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Journal of the Cardioprogress Foundation

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Journal of the «Cardioprogress» Foundation

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Editor's Welcome

Dear colleagues!

We present to your attention the next, 36th issue of the International Heart and Vascular Disease Journal that includes the leading articles, original and review articles, as well as a clinical case study.

The "leading article" section opens with the original paper by the authors from Novosibirsk. A population-based study within the framework of the World Health Organization MONICA-MOPSY project investigated sleep disturbances and sedentary lifestyle as risk factors for cardiovascular diseases. According to the authors, there is a need to study the combined effect of the above-mentioned factors on cardiovascular health.

The "Original Articles" section presents three articles. The first article identifies single-nucleotide polymorphisms of the ITGA2 integrin gene and their association with platelets in patients with arterial hypertension. For this purpose, patients were divided into three subgroups depending on the presence of coronary heart disease and diabetes mellitus. The frequency of the three ITGA2 gene genotypes varied in different patient subgroups. Further studies with a larger sample size are required. In the second article, Turkish researchers analyzed the relationship between fear of surgery and postoperative pain as well as sleep quality in patients after aorto-coronary bypass surgery. Preoperative patient education can be an effective measure to reduce the anxiety, as well as to reduce possible complications in the postoperative period. In the third original article, the open comparative prospective study involving 658 patients assessed the risk of premature cardiovascular events after COVID-19. The study group discovered that the risk of cardiovascular events was 74 % higher in individuals after COVID-19 than in a group of individuals of similar age and sex who did not have the condition. The authors draw attention to the timely correction of risk factors.

The "Review Articles" section presents the article on the effect of omega-3 polyunsaturated fatty acids on the cardiovascular system. The paper presents the key studies examining eicosopentaenoic and docosahexaenoic acids in primary and secondary prevention of CVDs, as well as describes potential mechanisms of their cardioprotective effects. Moreover, the authors evaluate recently published randomized clinical trials in the context of the existing scientific literature.

The section "Clinical case" presents the case of asymptomatic severe mitral regurgitation with the background of undifferentiated connective tissue dysplasia syndrome. In particular, a step-by-step algorithm of actions in patients' severe primary mitral regurgitation is presented considering the latest international guidelines on valve diseases.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Mekhman N. Mamedov

Editor-in-Chief

President of the "Cardioprogress" Foundation

International medical review

According to scientists, elevated levels of low-density lipoprotein (LDL) cholesterol increased the risk of myocardial infarction and ischemic stroke only in patients with signs of coronary atherosclerosis. The study included 23132 patients who were screened for coronary heart disease using coronary CT angiography. The association between LDL cholesterol levels and the incidence of myocardial infarction and ischemic stroke was assessed. The median follow-up period was 4.3 years. This study may be useful for the assessment of cardiovascular risk and further complications prevention.

According to the Circulation journal

Glimepiride can reduce cardiovascular and all-cause mortality, admissions, myocardial infarction and stroke in patients with type 2 diabetes and heart failure. The study showed that glimepiride reduced the risk of cardiovascular mortality by 66% and all-cause mortality by 53%. Researchers from Huazhong University of Science and Technology and the Chinese Academy of Sciences suggest that the protective effect of glimepiride may be explained by the increased levels of epoxyeicosatrienoic acid through inhibition of soluble epoxide hydrolase.

According to the European Journal of Preventive Cardiology

People after mild coronavirus infection had a higher risk of thrombosis than those who have never had this infection. Researchers followed 18,000 people who had coronavirus infection during the first year of pandemic and compared their health status to 34,000 people who have never had it. Those admitted with COVID-19 had a 28-fold increased chance of thrombosis, a 22-fold increased chance of heart failure, and a 17-fold increased chance of stroke.

According to the Heart journal

The risk of a significant increase of blood pressure during labor was lower in women with preeclampsia who received nifedipine. Administration of the drug reduced the likelihood of cesarean section and the need for admission of the newborn into the intensive care unit. According to the American Heart Association (AHA), a significant increase in blood pressure during pregnancy and labor increases the risk of complications, including placental detachment. At the same time, the prescription of intravenous drugs in order to reduce blood pressure causes an extreme drop in 10% of patients, which increases the occurrence of serious complications in both in mothers and the newborns.

According to the Hypertension journal

People aged over 60 can significantly reduce their risk of cardiovascular disease by walking from 6,000 to 9,000 steps a day. Scientists analyzed eight prospective studies that evaluated the effect of the number of steps walked per day on cardiovascular health. A total of 20,152 people from the United States and 42 other countries participated in the study. The average age was 63.2 years. The authors recommend that older people use step-tracking devices to assess physical activity levels, however it is also easy to track the number of steps without additional equipment.

According to the Circulation journal

The study from the University of Paris-Cité found that nitrates and nitrites, which manufacturers add to the processed meat as preservatives and pink coloring agents, do not benefit cardiovascular health. During the follow-up, authors identified 3,910 cases of hypertension and 2,075 cases of cardiovascular disease. Authors analyzed age, gender, daily energy intake, intake of alcohol, sodium, sugar, saturated fatty acids, fiber, heme iron, body mass index, physical activity level, smoking and other diseases. Scientists believe large-scale studies are needed to confirm the findings, and regulations on the use of nitrite supplements in foods should be updated.

According to the JAHA O journal

The Society for Cardiovascular Angiography and Interventions has issued an updated expert consensus statement to provide clearer guidance on what percutaneous coronary angioplasty cases can be done in outpatient settings such as ambulatory surgery centers (ASCs) and office-based laboratories and which are best left to more traditional settings, such as hospitals with full cardiac support.

PCI has evolved quickly since SCAI issued its last update almost 9 years ago. The updated statement, published online in the Journal of the Society for Cardiovascular Angiography and Interventions, notes that the proportion of same-day PCI discharges has increased from 4.5% in 2009 to 28.6% in 2017. The statement also notes that the Medicare facility fee for outpatient PCI in an ASC is about 40% less than the hospital fee.

According to the MDedge.com

The European Commission (EC) nod for the sodium-glucose cotransporter 2 (SGLT2) inhibitor follows the positive opinion of the Committee for Medicinal Products for Human Use of the European Medicines Agency in December 2022.

The committee's decision was based on the results from the DELIVER phase 3 trial, which showed clear clinical benefits of the SGLT2 inhibitor in patients with HF regardless of their left ventricular function.

The study was published last August in the New England Journal of Medicine and presented at the European Society of Cardiology's annual congress (ESC Congress 2023).

According to the theheart.org

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Sleep disturbances and physical activity as risk factors for cardiovascular diseases in an open population of Novosibirsk aged 45–64 years (WHO MONICA-MOPSY program)

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Abstract

Objective. This study aimed to assess the association between sleep disturbances and physical activity as the risk factors for cardiovascular diseases in an open population aged 45–64 years of Novosibirsk.

Materials and methods. The IVth screening of random representative sample of the population aged 45–64 years was carried out between 2003–2005 years and included 1650 participants (men (n = 576), mean age 54.23 ± 0.2 years, response rate 61 %; women (n = 1074), mean age — 54.27 ± 0.2 years, response — 72 %). Physical activity was assessed using the scale "Knowledge and attitude towards one's own health" of WHO "MONICA-Psychosocial" program. The Jenkins Sleep Evaluation Questionnaire wa s used to study sleep disorders.

Results. In an open population aged 45–64 years, 74.2 % of participants experienced sleep disturbances; 65.8 % of men (satisfactory sleep — 53.6 %, poor sleep — 12.2 %) and 78.6 % of women (satisfactory sleep — 58.9 % and poor sleep — 19.7 %) ($\chi^2 = 38.553$ df = 2; $p < 0.001$). Among men who described their sleep as "poor", 35.7 % believed that they "should exercises, but they don't" and 28.6 % "tried, but unsuccessfully" ($\chi^2 = 27.850$ df = 8; $p < 0.001$). Among women who believed that their sleep was "poor", 47.2 % answered "I should exercise, but I don't" ($\chi^2 = 26.453$ df = 8; $p < 0.001$). Men who spend their leisure time "physically passive" more often characterized their sleep as "poor" (24.3 %) than "good" (21.8 %) ($\chi^2 = 92.019$ df = 6; $p < 0,0001$). To the question: "Has your physical activity changed over the past 12 months?" 30.4 % of men and 35.3 % of women of working age answered that they became "less mobile", among them 40 % of men ($\chi^2 = 22.929$ df = 4; $p < 0.0001$) and 34.9 % of women ($\chi^2 = 58.992$ df = 4; $p < 0.0001$), believed that they had "poor" sleep. Among participants who answered to the question "How do you rate your physical activity compared to other people your age?" that they were "somewhat more passive", 7.1 % of men ($\chi^2 = 28.520$ df = 8; $p < 0.0001$), and 11.3 % of women ($\chi^2 = 90.554$ df = 8; $p < 0.0001$) had "poor" sleep.

Conclusion. The association between sleep disturbances and physical activity among men and women aged 45–64 years of Novosibirsk population was established. Considering close relationship between sleep disturbances and low physical activity, further prospects open up to investigate the combined effect of the above factors on cardiovascular health.

Keywords: sleep disturbance, physical activity, population, risk, cardiovascular disease.

