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Gender and age effects on coronary calcium index in patients with suspected CHD

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Abstract

Aim – to assess the influence of sex and age on the coronary artery calcium (CAC) score in patients with suspected coronary heart disease (CHD).

Material and methods. A prospective, observational, single-center study was conducted. The study included 733 patients (mean age 67 [58; 73] years, 43.37% male) with suspected CHD who underwent multi-slice computed tomography (MSCT) of the coronary arteries with CAC scoring (using the Agatston method), as well as a biochemical blood test assessing lipid profile, glucose level, creatinine level, and estimated glomerular filtration rate (eGFR). An analysis of baseline clinical and laboratory parameters and the distribution of CAC scores according to patient age and sex was performed. Statistical analysis was performed using SPSS Statistics 21.0, employing the Shapiro-Wilk test, Student's t-test, and ANOVA.

Results. It was found that CAC scores increased with advancing age, and men had significantly higher CAC scores than women of the same age category. In the group of patients with higher CAC scores, older men were more prevalent, and there were higher creatinine levels and a higher incidence of atrial fibrillation. The correlation analysis revealed moderate and strong associations between CAC scores and parameters of lipid metabolism, as well as eGFR.

Conclusion. The assessment of CAC scores, taking into account sex and age, improves the accuracy of cardiovascular risk stratification in patients with suspected CHD. The implementation of this approach into clinical practice helps optimize preventive and therapeutic strategies for reducing cardiovascular morbidity and mortality.

Keywords: coronary calcium, sex, dyslipidemia, risk factors, coronary artery disease, MSCT, calcium score.

Conflict of interest: nothing to disclose.

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Влияние пола и возраста на индекс коронарного кальция у пациентов с подозрением на ИБС

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Аннотация

Цель – оценить влияние пола и возраста на индекс коронарного кальция (ИКК) у пациентов с подозрением на ишемическую болезнь сердца (ИБС).

Материал и методы. Проведено проспективное наблюдательное одноцентровое исследование. В исследование включено 733 пациента (средний возраст 67 (58; 73) лет, из которых мужчин 43,37%, с подозрением на ИБС, проходивших мультиспиральную компьютерную томографию (МСКТ) коронарных артерий с определением ИКК (по методу Agatston), а также биохимическое исследование крови с оценкой липидного профиля, уровня глюкозы, креатинина и расчетом скорости клубочковой фильтрации. Был проведен анализ исходных клинико-лабораторных параметров и распределения ИКК в зависимости от возраста и пола пациентов. Статистическую обработку данных выполняли с использованием SPSS Statistics 21.0, применяли критерии Шапиро – Уилка, Стьюдента, ANOVA.

Результаты. Установлено, что с увеличением возраста пациентов возрастает значение ИКК, причем у мужчин ИКК значительно выше, чем у женщин той же возрастной категории. В группе пациентов с более

высокими значениями ИКК чаще встречались мужчины старших возрастных групп, наблюдались повышение уровня креатинина и фибрилляция предсердий. Проведенный корреляционный анализ выявил умеренную и высокую связи между ИКК и параметрами липидного обмена, а также скоростью клубочковой фильтрации.

Заключение. Оценка ИКК с учетом пола и возраста повышает точность стратификации риска сердечно-сосудистых осложнений у пациентов с подозрением на ИБС. Внедрение данного подхода в клиническую практику способствует оптимизации профилактических и лечебных стратегий снижения сердечно-сосудистой заболеваемости и смертности.

Ключевые слова: коронарный кальций, пол, дислипидемия, факторы риска, ишемическая болезнь сердца, МСКТ, кальциевый индекс.

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Список сокращений
ССЗ – сердечно-сосудистое заболевание; ИБС – ишемическая болезнь сердца; ИКК – индекс коронарного кальция; МСКТ – мультиспиральная компьютерная томография; КА – коронарная артерия; АГ – артериальная гипертензия; ХБП – хроническая болезнь почек; СД – сахарный диабет; ФП – фибрилляция предсердий; ФК – функциональный класс; ОХ – общий холестерин; ТГ – триглицериды; ЛНП – липопротеины низкой плотности; ЛВП – липопротеины высокой плотности.

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INTRODUCTION

Cardiovascular diseases (CVD), including coronary heart disease (CHD), represent a major medical and socioeconomic challenge and remain the leading cause of mortality worldwide [1]. Despite significant progress achieved in recent years, the risk of adverse cardiovascular events remains high.

