously existing cardiovascular disease [10].

The results of some of the above studies, and to a certain extent the results of this work, suggest that the results obtained in a randomized study with the selective selection of patients performed

**Table 2** Correlations of various variables with RDW

| Variables       | Spearman rank correlation coefficient | p-value |
|-----------------|---------------------------------------|---------|
| TTR (inpatient) | 0.132                                 | p<0.001 |
| Age             | 0.2588                                | p<0.001 |
| Gender (male)   | 0.0289                                | p=0.263 |
| TC              | -0.0348                               | p=0.178 |
| LDL             | -0.0408                               | p=0.114 |
| CRP             | 0.161                                 | p<0.001 |
| HB              | -0.3451                               | p<0.001 |
| RBC             | -0.1033                               | p<0.001 |
| WBC             | 0.0843                                | p=0.001 |
| ESR             | 0.2037                                | p<0.001 |
| PLAT            | 0.1623                                | p<0.001 |

TTR – type of treatment (outpatient or inpatient), TC – total cholesterol, LDL – low-density lipoprotein cholesterol, CRP – C-reactive protein, HB – hemoglobin, RBC – red blood cells (erythrocytes), WBC – white blood cells, ESR – erythrocyte sedimentation rate, PLAT – platelets

**Table 3** Comparative analysis of RDW and CRP level depending on the presence of severe hyperlipidemia

| Variable | Group             | LDL < 5.0 mmol/L<br>(n; mean±SD) | LDL ≥ 5.0 mmol/L<br>(n; mean±SD) | The Mann-Whitney U test | Z        | p-value  |
|----------|-------------------|----------------------------------|----------------------------------|-------------------------|----------|----------|
| RDW      | All patients      | n=4682<br>13.138±1.229           | n=410<br>12.997±0.926            | 913897                  | 1.608522 | 0.107722 |
| RDW      | Patients with CSD | n=2119<br>13.196±1.14            | n=173<br>12.57±0.82              | 161022                  | 2.660969 | 0.007792 |
| CRP      | All patients      | n=1490<br>0.804±2.9              | n=107<br>0.278±0.24              | 74037                   | 1.23218  | 0.217883 |
| CRP      | Patients with CSD | n=577<br>0.396±1.02              | n=39<br>0.263±0.20               | 9536.5                  | 1.59392  | 0.097550 |

on one sample from the population and the results obtained in the study of real clinical practice may have significant differences. In this regard, the results obtained in the analysis of real clinical practice in the study of registers involving a large number of patients are always of special scientific and clinical interest.

## CONCLUSIONS

Statistically significant differences were found in the level of RDW in patients with severe hyperlipidemia only in the group of patients with CSD (but not for the whole group). RDW should be considered as an additional biomarker in patients with cardiovascular diseases.

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**Информация об источнике поддержки в виде грантов, оборудования, лекарственных препаратов**

Финансовой поддержки со стороны компаний-производителей лекарственных препаратов и медицинского оборудования автор не получал

**Конфликт интересов:** отсутствует

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ВКЛАД АВТОРОВ

Разработка концепции и дизайна исследования: ГОВ  
Сбор материала: ГОВ  
Статистическая обработка данных: ГОВ  
Анализ полученных данных: ГОВ  
Подготовка текста: ГОВ  
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