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Introduction

Sleep disturbances, including chronic insomnia, are major public health issues [1]. The prevalence of sleep disorders ranges from 25 % to 48 % worldwide that indicates that these disorders are relatively common [2]. Sleep disturbances are mainly associated with chronic fatigue, impaired sustained attention and working memory, as well as reduced quality of life [3]. It is also noteworthy that numerous studies have demonstrated the association between sleep impairment and cardiovascular diseases as the leading causes of death [4].

Physical activity is one of the major factors for health maintenance [5]. Regular physical activity reduces the prevalence of cardiovascular [6], metabolic [7] and neurodegenerative disorders [8], and decreases all-cause mortality [5].

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Both insufficient sleep and low physical activity are associated with poor health outcomes, and those who are more physically active tend to have better sleep [9]. Therefore, physical activity may improve sleep quality, and vice versa sleep may lead to greater physical activity, however the direction of these relationship has not been clearly established yet [10].

Nevertheless, there is little evidence to establish optimal type or minimum level of daily physical activity that can positively affect sleep quality and provide clear guidance for public health or clinical interventions for insomnia. Given research data to date, the activity level that was recommended by the World Health Organization (WHO) in 2010 and have been included into the guidelines for promoting cardiovascular health worldwide seems to be the best candidate: 150 minutes of moderate-intensity physical activity per week that is usually mistaken for walking [11].

Therefore, this study aimed to assess the relationship between sleep disturbances and physical activity as cardiovascular risk factors in an open population aged 45–64 years in Novosibirsk.

The study has been approved by the Ethics Committee of the National Research Center for Therapy and Preventive Medicine — a branch of the Institute of Cytology and Genetics of the Russian Academy of Sciences, protocol № 1 from 14th of March, 2002, and protocol № 12 from 8th of December, 2020.

Materials and methods

The IVth population screening have been performed between 2003–2005 years and included 1650 people from Oktyabrsky district of Novosibirsk who formed random representative sample aged 45–64 years (men n = 576, mean age — 54.23 ± 0.2 years, response — 61 %; women — n = 1074, mean age — 54.27 ± 0.2 years, response — 72 %) [12]. response — 72 %). Daily physical activity was assessed using the scale "Knowledge and attitude towards one's own health". The Jenkins Sleep Evaluation Questionnaire was used to study sleep disorders and sleep duration. The scale has been validated in the course of large-scale epidemiological study carried out in the framework of the WHO MONICA program (Multinational Monitoring of Trends and Determinants of Cardiovascular Disease) and the MONICA-Psychosocial Optional Study (MOPSY) subprogram between 1988–1994 [13]. The questionnaires were filled out by the participants themselves.

Statistical analysis has been performed using the SPSS 19 software [12]. The Pearson's chi-square X^2 test has been used to assess the significance of differences between groups. The significance level was set as $p < 0.05$.

Results

In the open population aged 45–64 years, 74.2 % of participants experienced sleep disturbances: 65.8 % of men (satisfactory sleep — 53.6 %, poor sleep — 12.2 %) and 78.6 % of women (satisfactory sleep — 58.9 % and poor sleep — 19.7 %) ($x^2 = 38.553$; df = 2 $p < 0.001$) (Table 1).

Table 1. **Self-reported sleep quality in an open population aged 45–64 years old**

Sleep quality	men		women		total	
	n	%	n	%	n	%
Good sleep	197	34,2	229	21,3	426	25,8
Satisfactory sleep	309	53,6	633	58,9	942	57,1
Poor sleep	70	12,2	212	19,7	282	17,1
Total	576	100	1074	100	1650	100

Note. $\chi^2 = 38{,}553$ df = 2; $p < 0{,}001$

Among study participants aged 45–64 years, only 14 % of men and 10.3 % of women regularly exercised, and "good" sleep prevailed both among men (17.3 %) and women (15, 7 %) from this group. The most popular answer among both women (34.4 %) and men (40.8 %) was: "I should exercise, but I don't". Men who assessed their sleep as "poor" more often believed that they "should exercise, but they don't" — 35.7 %, and 28.6 % "tried, but unsuccessfully" ($\chi^2 = 27.850$ df = 8; $p < 0.001$). Among women who characterized that their sleep as "poor", the answer "I should exercise, but I don't" was more common: 47.2 % ($\chi^2 = 26.453$ df = 8; $p < 0.001$) (Table 2).

All responders were asked the question: "How do you spend your leisure time?". The majority of men (45.1 %) and women (37.1 %) answered "anything happens" and, in this category, 47.1 % of men ($\chi^2 = 29.683$ df = 6; $p < 0.0001$) and 44.3 % of women ($\chi^2 = 92.019$ df = 6; $p < 0.0001$) rated their sleep as "poor". 20.5 % of men and 17.4 % of women did not perform any physical activity during their leisure time (lying, sitting, watching TV, reading, writing, making something by hand, etc.). Men who spent their leisure time without physical activity more often had poor sleep (24.3 %) than good sleep (21.8 %) (Table 3).

To the question: "Has your physical activity changed over the past 12 months?" among people of working

Table 2. **Sleep disturbances and physical activity in an open population aged 45–64 years of Novosibirsk**

	Do you exercise (excluding daily professional activity)?	Good sleep		Satisfactory sleep		Poor sleep		Total	
		n	%	n	%	n	%	n	%
Men*	I don't need it	56	28,4	54	17,5	11	15,7	121	21,0
	I should exercise, but I don't	66	33,5	107	34,6	25	35,7	198	34,4
	I tried, but unsuccesfully	41	20,8	108	35,0	20	28,6	169	29,3
	I exersice regularly	34	17,3	37	12,0	11	15,7	82	14,2
	Physical exercises are contraindicated for me	0	0	3	1,0	3	4,3	6	1,0
	Total	197	100	309	100	70	100	576	100
Women**	I don't need it	23	10,0	51	8,1	26	12,3	100	9,3
	I should exercise, but I don't	93	40,6	245	38,7	100	47,2	438	40,8
	I tried, but unsuccesfully	71	31,0	271	42,8	62	29,2	404	37,6
	I exersice regularly	36	15,7	56	8,8	19	9,0	111	10,3
	Physical exercises are contraindicated for me	6	2,6	10	1,6	5	2,4	21	2,0
	Total	229	100	633	100	212	100	1074	100

Note. * $\chi^2 = 27{,}850$ df = 8; p < 0,001, ** $\chi^2 = 26{,}453$ df = 8; p < 0,001

Table 3. **Sleep disturbances and leisure time in an open population aged 45–64 years of Novosibirsk**

	How do you spend your leisure time?	Good sleep		Satisfactory sleep		Poor sleep		Total	
		n	%	n	%	n	%	n	%
Men*	Physically active (working in the garden, playing sports, walking, cycling, running, etc.)	50	25,4	61	19,7	19	27,1	130	22,6
	Anything happens	94	47,7	133	43,0	33	47,1	260	45,1
	Physically passive (lying, sitting, watching TV, reading, writing, making something by hand, etc.).	43	21,8	58	18,8	17	24,3	118	20,5
	I don't have leisure time	10	5,1	57	18,4	1	1,4	68	11,8
	Total	197	100	309	100	70	100	576	100
Women**	Physically active (working in the garden, playing sports, walking, cycling, running, etc.)	75	32,8	165	26,1	70	33,0	310	28,9
	Anything happens	92	40,2	212	33,5	94	44,3	398	37,1
	Physically passive (lying, sitting, watching TV, reading, writing, making something by hand, etc.).	55	24,0	94	14,8	38	17,9	187	17,4
	I don't have leisure time	7	3,1	162	25,6	10	4,7	179	16,7
	Total	229	100	633	100	212	100	1074	100

Note. * $\chi^2 = 29{,}683$ df = 6; p < 0,0001, ** $\chi^2 = 92{,}019$ df = 6; p < 0,0001

Table 4. **Sleep disturbances and physical activity in an open population aged 45–64 years of Novosibirsk**

Has your physical activity changed (total mobility, sports, etc.) over the last 12 months?		Good sleep		Satisfactory sleep		Poor sleep		Total	
		%	n	%	n	%	n	%	n
Men*	Yes, I have become more active	20	10,2	25	8,1	5	7,1	50	8,7
	It hasn't change	142	72,1	172	55,7	37	52,9	351	60,9
	I've become less active	35	17,8	112	36,2	28	40,0	175	30,4
	Total	197	100,0	309	100,0	70	100,0	576	100,0
Women**	Yes, I have become more active	38	16,6	34	5,4	7	3,3	79	7,4
	It hasn't changed	145	63,3	340	53,7	131	61,8	616	57,4
	I've become less active	46	20,1	259	40,9	74	34,9	379	35,3
	Total	229	100,0	633	100,0	212	100,0	1074	100,0

Note. * $\chi^2 = 22{,}929$ df = 4; p < 0,0001, ** $\chi^2 = 58{,}992$ df = 4; p < 0,0001

age, 30.4 % of men and 35.3 % of women answered that they have become "less mobile". Among those who answered that they have become "less mobile", 40 % of men ($\chi^2 = 22.929$ df = 4; p < 0.0001) and 34.9 % of women ($\chi^2 = 58.992$ df = 4; p < 0.0001), believed that their sleep was "poor". Only 8.7 % of men and 7.4 % of women answered that they became "more physically active", among them 10.2 % of men and 16.6 % of women had "good" sleep (Table 4).