Recommendations of the European Society of Cardiology on treatment of the chronic coronary syndrome (2024) suggest the use of the multi-slice computed tomography (MSCT) of the coronary arteries with coronary artery calcium (CAC) scoring to re-stratify the risk of CHD [2, 3]. According to the national clinical recommendations (2024), in cases of suspected CHD it is also recommended to perform MSCT with CAC calculation as a method of assessment of CHD probability [4]. The final choice of diagnostic strategy is to be based on sensitivity, specificity and accuracy of methods of visualization in each clinical case [5, 6]. At the same time, the recommendations do not specify the age of patients for whom such strategy is to be used.

AIM

To assess the influence of sex and age on the coronary artery calcium (CAC) score in patients with suspected coronary heart disease (CHD).

MATERIAL AND METHODS

The prospective, observational, single-center study was conducted from January to December 2023. Inclusion criteria: age over 18; suspected CHD based on clinical data and/or results of stress test (bicycle ergometry); availability of consent for analysis. Exclusion criteria: permanent atrial fibrillation; an episode of atrial fibrillation at the time of the study; exacerbation of chronic hematologic, hepatic, renal, or autoimmune diseases; decompensated diabetes mellitus; pregnancy at any stage; body weight over 140 kg; allergic reactions to iodine and iodine-containing drugs.

MSCT of the coronary arteries was performed with pro- and retrospective ECG-synchronization and intravenous administration of non-ionic iodine-containing radiopaque agent on the RevolutionEVOGE scanner with 128 rows of detecting elements and detector width of 160 mm. In order to assess the degree of the coronary bed lesion, modified criteria of the American Heart Association were used; the CAC was assessed using the Agatston method by adding the scores of all identified areas of calcification [7].

All patients underwent biochemical blood assays with analysis of the following parameters: total cholesterol (TC), low-density lipoproteins (LDL), high-density lipoproteins (HDL), triglycerides, and creatinine with subsequent calculation of glomerular filtration rate (GFR) using the CKD-EPI formula for individuals of Caucasian ethnicity.

Parameter	N=733
Male sex, %	43,37%
Mean age, years M [25; 75]	67 (58; 73)
AH, %	93,7
CKD, n/%	212/28,9
Stage 1	*109/14,9*
Stage 2	*76/10,4*
Stage 3a	*22/3,0*
Stage 3b	*5/0,7*
AF, %	12,4
DM, %	28,6
CHF, n/%	
FC I	*112/15,2*
FC II	*574/78,2*
FC III	*46/6,2*
FC IV	*1/0,1*
Smoking, %	11,8
TC, mmol/L	5,37±1,73
LDL, mmol/L	3,23±1,13
HDL, mmol/L	1,39±0,44
TG, mmol/L	1,68±1,14
Creatinine, μmol/L	133,45±29,85
Glucose, mmol/L	5,8±1,19
Hemoglobin, g/L	139,32±13,59

Table 1. *Initial clinical and laboratory characteristics of the patients*
Таблица 1. *Исходные клинико-лабораторные характеристики пациентов*

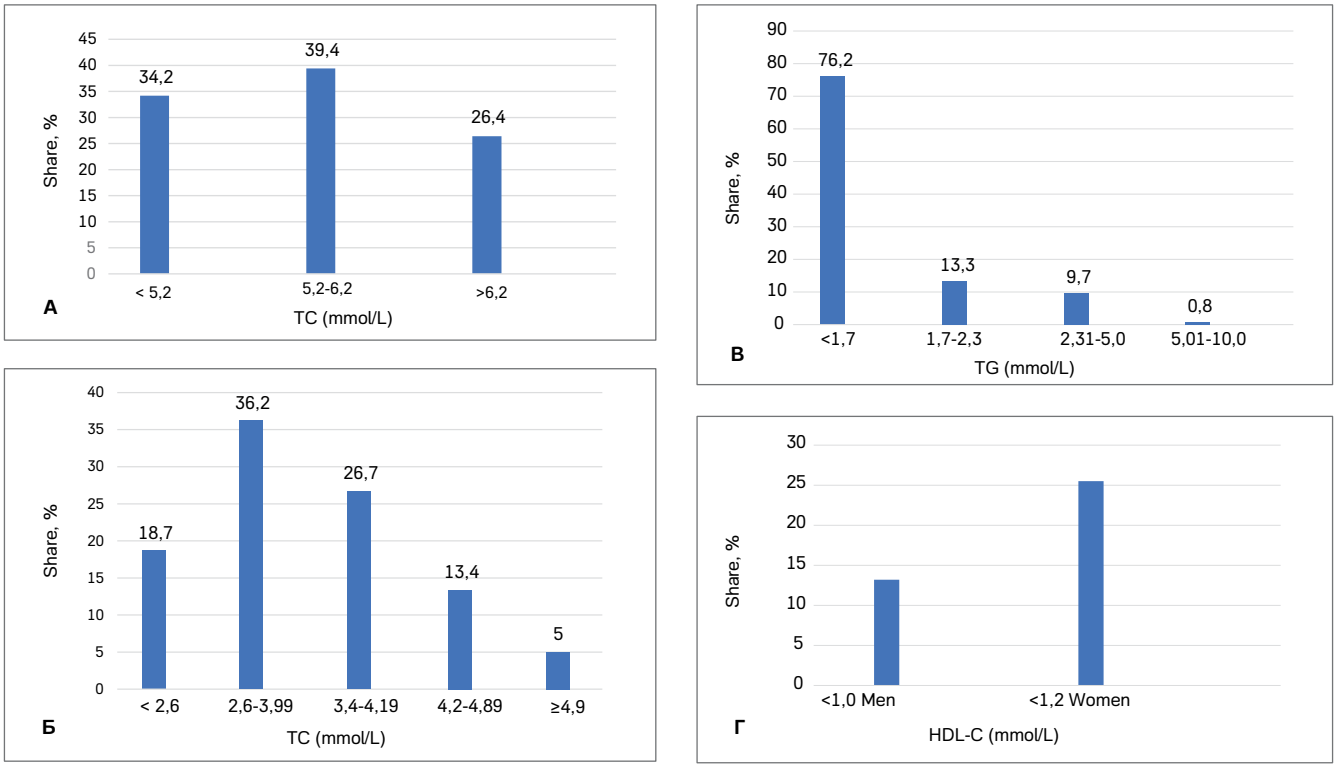

Figure 1. *Distribution of patients according to lipid profile parameters. A: total cholesterol (TC) Level; B: low-density lipoprotein cholesterol (LDL-C) level; C: triglyceride (TG) Level; D: proportion of patients with low high-density lipoprotein cholesterol (HDL-C) level.*

Рисунок 1. *Распределение пациентов по уровню показателей липидного спектра. А – по уровню ОХС; Б – по уровню ХС ЛНП; В – по уровню ТГ; Г – доля пациентов с низким уровнем ХС ЛВП.*

The obtained data was processed in SPSS Statistics 21.0. To test the normality of data distribution, Shapiro-Wilk test was used, and to test the significance of differences between groups, Student's t-test was used. To compare statistically significant differences in mean values between data groups, ANOVA was used. Differences were considered significant at $p < 0.05$.

RESULTS

The study consecutively included 733 patients (mean age: 67 (58; 73) years, 43.37% men) with suspected CHD based clinical data and/or results of stress test (bicycle ergometry). The initial data of all patients is shown in Table 1. Smoking status was determined as smoking at the time or long-term (5+ years) history of smoking. The average score on the Fagerström test was 6. Atrial fibrillation (AF) was determined as per history data and medical documents; at the moment of MSCT no paroxysms of AF were registered.

The presented patient cohort is characterized by a very high overall cardiovascular risk. It is attributed to advanced age, a high prevalence of key modifiable risk factors (arterial hypertension, dyslipidemia, and diabetes mellitus), and the

Parameter	Group 1	Группа 2 (n=217)	Группа 3 (n=169)	Группа 4 (n=129)	ANOVA
CAC, mean value	Group 2	34,45 [22,7; 59,3]	222,99 [164,1; 307,5]	966,19 [505,6; 1233,8]	<0,001
Age, years	Group 3	56,6±6,7	61,4±8,8	72,3±13,2	<0,001
Men, n/%	Group 4	84/38,7	71/42,3	77/60,4	<0,001
TC, mmol/L	ANOVA	5,46±1,57	5,31±2,19	4,93±1,56	0,852
LDL, mmol/L	3,36±1,07	3,31±1,14	3,13±1,13	2,98±1,13	0,088
HDL, mmol/L	1,42±0,44	1,38±0,36	1,37±0,5	1,37±0,49	0,534
TG, mmol/L	1,68±1,12	1,76±1,27	1,7±1,08	1,58±0,98	0,612
Creatinine, μmol/L	89±18,52	92,29±21,34	95,82±22,82	100,72±57,12	0,021
Glucose, mmol/L	6,06±2,12	6,38±2,12	6,29±1,89	7,25±3,59	0,534
Hemoglobin, g/L	140,81±14,81	139,04±17,99	139,16±17,56	138,07±18,08	0,789
Smoking, %	11,9±2,33	9,2±2,08	10,6±1,65	10,0±1,45	0,693
DM, %	24,7±1,47	26,0±2,09	25,8±1,89	27,3±2,54	0,554
Hypertension, %	95,9±2,08	92,2±3,78	93,5±3,06	93,0±2,45	0,602
AF, %	8,9±1,56	9,3±2,16	15,49±2,5	15,03±1,53	0,031