To the question: "How do you rate your physical activity compared to other people your age?" the majority of respondents answered "the same as others" — 60.2 % of men and 53.7 % of women. Among those who believed that they were "significantly more

Table 5. **Sleep disturbances and physical activity in an open population aged 45–64 years of Novosibirsk**

	How do you rate your physical activity compared to other people your age?	Good sleep		Satisfactory sleep		Poor sleep		Total	
		n	%	n	%	n	%	n	%
Men*	Significantly more active	31	15,7	32	10,4	2	2,9	65	11,3
	Somewhat more active	49	24,9	59	19,1	18	25,7	126	21,9
	Same as others	108	54,8	199	64,4	40	57,1	347	60,2
	Somewhat more passive	9	4,6	14	4,5	5	7,1	28	4,9
	Significantly more passive	0	0	5	1,6	5	7,1	10	1,7
	Total	197	100	309	100	70	100	576	100
Women**	Significantly more active	56	24,5	44	7,0	24	11,3	124	11,5
	Somewhat more active	74	32,3	137	21,6	47	22,2	258	24,0
	Same as others	83	36,2	391	61,8	103	48,6	577	53,7
	Somewhat more passive	13	5,7	43	6,8	24	11,3	80	7,4
	Significantly more passive	3	1,3	18	2,8	14	6,6	35	3,3
	Total	229	100	633	100	212	100	1074	100

Note. * $\chi^2 = 28{,}520$ df = 8; $p < 0{,}0001$, ** $\chi^2 = 90{,}554$ df = 8; $p < 0{,}0001$

active" than others, 15.7 % of men and 24.5 % of women had good sleep. On the contrary, among men and women who answered that they were "somewhat more passive" than others, "bad" sleep prevailed both among men — 7.1 % and women — 11.3 % (men $\chi^2 = 28.520$ df = 8; $p < 0.0001$ and women $\chi^2 = 90.554$ df = 8; $p < 0.0001$) (Table 5).

Discussion

One of the promising and modern issues for epidemiological and experimental research is: does regular physical activity improve the quality of sleep? The expectation that exercise will improve sleep can be explained by traditional hypotheses that sleep is considered as energy conservation strategy and is essential for body repair or thermoregulatory functions that underpins much of the research in this area. Regular exercise can be beneficial for overall well-being, but can also cause stress [15].

Considering mentioned above background, we analyzed self-reported sleep quality and physical activity among working population aged 45–64 years old. According to our data, ⅓ of population experienced sleep disturbances. Sleep and physical activity affect each other through complex reciprocal relationship that involve various physiological and psychological mechanisms. Physical activity is usually considered beneficial for sleep; however, this association depends on several factors such as gender, age, fitness level, sleep quality and exercise characteristics (intensity, duration, time of the day, environment) [16]. In our study all the participants answered the question "Do you exercise (excluding daily professional activity)?" It turned out that only 14 % of men and 10.3 % of women regularly exercised, and they more often had "good" sleep. Men who answered "I should exercise, but I don't" or " I tried, but unsuccessfully" were more likely to rate their sleep quality as "poor". Women who rated sleep as "poor" more often believed that "they should exercise, but they don't."

WHO in 2010 followed by international healthcare systems recommended to achieve at least minimum level of 150 minutes of moderate-intensity physical activity per 5 days a week [11]. It is also significant not only to do physical exercises, but also to spend leisure time actively in order to achieve result. To the question: "How do you spend your leisure time?" — 2/3 of men and 1/3 of women answered that "anything happens", and in this category of participants "poor" sleep prevailed. Similarly, among men who spend their leisure time physically passively, "poor" sleep was the most common answer.

It is noteworthy that the change in physical activity affected the quality of sleep just in one year. About ⅓ of the men and women responded that they have become "less active" and the quality of sleep in this category decreased. On the other hand, men and women who answered that they have become "more active" also improved their sleep. In addition, men and women who felt that they have become "significantly more active" than others were more likely to rate their sleep as "good". Among those who believed that they were "somewhat less active" than people around them "poor" sleep prevailed. Thus, this study confirms that the increase of the level of physical activity improves the quality of sleep and, conversely, the decrease of physical activity leads to sleep impairment [11].

To sum up our findings, exercise can positively affect sleep. The clinical significance of this study is that exercise may represent an alternative or ad-

ditional tool to existing treatment for sleep disturbances. Moreover, physical activity can be used as preventive strategy in clinical practice to manage the first symptoms insomnia before the onset of severe chronic insomnia [17].

Conclusion

The association between sleep disturbances and physical activity in the population of Novosibirsk aged 45–64 years was established.

For the first time in the population of Novosibirsk, it has been shown that men who assessed their sleep as "poor" more often believed that "they should do exercises, but they don't," or "tried, but failed." Men with sleep disturbances more often spent their leisure time "physically passive". Among women who believe that their sleep is "poor," the most common answer was: "I should exercise, but I don't". On the other hand, those who were "significantly more active" than others, more often positively assessed their sleep.

Conflict of interest: None declared.

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Identification of single-nucleotide polymorphisms of the ITGA2 integrin gene and their association with platelets in patients with arterial hypertension

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Abstract

Arterial hypertension (AH) is one of the most socially significant pathologies associated with human nuclear genome mutations. The aim was to study the polymorphisms of the ITGA2B gene and its association with platelet parameters among Azerbaijanis with AH.

Methods. The study included 76 patients with AH (main group) and 24 patients without this pathology (control group). The main group was divided into 3 subgroups: group I — 29 patients with AH, group II — 23 patients with AH and coronary heart disease (CHD), group III — 24 patients with AH, CHD and type 2 diabetes mellitus (DM). The analysis of platelets was carried out using hematologic analyzer, the polymorphism of ITGA2 gene — using mass spectrometry (MALDI-TOF).

Results. The prevalence of C/C, T/C and T/T genotypes of the ITGA2 gene was 69.0 %, 17.2 % and 13.8 % in patients with AH; 65.2 %, 21.7 % and 13.0 % in patients with AH and CHD, respectively; 62.5 %, 29.2 % and 8.3 % in patients with AH, CHD and type 2 DM. The prevalence of the T allele among patients with AH was 31.0 %, among patients with AH and CHD — 34.8 %, and among patients with AH, CHD, and type 2 DM — 37.5 %. The highest level of platelet count (PLT), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR) were determined in group III, and the highest level of mean platelet volume (MPV) was seen in group II. The highest PLT was observed in T/T genotype carriers from group III; MPV in T/T genotype carriers from group I; PDW in T/T genotype carriers from group III; PCT in T/T genotype carriers from group III; P-LCR in T/T genotype carriers from group I.

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Conclusions. According to the results obtained, the highest level of PLT, PDW and P-LCR were detected in patients with AH, CHD and DM-2, and MPV — in patients with AH and CHD. Marked changes in platelet parameters were noted in carriers of T/T and T/C genotypes. The prevalence of the C/C, T/C, and T/T genotypes of the ITGA2 gene was 69.0%, 17.2%, and 13.8% in patients with AH; 65.2%, 21.7%, and 13.0% in patients with AH and CHD; and 62.5%, 29.2%, and 8.3% in patients with AH, CHD, and DM-2, respectively. Studies with larger samples are needed to confirm the results.

Keywords: arterial hypertension, ITGA2 gene, genotypes, allele, platelet parameters.

Conflict of interest: none declared.

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Introduction

Arterial hypertension (AH) is the leading preventable risk factor for cardiovascular diseases (CVD) and all-cause mortality worldwide [1–3]. A joint press release of the the World Health Organization (WHO) and Imperial College London noted that according to the first comprehensive global analysis of AH prevalence, the number of adults aged 30–79 years with AH has increased from 650 million to 1.28 billion over the past thirty years [4].

AH is caused by a complex interaction of environmental and pathophysiological factors, as well as genetic predisposition. Evidence of the genetic basis of AH provides valuable information on the regulation of blood pressure (BP). Over 100 single nucleotide polymorphisms (SNP — Single Nucleotide Polymorphism) associated with BP phenotypes have been identified based on genome-wide association studies (GWAS)) [5]. AH is one of the most socially significant pathologies associated with mutations in the human nuclear genome. Identification of genes associated with this disease will provide a mechanism for classification of hypertensive phenotypes, will allow the creation of diagnostic markers for individual patients and families who are at highest risk of complications such as atherosclerosis, stroke, coronary heart disease (CHD), myocardial infarction. Platelet aggregation plays the main role in the pathogenesis of acute thrombosis in patients with CHD, stroke and peripheral arterial disease [3].

Integrin alfa-2 gene (ITGA2B) is a receptor for fibronectin, fibrinogen, plasminogen, prothrombin, thrombospondin and vitronectin and participates in platelet activation [5, 6]. Platelets are key components of blood that play a physiological role in the initiation of endogenous hemostasis and effective endothelial repair after vascular damage. The key functions of platelets, such as adhesion, activation, aggregation and interaction with clotting factors, work in the context of a complex and balanced interaction of receptors and mediators that provide control of this process and its targeted effect on sites of vascular damage [7].

Current data suggest that several genetic polymorphisms of ITGA2B are associated with wide range of clinical events, including stroke and antiplatelet drugs resistance [8, 9]. In addition, various mutations of this gene have been found to result in loss of aggregation ability and immune response production.