Note. Quantitative features are presented as mean values and standard deviation M±SD, p – significance of difference of parameters between patients in the studied groups in their comparison, statistically significant differences at p < 0.05.

Примечания. Количественные признаки представлены в виде среднего значения и стандартного отклонения M±SD, p – значимость отличия признаков между пациентами в исследуемых группах в сравнении, статистически достоверные различия при p < 0,05.

Table 2. *Patient baseline characteristics stratified by coronary artery calcium (CAC) score*

Таблица 2. *Исходные характеристики пациентов в зависимости от ИКК*

Total, n=733	CAC=0, n=218	CAC=1–100, n=217	CAC=101–399, n=169	CAC=400+n=129	p-value(paired comparison) ANOVA	p-значение (парное сравнение) ANOVA
below 40	23	22	1	0	0	
M	15	14	1	0	0	0,899
F	8	8	0	0	0	
40–49	63	37	17	8	1	***, #, ##
M	40	25	12	2	1	0,285
F	23	12	5	6	0	
50–59	135	55	36	25	19	*,**, #, ##
M	88	23	28	19	18	<0,001
F	47	29	8	6	4	
60–69	232	56	79	56	41	*,**,***
M	103	15	29	26	33	<0,001
F	129	41	51	30	7	
70+	280	51	83	83	63	*,**,***
M	71	8	14	24	25	<0,001
F	209	43	66	59	41	
p-value (multiple group comparison)	<0,001					

*Notes. 1. Statistically significant differences at p < 0.05, * p<0.05 as compared to the group of patients below 40 years of age, ** p<0.05 as compared to the group of patients of 40–49 years of age, *** p<0.05 as compared to the group of patients of 50–59 years of age, # p<0.05 as compared to the group of patients of 60–69 years of age, ## p<0.05 as compared to the group of patients of 70+ years of age; ANOVA - testing the hypothesis of similarity of mean values in \ groups. M – male, F – female patients.*

*Примечания. 1. Статистически достоверные различия при p < 0,05, * p<0,05 по сравнению с группой пациентов до 40 лет, ** p<0,05 по сравнению с группой пациентов 40–49 лет, *** p<0,05 по сравнению с группой пациентов 50–59 лет, # p<0,05 по сравнению с группой пациентов 60–69 лет, ## p<0,05 по сравнению с группой пациентов возраста 70+; ANOVA – для проверки гипотезы о равенстве средних значений в группах. 2. М – мужской, Ж – женский.*

Table 3. *Age and sex characteristics stratified by coronary artery calcium (CAC) score*

Таблица 3. *Половозрастные характеристики в зависимости от ИКК*

presence of target organ damage (chronic kidney disease, chronic heart failure).

The specific features of lipid metabolism disorders are shown in Fig. 1. Every third patient's TC level was below 5.2 mmol/L, LDL-C level > 3.4 mmol/L was observed in 45% (n=330) patients, triglyceride level > 1.7 mmol/L in 24% (n= 176) patients, low level of HDL-C was seen almost twice as often in women. Lipid-lowering therapy started in 41.4% of patients prior to inclusion in the study. However, none of the patients reached target levels of TC and LDL-C, thus, the efficiency of that therapy may be evaluated as insufficient and requiring adjustment.

The patients were then divided into groups depending on the CAC: 0 – no calcification (low risk of cardiovascular complications); 1–10 – low level of calcification (moderate risk); 11–100 – moderate level of calcification (increased risk); 101–400 – high level of calcification (high risk); over 400 – very high level of calcification (very high risk). The group characteristics are sown in Table 2.

CAC increased over the age of patients; at the same time, with the increasing age in the subgroups the number of male patients increased as well. Besides, with the increasing age the increase of creatinine level in the blood increased as well as the number of patients with AF. In other parameters, the groups did not differ.

For a more detailed assessment of sex and age differences on the CAC level, we studies the value in five age groups: below 40 years, 40–49 years, 50–59 years, 60–69 years, and over 70 years of age (Table 3).

In the groups below 40 years and 40–49 years of age, the CAC score did not reliably differ. In the remaining age periods, there is a statistically significant difference in the CAC score between men and women (comparison using

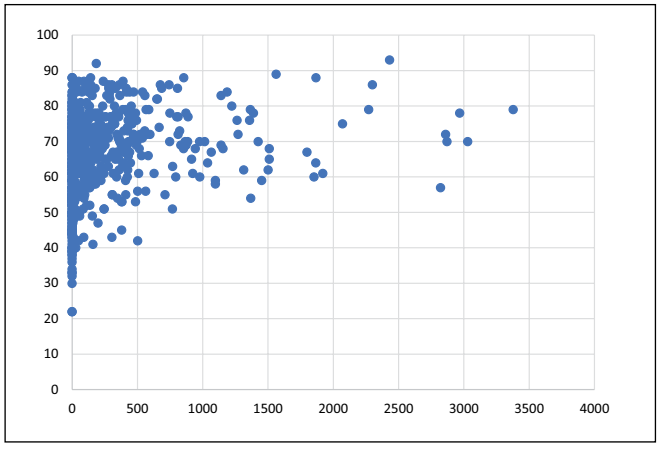

Figure 2. *Correlation between age and coronary artery calcium (CAC) score.*

Рисунок 2. *Взаимосвязь возраста с ИКК.*

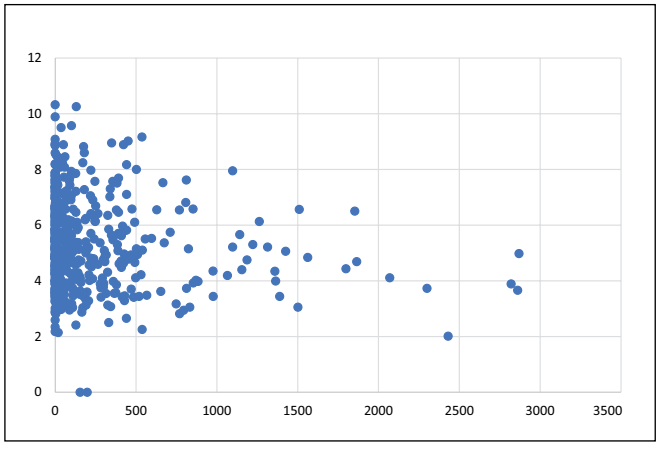

Figure 3. *Correlation between total cholesterol (TC) and coronary artery calcium (CAC) score.*

Рисунок 3. *Взаимосвязь ОХС и ИКК (r=0,64; p=0,047).*

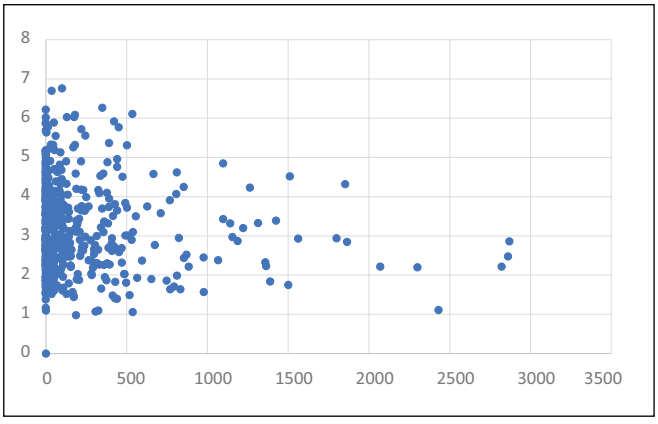

Figure 4. *Correlation between LDL-C and coronary artery calcium (CAC) score.*
Рисунок 4. *Взаимосвязь ХС ЛНП и ИКК (r=0,58; p=0,057).*