The aim of this study was to investigate the polymorphisms of the ITGA2B gene and its association with platelet parameters in Azerbaijan residents with AH.

Materials

The study included 76 patients with AH (main group) and 24 patients without this pathology (control group).

Inclusion criteria: age from 32 to 77 years; patients of both sexes; patients with AH, CHD, and type 2 diabetes mellitus (type 2 DM).

Exclusion criteria: patients younger than 20 years and older than 80 years, pregnancy, congenital heart disease, congenital and acquired beeding disorders, patients with cancer, patients receiving chemotherapy, and patients with mental disorders.

Patients who took part in the study were informed about the purpose of the study and signed written in-

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Table 1. **Demographical characteristics of the study groups**

Parameters	I group (n = 29)	II group (n = 23)	III group (n = 24)	Control group (n = 24)	p
Mean age, years	50,62 ± 8,55	58,30 ± 7,59	59,21 ± 4,62	45,87 ± 8,35	> 0,05
Male, n (%)	19 (65,5)	17 (73,9)	15 (62,5)	15 (62,5)	> 0,05
Female, n (%)	10 (34,5)	6 (26,1)	9 (37,5)	9 (37,5)	> 0,05
BMI, kg/m^2	30,49 ± 3,72	29,66 ± 3,80	31,44 ± 3,33	28,08 ± 2,76	> 0,05
SBP, mmHg	148,97 ± 14,86	139,78 ± 15,48	144,88 ± 18,45	119,58 ± 6,42	> 0,05
DBP, mmHg	93,08 ± 11,06	85,65 ± 11,98	85,46 ± 13,0	76,75 ± 5,21	> 0,05

Note. p — statistical significance of differences between study groups.

formed consent in order to participate in the study. The study procedure followed the principles of the Helsinki Declaration. The examination of patients was performed according to the practice guidelines of the International Society of Hypertension 2020. [10]. The study was approved by the Ethics Committee of the Azerbaijan State Institute of Advanced Medical Education named after A.Aliyev on 5th of May, 2019, protocol № 4.

The main group and the control group included patients aged 32 to 77 years and 26 to 61 years, respectively. The main group was divided into 3 clinical groups depending on the presence of CHD and DM: Group I included 29 patients with AH, Group II included 23 patients with AH and CHD, and Group III included 24 patients with a combination of AH with CHD and DM-2. The control group consisted of patients without these diseases.

All patients underwent complete blood count, blood pressure measurement (systolic BP/diastolic BP), body mass index (BMI) was calculated according to the following formula:

$$BMI = \frac{\text{weight } (kg)}{\text{height } (m^2)}$$

Platelets were examined using the Quintus hematology analyzer (Sweden) and Swelab Alfa Standard (Sweden) using control and calibration reagents. The venous blood sample placed in the tube containing anticoagulant K-EDTA. Blood test was performed on an empty stomach. The following platelet parameters were determined using hematology analyzer: PLT (10^9/L) — platelet count (impedance method), PDW (%) — platelet distribution width, MPV (fl-femtoliters) — mean platelet volume, P-LCR — platelet-large cell (over 12 fl) to total platelet volume ratio, PCT (%) — plateletcrit. ITGA2 gene polymorphism was determined by mass spectrometry (MALDI-TOF) using Seguenon mass spectrometer (USA). The material for the study was whole blood.

Statistical processing of the results and construction of tables and graphs was performed using Microsoft Office Excel, Statistica 16.0 software using standard methods of variation statistics. The mean value and mean deviation were calculated. Frequency of individual genotypes was determined as the percentage of individuals to the total number of those examined. Differences between qualitative parameters were determined by the x^2 test, and differences between quantitative parameters were determined by the T-criterion. The level of significance for all tests was set as $p < 0.05$.

Results

Groups did not differ significantly by age and gender (Table 1).

Table 1 demonstrates that the BMI was slightly higher in the control group compared with other groups. SBP and DBP were 19.7 % and 17.5 %, 14.4 % and 10.4 %, 17.5 % and 10.2 % higher in groups I, II and III, respectively, compared to the control group.

Analysis of the polymorphism of the integrin ITGA2 gene indicated the prevalence of the normal homozygous C/C genotype in all study groups (Fig. 1).

As follows from figure 1, the distribution of the C/C genotypes of the ITGA2 integrin polymorphism did not differ significantly between the clinical groups despite prevalence of normal homozygous C/C genotype in all study groups There was no significant difference between the frequency of C/C genotype in patients from group I ($\chi^2 = 1.974$, $p = 0.160$), group II ($\chi^2 = 1.113$, $p = 0.292$) and group III ($\chi^2 = 0.752$, $p = 0.383$) and the control group. There was also no significant difference in the frequency of this genotype between clinical groups ($p > 0.05$).

There were no significant differences in the frequency of heterozygous mutant genotype T/C and homozygous mutant genotype T/T genotypes between patients from groups I, II, and III and controls, as well as between clinical groups ($p > 0.05$). The prevalence

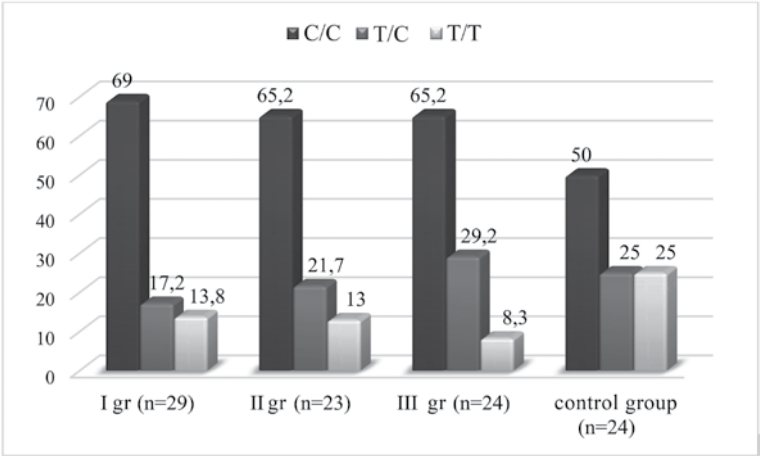

Fig. 1. Distribution of ITGA2 gene genotypes between study groups

of the T allele in group I was 31.0%, and in groups II and III — 34.8% and 37.5%, respectively.

The platelet parameters of the clinical groups are shown in Table 2.

Platelet parameters did not differ significantly between the clinical groups and the control group, as well as between the clinical groups. The data in Table 2 show that the highest platelet count (PLT), platelet distribution width (PDW) and platelet-large cell ratio (P-LCR) were determined in group III, the mean platelet volume (MPV) — in group II patients.

When determining the platelet parameters in patients with different genotypes, the highest PLT was observed in the carriers of homozygous mutant T/T genotype in group III (t = 1,05, p > 0,05 compared with the control group), the lowest — in the carriers of heterozygous mutant T/C genotype in group II (t = 0.99, p > 0.05 compared with the control group) and in the carriers of homozygous mutant T/T genotype in group I (t = 1.74, p > 0.05 compared with the control group) (Table 3).

Table 3 shows that the highest MPV (mean platelet volume) was in the homozygous mutant T/T genotype carriers in group I (t = 1.03, p > 0.05 compared with the control group), the lowest MPV was in group III patients with this genotype (t = 0.32, p > 0.05 com-

Table 2. **Platelet parameters in the study groups**

Parameter	I group (n = 29)	II group (n = 23)	III group (n = 24)	Control group (n = 24)	p
PLT, 109/l	188,95 ± 35,52	205,09 ± 45,41	213,42 ± 39,21	201,71 ± 29,66	> 0,05
MPV, fl	8,38 ± 0,71	8,44 ± 0,65	7,94 ± 1,23	8,14 ± 1,28	> 0,05
PDWsd, fl	12,22 ± 2,97	11,54 ± 2,05	12,65 ± 2,61	11,46 ± 1,74	> 0,05
PCT, %	0,15 ± 0,03	0,16 ± 0,04	0,16 ± 0,04	0,16 ± 0,03	> 0,05
P-LCR	18,71 ± 5,30	17,79 ± 4,60	19,56 ± 4,79	18,16 ± 4,62	> 0,05

Table 3. **Platelet parameters in study groups with various ITGA2 polymorphisms**