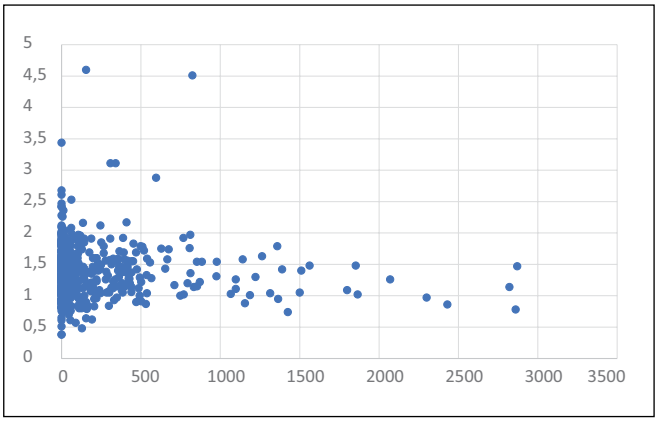

Figure 5. *Correlation between HDL-C and coronary artery calcium (CAC) score.*
Рисунок 5. *Взаимосвязь ХС ЛВП и ИКК (r=0,47; p=0,049).*

Pearson's test). On the whole, there was a high level of correlation between the age and the CAC score (Fig. 2).

The high correlation (r=0.71) indicates that age largely predetermines the "calcium burden" in the coronary arteries. However, despite the strong correlation, age is not the sole factor. CAC is also significantly influenced by sex, genetic predisposition, smoking, dyslipidemia, hypertension, and diabetes mellitus. We demonstrated that the CAC score showed a moderate to high correlation with lipid profile parameters (Fig. 3–6).

The graph shown in Fig. 3 illustrates a positive correlation between the TC level and the CAC score. The graph shows a cloud of dots demonstrating the ascending trend meaning that the growth of total cholesterol in the blood comes with the CAC score tending to increase as well. This visualizes an important pathophysiological process: the high level of cholesterol promotes development and progression of atherosclerosis, the key manifestation of which is the calcification of coronary arteries.

The graph in Fig. 4 demonstrates a moderate trend of CAC score with increasing levels of LDL-C, a trend that had not yet achieved statistical significance. This means that in the specific group of patients the strength of relation was not sufficient to reach statistical significance; however the result does not disprove the generally recognized role of LDLs in the development of atherosclerosis and calcinosis.

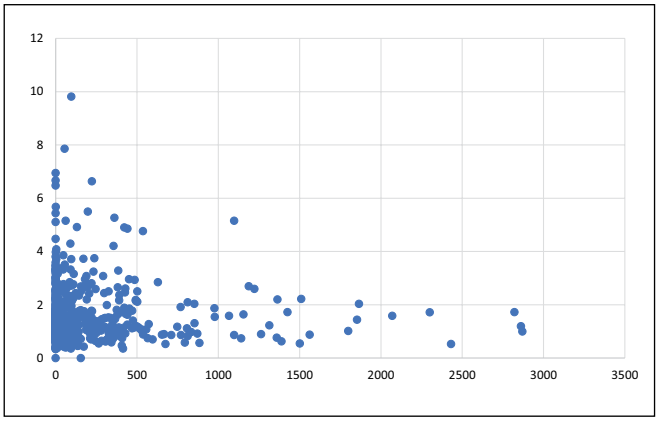

Figure 6. *Correlation between triglyceride levels (mmol/L) and coronary artery calcium (CAC) score. r=0.62 (p=0.043).*
Рисунок 6. *Взаимосвязь уровня ТГ (ммоль/л) с ИКК. r=0,62 (p=0,043).*

Graph 5 shows a statistically unstable relation between the level of HDL-C and CAC score. This is most likely explained by the influence of confounding factors (in the first place, age), not by the presence of a direct cause-and-effect relation. This finding does not deny the significant role of the HDLs but emphasizes its relation to other factors.

The result presented in Fig. 6 is clinically expected and justified. Triglycerides are not only an independent risk factor of atherosclerosis but a key component of metabolic syndrome and diabetes mellitus. The high level of TGs promotes formation of small dense particles of LDLs that are most atherogenic. The moderately high correlation (r=0.62) confirms that the TG level is an important marker associated with the burden of atherosclerosis. At the same time, this correlation does not indicate a cause-and-effect correlation; the high level of TG is most likely a part of the total negative metabolic profile that leads to artery calcification. The chart shows a moderately positive relation between the TG level and CAC score.