ITGA2 genotype	Groups	PLT, 109/l	MPV, fl	PDWsd, fl	PCT, %	P-LCR
C/C	I (n = 20)	190,72 ± 29,60	8,19 ± 0,61	11,73 ± 2,59	0,15 ± 0,03	16,64 ± 4,67
	II (n = 15)	224,47 ± 48,83	8,37 ± 0,78	12,17 ± 2,61	0,17 ± 0,04	18,59 ± 5,52
	III (n = 15)	211,87 ± 38,81	8,07 ± 1,18	12,66 ± 2,47	0,17 ± 0,04	20,03 ± 5,02
	Control group (n = 12)	204,83 ± 38,44	8,0 ± 1,68	12,2 ± 1,88	0,16 ± 0,05	19,95 ± 4,81
T/C	I (n = 5)	205,0 ± 66,4	8,56 ± 0,68	14,92 ± 4,86	0,16 ± 0,04	23,97 ± 5,72
	II (n = 5)	159,4 ± 22,08	8,54 ± 0,17	10,36 ± 0,25	0,13 ± 0,02	16,52 ± 0,94
	III (n = 7)	205,86 ± 41,31	7,77 ± 1,43	12,26 ± 2,46	0,15 ± 0,04	18,39 ± 3,62
	Control group (n = 6)	185,17 ± 15,17	8,53 ± 0,49	10,12 ± 0,65	0,15 ± 0,01	15,88 ± 3,39
T/T	I (n = 4)	160,0 ± 17,0	9,28 ± 0,32	11,3 ± 0,55	0,14 ± 0,01	21,92 ± 2,22
	II (n = 3)	184,33 ± 18,22	8,57 ± 0,82	10,37 ± 1,15	0,16 ± 0,03	16,13 ± 5,84
	III (n = 2)	251,5 ± 28,5	7,55 ± 0,95	13,95 ± 3,95	0,18 ± 0,01	20,10 ± 5,20
	Control group (n = 6)	212,0 ± 24,67	8,03 ± 1,17	11,32 ± 1,88	0,17 ± 0,03	16,85 ± 5,29

pared with the control group) and heterozygous mutant T/C genotype carriers (t = 0.50, p > 0.05 compared with the control group). The maximum level of platelet distribution width (PDW) was determined in the carriers of homozygous mutant T/T genotype in group III (t = 0.60, p > 0.05 compared with the control group), the minimum level was in the patients carrying heterozygous mutant T/C genotype (t = 0.34, p > 0.05 compared with the control index) and homozygous genotype T/T in group II (t = 0.43, p > 0.05). The highest value of plateletcrit (PCT) among homozygous T/T genotype carriers was observed in group III (t = 0.32, p > 0.05 compared with the control group), the lowest value was observed among heterozygous T/C genotype carriers in group II (t = 0.89, p > 0.05 compared with the control group). The highest platelet large cell ratio (P-LCR) was detected in heterozygous T/C genotype carriers in group I (t = 1.22, p > 0.05 versus control group), the lowest P-LCR was detected in homozygous T/T genotype carriers in group II (t = 0.09, p > 0.05 versus control group).

Discussion

In recent decades, the genomics of cardiovascular diseases (CVDs) has attracted increasing interest: it has become possible to identify polymorphic genes responsible for predisposition to CVDs, including CHD. It is known that integrins are adhesion molecules that promote platelet aggregation, leading to clot formation [11]. Discovery of integrins has been going on for a long time, and the knowledge in this field is constantly expanding.

We genotyped ITGA2 in patients with AH (group I), patients with AH and CHD (group II) and patients with AH, CHD and DM-2 (group III). According to the results obtained, carriers of the normal homozygous C/C genotype and carriers of the mutant homozygous T/T genotype were more frequent in all groups. Our results slightly differ from those of Shishkina E.A. et al. [11], who identified heterozygous mutant C/T genotype and homozygous mutant T/T, carriage of the T allele of the ITGA2 gene, among patients with AH in 61.7% of cases.

The T allele of the C807T polymorphic marker of the ITGA2 gene (rs 1126643) is associated with increased expression of platelet GPIa-receptors and increased platelet adhesion to collagen [12]. Adhesion molecules are glycoproteins that can mediate interactions between cells or between cells and the extracellular matrix. These proteins can help leukocytes and platelets to adhere to the vascular endothelium, thus contributing to the formation of cerebral atherosclerotic plaques [12]. The literature presents data on the association of the T allele with increased platelet adhesion rate [13].

It is known that platelets are cytoplasmic fragments of bone marrow megakaryocytes 3–5 μm in diameter and 4.5–11 femtoliters in volume. We determined platelet parameters in patients carrying ITGA2 genotypes. Platelet indices can be considered as promising diagnostic and prognostic markers for thrombotic complications [14]. The measurements were: platelet count (PLT — platelet count); mean platelet volume (MPV); platelet distribution width (PDW); plateletcrit (PCT); platelets large cell ratio (P-LCR). Platelet parameters in patients in the clinical groups differed from those in the control group, but the changes were statistically insignificant (p > 0.05).

Platelets with high hemostatic activity play a pivotal role in the pathophysiology of CHD, and mean platelet volume (MPV) has been proposed as an indicator of platelet reactivity. There are data on the association of high MPV with CHD [15]. According to our data, the maximum MPV level was detected in patients with AH, carriers of mutant homozygous T/T genotype. Patients with AH and CHD had the maximum elevated MPV compared with other clinical groups and the controls. It has been reported that platelet volume parameters (PVP), such as mean platelet volume (MPV), platelet distribution width (PDW) and platelet-to-large cell ratio (P-LCR), may be elevated in patients with acute coronary syndrome, which may be due to larger platelets containing more proaggregating mediators and representing more expanded functions [16]. Researchers suggest that platelets are not only involved in coronary artery thrombosis, but also contribute to atherosclerosis and endothelial damage by secreting mediators during CHD development [17, 18]. It is also noteworthy that platelet parameters, markers of platelet activation, are parameters obtained daily as part of automatic blood analysis.

PDW, also known as an indicator of platelet diversity, increases in CVD as a result of platelet activation [19]. The results of comparative analysis presented in the literature are confirmed by the revealed positive correlation between the presence of CHD and PLT and negative correlation with PDW and P-LCR [20].

Our results indicated an increased level of PLT in mutant homozygous T/T genotype carriers suffering from AH combined with CHD and type 2 diabetes mellitus.

The data studied in the present study are the subject for research due to the key role of platelets in hemostasis, inflammation, protection against pathogens, wound healing and angiogenesis.

Conclusion

According to the results obtained, elevated PLT, PDW, and P-LCR parameters were detected in patients with AH, CHD, and type 2 diabetes mellitus, and a high MPV level was found in patients with AH and CHD.

The prevalence of the normal homozygous C/C, mutant heterozygous T/C, and mutant homozygous T/T genotypes of the ITGA2 gene was 69.0%, 17.2%, and 13.8% in AH patients; 65.2%, 21.7%, and 13.0% in patients with AH and CHD; and 62.5%, 29.2%, and 8.3% in those with AH, CHD, and type 2 DM, respectively. The prevalence of the T allele among patients with AH was 31.0%, among patients with AH and CHD — 34.8%, and among patients with AH, CHD, and type 2 diabetes — 37.5%. Platelet parameters, PLT, PDW, and PCT in particular, tended to be higher among patients with AH, CHD, and type 2 DM and mutant homozygous T/T genotype carriers ($p > 0.05$). elatively high MPV level was observed among mutant homozygous T/T genotype carriers with AH ($p > 0.05$), P-LCR — among mutant heterozygous T/C genotype carriers with AH. However, differences were not statistically significant ($p > 0.05$). Studies with larger samples are needed to confirm the results.

Conflict of interest. None declared.

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Relationship Between Surgical Fear Level and Postoperative Pain and Sleep Quality in Coronary Artery Bypass Graft Patients

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Abstract

Objective. This study aimed to investigate the relationship between surgical fear level and postoperative pain and sleep quality in patients undergoing coronary artery bypass graft (CABG) surgery.

Methods. The study was conducted with 70 patients. The data for the descriptive and cross-sectional study were collected using the Surgical Fear Questionnaire (SFQ), Anxiety Specific to Surgery Questionnaire (ASSQ), Richard-Campbell Sleep Questionnaire (RCSQ), and Visual Analog Scale (VAS).

Results. The average age of participants was 65.23 ± 8.39; 65.7% of them were males. Female patients had significantly higher ASSQ total scores than male patients ($p < 0.05$). A statistically significant positive correlation was found between the surgical fear and anxiety levels of the patients prior to CABG surgery and postoperative pain and sleep quality ($p < 0.05$).

Conclusion. Preoperative fear and anxiety were determined to be effective factors in the severity of pain and sleep quality during the postoperative period. it is considered that the training to be provided to the patients during the preoperative period may be effective in reducing the fear and anxiety of the patients and reducing the possible complications in the postoperative period.

Keywords: coronary artery bypass graft (CABG), surgical fear, preoperative anxiety, postoperative symptoms.

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Introduction

CABG is a standard procedure in cardiac surgery and is among the most commonly performed surgeries in the world [1, 2]. However, much as these surgeries are routine procedures, they create fear and anxiety for patients [3,4]. Anxiety and fear are two terms that are not the same while they are similar. Although fear is a response to a particular threat to protect oneself, anxiety is an unconscious response to a threat, generally unknown or based on internal conflict [5, 6]. Surgical fear and anxiety start when the patient is told that he or she should have surgery and increase gradually with the hospitalization process [7, 8]. The level of fear and anxiety of each patient is based on numerous factors, such as the patient's sensitivity, age, gender, previous experience with the surgery, education level, type and extent of the proposed surgery, current health status, and socioeconomic status [9, 10].

Numerous patients awaiting surgery know the fact that this fear and anxiety prior to surgery is normal [11, 12]. However, if the patient experiences excessive and prolonged fear and anxiety, the body's autonomic nervous system is stimulated leading to an increase in the neuroendocrine stress response [13, 14]. As a result, this situation leads to more anesthetic substance employment throughout the operation, more pain in the postoperative period, and accordingly more analgesic requirement, gastrointestinal (such as nausea, vomiting), cardiac (such as tachycardia) and insomnia issues, life quality are being affected, prolongation of the hospital stay increase in the costs [15-17].

Fear and anxiety felt prior to surgery have some postoperative complications on the patient [18,19]. Pain is one of the common complications observed in patients subsequent to CABG surgery [20]. Due to the stress response developed as a result of the anxiety experienced by the patients prior to surgery, their pain complaints and analgesic needs to increase accordingly [21, 22]. Furthermore, increased pain level also increases anxiety, stress response intensifies, and this situation leads to a vicious cycle [23].

The patient should be allowed to ask questions and express concerns regarding pain in order to reduce anxiety and fear. Numerous postoperative factors are related to the development of sleep disorders. Among these, pain is probably the most important one [24, 25]. Hence, management of pain is also significant in terms of ensuring sleep quality in patients. Studies conducted to reveal the fact that the sleep cycle is also disrupted in individuals who experience fear and anxiety prior to the surgical procedure [25].

It is very significant to reduce the fear and anxiety experienced prior to a surgical procedure such as CABG, which changes the lifestyle and affects the quality of life of the patient. It is important to determine the surgical fear and anxiety levels of the patients, to consider the reaction to this situation in the patients who are planning for surgery, and to prevent issues such as pain and insomnia that may develop after surgery.

When we examine the literature, we find that there are a limited number of studies examining the effects of preoperative anxiety and fear on the symptoms observed in the postoperative period. This study was considered necessary to carry out based on this aspect.

Research questions

- Do the descriptive characteristics of patients who are scheduled for CABG surgery affect their fear and anxiety levels?
- Does the level of fear and anxiety felt by the patients who are scheduled for CABG surgery prior to the surgery negatively affect the postoperative period?
- Do patients fear and anxiety prior to CABG surgery affect the level of pain and sleep quality subsequent to surgery?
- Is there a relationship between pain and sleep quality subsequent to CABG surgery?

Matherials and methods

Design and study participants

The population of the study included 90 patients scheduled for CABG surgery in the cardiovascular surgery service of a university hospital in eastern Turkey. The sample included the patients who accepted to participate in the study, met the inclusion criteria, and whose verbal/written consent was obtained. Due to not meeting the eligibility criteria, 20 patients were excluded from the study. The study was carried out with 70 patients (Fig. 1).

Eligibility criteria

Patients over 18 years of age who were scheduled for CABG surgery without communication problems,

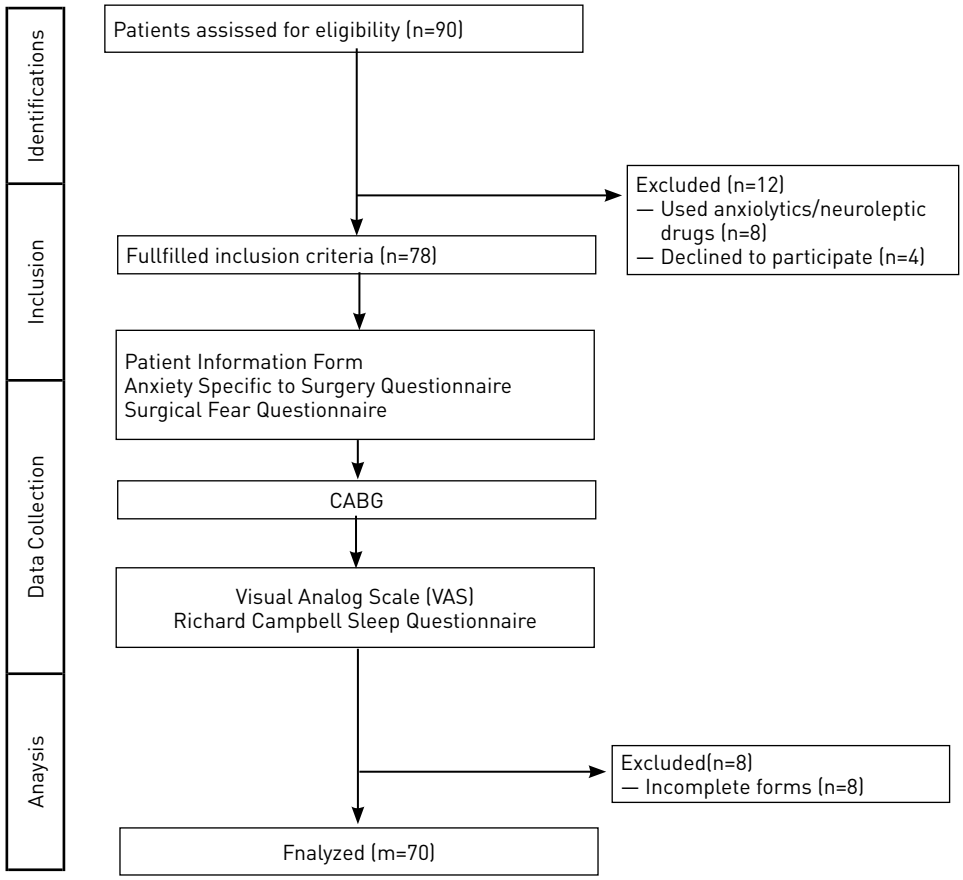

Figure 1. Study flow

psychiatric illness, severe cognitive impairments, and anxiolytic and/or antidepressant use were included in the study.

Data collection

The data of the study were collected through face-to-face interviews with the patients by using the "Patient Information Form," "Surgical Fear Questionnaire (SFQ)", "Anxiety Specific to Surgery Questionnaire (ASSQ)", and "Visual Analog Scale (VAS)". The Patient Information Form was filled in by the patients on the day of admittance to the clinic. SFQ and ASSQ scales were completed before coronary bypass graft surgery. VAS was filled within three days after the patients were post-operatively transferred from the intensive care unit.

Data collection tools

Patient Information Form. It consists of 9 questions aimed at evaluating the socio-demographic characteristics such as age, gender, and education level of the patients, as well as the properties related to the disease and postoperative period used. Data were obtained on the day of the patient's admittance to the clinic.

Surgical Fear Questionnaire (SFQ)

This questionnaire was developed by Theunissen et al in 2014 to determine the level of fear that patients about to undergo elective surgery have because of the short- and long-term outcomes of the surgical procedure. The questionnaire includes eight items, which are scored between 0 and 10, with a score of 0 indicating not afraid at all and a score of 10 indicating very afraid. The scale has two subscales, each containing four items related to the cause of fear. Items 1 through 4 assess anxiety about the short-term consequences of surgery, whereas items 5 through 8 assess anxiety about the long-term consequences of surgery. The minimum and maximum total scores are 0 and 80, respectively. A high score indicates a high level of fear about surgery [26].

Anxiety Specific to Surgery Questionnaire (ASSQ)

The Anxiety Specific to Surgery Questionnaire was first developed by Karancı and Dirik in 2003 to determine the level of anxiety in patients scheduled to have urgent surgery. The scale was on 5-point Likert-type including 10 questions related to the worries/anxiety

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patients were possible to experience about the surgery. For the assessment related to the scale, the total score obtained by summing the responses given to all items (1 point: I totally disagree, 5 points: I totally agree) was used. Only item 8 including the statement "I think I will get rid of all my pain and distress after the surgery" was scored coding reversely. High scores in scoring the scale indicated anxiety about feeling pain, death during surgery, and postoperative complications and restrictions. Dirik & Karancı determined the Cronbach Alpha Coefficient of the scale as 0.79. [27].

Visual Analog Scale (VAS)

It was a scale with a scoring system indicating "no pain" on one side and "worst possible pain" on the other. It was a one-dimensional scale that was frequently used in clinics, and its reliability and sensitivity were high. The values ranged from 0 to 10. "No pain" was defined as "0 points" and "worst possible pain" was defined as "10 points". It could be used horizontally and vertically, but it was stated by the patients that the level of understanding was better when it was vertical [28].

Richard Campbell Sleep Questionnaire (RCSQ)

Sleep quality was assessed using the Richard Campbell Sleep Questionnaire (RCSQ). The questionnaire consists of five items, each of which has a visual scale of 0–100, and the participant reports sleep sensations during this interval. Depth of sleep, ease of falling asleep, frequency of waking, ease of falling back asleep, and subjective sleep quality are the domains. The overall quality of sleep is calculated using an average score of 5 items. A score of zero represents the worst quality of sleep and a score of 100 represents the best quality of sleep.

Statistical analysis

Analysis of the research data was performed by using descriptive statistics with the SPSS version 23.0 (IBMCorp) package program. The values related to the demographic characteristics of the patients, disease, and surgery process were indicated as a number, percentage, average, and standard deviation. The nonparametric Mann–Whitney U and Kruskal–Wallis H tests were used in the comparison of the groups without normal distribution. Spearman correlation analysis was performed to analyze the relationship between two numerical variables.

Ethical principles of the study

This study was carried out in accordance with the principles of the World Medical Association Declaration of Helsinki. The ethical approval required for this study to be carried out was obtained from the University's Clinical Research Ethics Committee. The participants were ensured to have the right to refuse to participate in the study and all information received would be kept confidential.