DISCUSSION

The CAC score may be seen as a marker of re-stratification of cardiovascular risk which, taken together with other (conventional) risk factors may increase or decrease the patient's global cardiovascular risk. We noted a clear correlation between the parameters of the lipid profile (TC, LDL-C, HDL-C, TG) and the increase of CAC score. It is important that despite the earlier initiated lipid-lowering treatment in 41.4% of patients included in the study, none has reached target values. It is well known that the used of visualization methods in the early stage (CA MSCT, ultrasonic examination of vessels) results in the patients' stronger compliance with the optimal pharmacological therapy.

In the near future, the cornerstone of CVD prevention will be a personalized approach based on assessing both traditional and individual risk factors of a particular patient. This approach will require the integration of new risk factors into traditional risk scores, as well as the use of various biological and instrumental markers that enable highly accurate and reliable stratification of the risk for developing CHD [8, 9].

In the last two decades, the prognostic value of the CAC score has been studied causing its inclusion in the national

and international recommendations for CVD prevention [10, 11]. Measurement of CAC score, according to clinical recommendations, is a promising approach to identify people with high risks and to expand the range of preventive measures [12, 13]. Among the most notable projects there are the MESA study that included 6814 patients aged 45–84 and showed that the CAC score was instrumental in predicting cardiovascular diseases independently from conventional risk factors [14].

To perform a more detailed analysis of sex and age influences on the CAC score, we performed it in five age groups. The CAC score increased with the increase of the patients' age, especially in men, and in patients with a high level of GFR and, respectively, positive status of CKD. This, the important factors influencing the development of CVDs included not only the age, but the gender as well. Besides, it follows from literature that the CAC score may have prognostic value in patients with arterial hypertension, oncological diseases, high level of sudden death, and be a predictor of development of dementia [15–17]. L.M. Severance et al. (2021) showed a correlation between the polygenic risk assessment and identification of CAC score ИКК [11].

Thus, CAC scoring is an accessible, well-reproducible, and low-cost method for the stratification and re-stratification of cardiovascular complication risk, particularly in asymptomatic patients, for the purpose of planning primary prevention measures [18]. Integrating artificial intelligence systems into the analysis and prediction process, which enables evaluative judgments based on the mathematical processing of large datasets, improves the final outcome [19, 20]. Currently, such systems are rapidly evolving, incorporating and analyzing an increasing number of prognostic factors.

Evaluation of calcination of coronary arteries may become clinically important in various stages of life. At the same time, the predictive value of CAC score in advanced age group is not yet clear: despite the high CAC scores, the patients may have no significant lesions of the coronary arteries [21–22].

CONCLUSION

CAC scoring, taken with traditional risk factors, may significantly improve early diagnostics and prevention of CHD. Our study confirms the importance of inclusion of measurement of coronary artery calcification in the standards of patient examination, including those with mild cardiovascular risk. This will enable optimization of treatment strategies and improvement of prevention measures aimed at lowering morbidity and mortality of cardiovascular diseases.

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethics approval. The study was approved by the LEC of SamSMU (protocol No.11 dated 16.12.2024).	***Этическая экспертиза.*** Проведение исследования одобрено ЛЭК СамГМУ (протокол №11 от 16 декабря 2024 г.).
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Zolotovskaya I.A., Duplyakov D.V., Rubanenko O.A.: study concept and design; critical analysis and interpretation of clinical trial data; editing of the article. Shatskaya P.R., Adonina E.V.: analysis and summary of current literature data on the topic; writing of the text. All authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Золотовская И.А., Дупляков Д.В., Рубаненко О.А. – концепция и дизайн исследования; критический анализ и интерпретация данных клинических исследований; редактирование статьи. Шацкая П.Р., Адонина Е.В. – анализ и обобщение современных литературных данных по теме; написание текста. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью или добросовестностью любой части работы.
Statement of originality. No previously published material (text, images, or data) was used in this work.	***Оригинальность.*** При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).
Data availability statement. The editorial policy regarding data sharing does not apply to this work.	***Доступ к данным.*** Редакционная политика в отношении совместного использования данных к настоящей работе не применима.
Generative AI. No generative artificial intelligence technologies were used to prepare this article.	***Генеративный искусственный интеллект.*** При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.
Provenance and peer review. This paper was submitted unsolicited and reviewed following the standard procedure. The peer review process involved 2 external reviewers.	***Рассмотрение и рецензирование.*** Настоящая работа подана в журнал в инициативном порядке и рассмотрена по обычной процедуре. В рецензировании участвовали 2 внешних рецензента.

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