Results

Distribution of patients by personal and clinical characteristics

The average age of the patients participating in the study was 65.23 ± 8.39 years. Of all patients, 65.7% were male, 97.1% were married, 60% were primary school graduates, and almost all of them had health insurance (Table 1).

Table 1. **Descriptive characteristics of patients**

	N (70)	Percentage %
Age (X ± SD 65.23 ± 8.39)		
Gender		
Female	24	34.3
Male	46	65.7
Marital Status		
Married	68	97.1
Single	2	2.9
Educational Status		
Literate	8	11.4
Primary	42	60
High School	18	25.7
Graduate	2	2.9
Postgraduate	—	—
Health Insurance		
Available	64	91.4
Not available	6	8.6
Income Status		
Income less than expenses	2	2.9
Equal income and expenses	65	92.9
Income more than expenses	3	4.3
Smoking		
Yes	20	28.6
No	50	71.6

When the properties of the patients related to the disease and surgical process were evaluated, it was

Table 2. **Distribution of patients clinical characteristics**

		N	%
Presence of chronic disease	Yes	19	27.1
	No	51	72.9
Chronic diseases *	HT	8	42.1
	DM	5	26.3
	DM + HT	6	31.6
Previous surgery	Yes	4	5.7
	No	66	94.3
Cardiac disease history in the family	Yes	4	5.7
	No	66	94.3
The postoperative day when the patient was evaluated	x ± Ss	3.41 ± 1.62	
Length of stay in the intensive care unit	x ± Ss	2.43 ± 0.65	
Day of postoperative discharge	x ± Ss	7.29 ± 1.20	
Problems observed postoperatively*			
Respiratory distress		6	21.4
Gradual increase at tenderness and pain at the wound site		2	7.14
Fever		2	7.14
Abdominal pain diarrhea/constipation		4	14.2
Clouding of consciousness		–	–
Nausea vomiting		8	28.5
Chest pain		4	14.2
Redness and swelling beyond the wound edges		2	7.14

Note. *More than one answer was given.
Abbreviations: DM: Diabetes Mellitus; HT: Hypertension

determined that 27.1 % (n = 19) had a chronic disease and 42.1 % of the patients with chronic disease had hypertension. 94.3 % (n = 66) had no previous surgery, and 94.3 % (n = 66) were found not to have a family member with cardiac disease. The patients were evaluated on average at 3.41 ± 1.62 after surgery. The patients who stayed in the intensive care unit for an average of 2.43 ± 0.65 days were determined to be discharged from the hospital in the postoperative average of 7.29 ± 1.20 days. The frequently encountered problems for the patients evaluated during the postoperative period during the stay in the intensive care unit and service were nausea-vomiting (28.5 %, n = 8), respiratory distress (21.4 %, n = 6), and abdominal pain (14.2 %, n = 4), respectively (multiple responses were given) (Table 2).

Descriptive statistics related to the scales

It was determined in terms of the preoperative period that the average ASSQ score of the patients was 32.7 ± 10.5, and in the postoperative period, the average pain level was 4.17 ± 2.27, and pain at a moderate level was experienced. The distribution of the total mean scores of the SFQ subscales was as follows: SFQ-S (13.1 ± 10.2); SFQ-L (13.1 ± 10.8). The patients' mean score on the SFQ was 26.2 ± 20.8. After the CABG surgery, the total RCSQ score was 306.5 ± 117.4. The patients' mean scores for sleep depth, sleep latency, awakenings, returning to sleep, sleep quality, and the noise level was 60.1 ± 23.1, 61.8 ± 24.1, 61.2 ± 24.1, 62.7 ± 24.1, 60.5 ± 25.5, 60.3 ± 27.0, respectively (Table 3).

Comparing scale score averages according to the demographic properties of the patients

Whereas there was no statistically significant difference between the gender groups in terms of SFQ and RCSQ score averages ($p > 0.05$), a statistically significant difference was determined in terms of the average scores of ASSQ ($p < 0.05$). Accordingly, the anxiety levels of females were higher rather than males ($p < 0.05$). No statistically significant difference was specified between marital status, smoking, presence of chronic disease, previous surgery, cardiac disease history in the family, and age in terms of SFQ and ASSQ average scores ($p > 0.05$) (Tab. 4). A statistically significant difference was found between the presence of chronic disease in terms of RCSQ scores.

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Table 3. **Descriptive statistics related to the scales**

	X ± SD	min-max.
VAS	4.17 ± 2.27	0–10
ASSQ	32.7 ± 10.5	10–50
SFQ		
Subdimensions of the Scale		
SFQ-S	13.1 ± 10.2	0–40
SFQ-L	13.1 ± 10.8	0–40
Total Score	26.2 ± 20.8	0–80
RCSQ		
Subdimensions of the Scale		
Sleep depth	60.1 ± 23.1	0–100
Falling asleep	61.8 ± 24.1	0–100
Frequency of awakening	61.2 ± 24.1	0–100
Percentage of time awake	62.7 ± 24.1	0–100
Quality of sleep	60.5 ± 25.5	0–100
Noise	60.3 ± 27.0	0–100
Total Score	306.5 ± 117.4	0–500

Note. Abbreviations: VAS: Visual Analog Scale, ASSQ: Anxiety Specific to Surgery Questionnaire SFQ-S: Surgical Fear Questionnaire: — short term; SFQ-L: Surgical Fear Questionnaire: long term; RCSQ: Richard-Campbell Sleep Questionnaire

Accordingly, the sleep quality of patients with chronic disease was significantly lower compared to those without.

As a result of the Spearman correlation analysis performed to determine whether there was a relationship between the scales used in the study, it was determined that there was a statistically significant positive correlation between surgical fear levels of the patients before CABG surgery and the level of postoperative pain ($p < 0.01$), while a negative correlation was found between postoperative RCSQ score ($p < 0.01$) (Tab. 5).

Similarly; it was determined that there was a statistically significant positive correlation between anxiety levels of the patients before CABG surgery and the level of postoperative pain ($p < 0.01$), while a negative correlation was found between postoperative RCSQ scores ($p < 0.01$) (Tab. 6).

Table 4. **Comparing the scale scores with some variables**

		SFQ-S	SFQ-L	SFQ-Total	ASSQ	RCSQ
		X ± SD	X ± SD	X ± SD	X ± SD	X ± SD
Gender	Female Male	37.8 ± 9.95 34.2 ± 10.5 p = 0.48	39.1 ± 10.5 33.5 ± 11.1 p = 0.27	38.7 ± 20.2 33.7 ± 21.1 p = 0.33	42.7 ± 8.01 31.7 ± 11.2 p = 0.03*	340.4 ± 141.8 380.6 ± 144.2 p = 0.20
Marital status	Married Single	35.5 ± 10.1 33.2 ± 19.1 p = 0.87	35.4 ± 10.6 38.2 ± 23.3 p = 0.84	35.5 ± 20.4 34.7 ± 21.5 p = 0.95	35.5 ± 10.3 34 ± 22.6 p = 0.91	366.8 ± 140.2 367.5 ± 328.8 p = 0.93
Smoking	Yes No	41.9 ± 10.3 32.9 ± 10.1 p = 0.09	39.9 ± 10.7 33.7 ± 10.9 p = 0.26	40.7 ± 20.4 33.4 ± 20.7 p = 0.17	33.9 ± 11.5 36.1 ± 10.2 p = 0.68	391.2 ± 127.9 357.1 ± 149.6 p = 0.46
Presence of chronic disease	Yes No	36.4 ± 11.3 35.1 ± 9.92 p = 0.81	36.8 ± 12.2 35.1 ± 10.4 p = 0.74	36.6 ± 23.3 35.1 ± 20.1 p = 0.77	36.4 ± 11.5 35.1 ± 10.3 p = 0.81	348.9 ± 174.5 373.5 ± 131.7 p = 0.04*
Previous surgery	Yes No	39.7 ± 14.5 35.2 ± 10.1 p = 0.66	44.2 ± 16.9 34.9 ± 10.4 p = 0.37	41.5 ± 31.5 35.1 ± 20.2 p = 0.54	31.7 ± 15.9 35.7 ± 10.2 p = 0.71	322.5 ± 207.9 369.5 ± 140.7 p = 0.51
Cardiac disease history in the family	Yes No	40.7 ± 19.1 35.1 ± 9.67 p = 0.59	38.8 ± 17.1 35.3 ± 10.5 p = 0.73	40.0 ± 36.1 35.2 ± 19.9 p = 0.64	32.0 ± 16.2 35.7 ± 10.2 p = 0.72	341.2 ± 213.1 368.4 ± 140.6 p = 0.85
Age	r, p**	r = −.164 p = 0.17	r = −.186 p = 0.12	r = −.170 p = 0.16	r = 0.07 p = 0.54	r = .101 p = 0.41

Note. Mann Whitney U Test; ** Spearman correlation analysis, $p < 0.05$
Abbreviations: SFQ-S: Surgical Fear Questionnaire: — short term; SFQ-L: Surgical Fear Questionnaire: long term; ASSQ: Anxiety Specific to Surgery Questionnaire; RCSQ: Richard-Campbell Sleep Questionnaire

Table 5. **Analysis of correlations between preoperative ASSQ, SFQ and postoperative VAS and RCSQ.**

	SFQ						ASSQ	
	SFQ-S		SFQ-L		SFQ-Total			
	r	p	r	p	r	p	r	p
VAS	.654**	.000	.713**	.000	.686**	.000	.564**	.000
RCSQ-Total	−.455**	.000	−.529**	.000	−.497**	.000	−.427**	0.00

Note. Spearman correlation analysis, *p < 0.05*
Abbreviations: VAS: Visual Analog Scale; SFQ-S: Surgical Fear Questionnaire: — short term; SFQ-L: Surgical Fear Questionnaire: long term; ASSQ: Anxiety Specific to Surgery Questionnaire; RCSQ: Richard-Campbell Sleep Questionnaire

Table 6. **Analysis of correlations between postoperative VAS and RCSQ (N:70)**

	VAS	RCSQ
VAS	1	
RCSQ	–,358*	1

Note. *:*p < 0.01*
Abbreviations: VAS: Visual Analog Scale; RCSQ: Richard-Campbell Sleep Questionnaire; RINVR: Rhodes Index of Nausea, Vomiting and Retching

Discussion

Patients who will have cardiac surgery experience a lot of fear and anxiety prior to the surgery. It is mentioned in the literature, that the process of hospitalization is a source of anxiety on its own, and that patients hospitalized in surgical clinics experience more anxiety due to the addition of anxieties such as bleeding, death, and fear of the unknown [22, 30]. This fear and anxiety they experience affect the course of the surgery, the recovery process subsequent to the surgery, and during discharge [31,32]. It is reported In the studies carried out that 50–90 % of patients experience fear prior to surgery [33]. Furthermore, the patient's existing diseases, the patient's point of view towards the surgery, and the previous surgical experience of the patient can also affect the level of fear [34]. The level of fear of surgery of the patients was close to moderate (26.2 ± 20.8) in the preoperative period In this study was carried out with patients who underwent CABG.

Shahmansouri et al. investigated the prevalence of anxiety and fear in CABG surgery patients (N = 277) and found that patients experienced low, moderate, and severe anxiety with a prevalence of 19.7 %, 69.14 %, and 11.15 %, respectively [35]. Akinsulore et al., found that 51 % of the patients [10], and Nigussie et al., found that 70.3 % of the patients experienced high levels of anxiety prior to surgery [9]. The literature reports that some socio-demographic variables are effective on the level of anxiety [36,37]. In our study, there was no statistically significant difference between the total ASSQ scores of the patients participating in the study according to their marital status, education level, income, and health insurance status ($p > 0.05$), while the scores of the patients from the ASSQ according to the gender factor were found to be statistically significant. ($p < 0.05$).

In this study, the mean ASSQ score of the patients prior to CABG surgery was found to be 32.7 ± 10.5. It was determined that the patients experienced anxiety above moderate levels. The study findings are consistent with the literature.

Postoperative pain is a surgical complication with a high prevalence. It was reported in previous studies that between 30 and 90 % of patients experience pain in the first 24 hours subsequent to surgery [38]. Postoperative pain is a subjective phenomenon and is affected by the type and duration of the surgery, individual characteristics and experiences, type of anesthesia, and emotions such as fear and anxiety; therefore varies from person to person. Pain may persist for days, weeks, or months. Figures may vary based on the methods utilized. Much as anxiety experienced prior to surgery affects postoperative pain, it should not be forgotten that numerous factors may have affected the pain of patients having cardiac surgery [39,40].

It was found that the anxiety level prior to cardiac surgery was positively correlated with postoperative pain in the study conducted in 2011 by Navarro — Garcia et al. [41]. It was found that patients with high preoperative anxiety scores had high postoperative pain scores according to Dualé et al. in a retrospective study including 2397 patients [42]. Sobol — Kwapinska et al., observed that there was a significant relationship between preoperative anxiety and postoperative pain in a meta-analysis of 53 studies. Studies have revealed the fact that psychological factors such as anxiety and fear can affect the individual response to surgical intervention and postoperative pain management [43,44].

Approximately three-quarters of patients having surgery develop acute pain, and 80 % of them have moderate to severe pain [20]. It was determined in this study, that the patients experienced moderate pain in the postoperative period (4.17 ± 2.27) and that the surgical fear and anxiety experienced prior to the operation affected the postoperative pain. In our study, it is thought that the high postoperative pain levels of the patients with high surgical fear and anxiety levels are due to the physiological effects of fear and anxiety increase the perception of pain. The study findings are consistent with the literature.

There are numerous factors that lead to insomnia in patients. Numerous factors such as heat, light, stress, and diseases lead to insomnia. Emotional conditions such as increased fear and anxiety prior to surgery in patients lead to difficulty in falling asleep at night and may lead to deterioration of sleep

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quality [25]. Individuals sleep less compared to what they need in such situations, and their REM sleep is shortened. Feeling fear or anxiety activates the neuroendocrine response, causing a response in both the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis and an increase in stress hormones. The neuroendocrine response created by stress can also lead to disruption of the circadian rhythm and lead to a decrease in sleep quality [45]. Studies have reported that surgical patients have poor sleep quality prior to surgery, varying from 8.8 % to 79.1 % [46], and sleep issues persist for a long time subsequent to surgery [47]. Yılmaz et al., examined the sleep status of patients hospitalized in surgical clinics, and it was observed that the sleep quality of cardiovascular surgery patients was worse compared to that of urology and general surgery patients [48]. In the study of Yang et al., (n = 87), it was determined that 87 % of the patients had poor postoperative sleep quality, and a relation was found between anxiety and sleep quality [49]. In another study on the subject, Liao et al. determined that sleep issues subsequent to cardiovascular surgery are related to environmental factors such as pain, dyspnea, nocturia, noise, and light, and that anxiety and depression affect sleep quality [50].

In our study, it was observed that the sleep quality of patients with chronic diseases such as hypertension and DM was significantly lower compared to those without. During the treatment and care process of both diseases, the patient's sleep is interrupted numerous times during the night, as nurses frequently monitor patients for vital signs and blood sugar. The poor sleep quality of this patient group is an expected result. The results of this study showed that surgical fear and anxiety is a significant factors in reducing the postoperative sleep quality of patients.

Conclusion

As a result, the level of preoperative fear and anxiety about surgery in patients undergoing CABG surgery may affect the early postoperative period, increase the postoperative pain score and impair sleep quality. The results of this study were limited to the views of the patients who agreed to participate in the study at the selected university hospital. Therefore, the results of the study were only possible to be generalized for these patients.

The following recommendations were offered in accordance with the results obtained from this research:

It should be known that anxiety experienced in the preoperative period can cause problems at every stage of the surgery, and patients should be followed up for the effects of anxiety.

In the preoperative period, necessary explanations should be given about the CABG surgery and type of anesthesia in a way that the patient can understand, and the patient should be given the opportunity to talk about their fears and anxieties.

Preoperative psychological preparation of patients should take into account the patient's descriptive characteristics as well as their fear of surgery and anxiety level.

The patient's sleep quality, stress, and anxiety level should be assessed during the preoperative period. For patients with severe anxiety, an individualized multidisciplinary approach that includes a psychologist is recommended.

Carrying out similar multicenter studies with large sample groups is recommended in order to obtain further results in terms of different variables in the preoperative period.

Conflict of interest. None declared.

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COVID-19 as additional cardiovascular risk factor in young and middle-aged patients

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Objective. This study aimed to determine the prevalence and risk factors of new cases of coronary heart disease (CHD), arterial hypertension (AH) and diabetes mellitus in patients with new coronavirus infection (COVID-19).
Methods. This open comparative, prospective study included 658 patients: 111 (16.8%) men and 547 (83.2%) women aged from 25 to 44 years — 432 (65.6%), from 45 to 59 years — 226 (34.4%) subjects. Depending on the history of COVID-19 infection (between March 2020 and June 2021) patients were divided into two groups. The main group included 416 patients (63.2%) aged 40 (33; 47) years who had history of COVID-19 (343 (82.5%) with mild, 56 (13.5%) with moderate-to-severe course, 17 (4%) with severe course); the comparison group included 242 (36.8%) patients aged 41 (32.8; 47) years who did not have COVID-19.
Results. There was a statistically significant increase of systolic blood pressure (SBP) (from 127 to 129 mm Hg, p = 0,006), number of hypercholesterolemic (from 6,7% to 48,3%, p < 0.001) and overweight patients (from 40.1% to 75.9%, p < 0.001). During the observation period, one in four (23.3%) young and middle-aged subjects developed: 8.6% hypertension, 6.3% diabetes mellitus (DM), and 5.5% CHD. The estimated risk of premature cardiovascular events after COVID-19 was 74% higher than in the comparison group. In the group of patients who developed new cases of AH, CHD and DM, moderately severe (p < 0.001) and severe course (p = 0.002) of COVID-19 with subsequent admission to hospital were registered more frequently. In the group of patients who did not develop new cases of studied events mild disease course (p < 0.001) of COVID-19 was more prevalent.
Conclusions. One in four patients aged 18 to 59 years may develop cardiovascular event as the long term COVID-19 complication. The risk of premature cardiovascular events after COVID-19 infection was 74% higher than in

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a group of people of similar age and sex. Smoking, hypercholesterolemia, excess body weight, three or more cardiovascular risk factors may be considered as factors for timely stratification of patients due to the risk of developing CHD or DM.
Keywords: COVID-19, risk factors, cardiovascular diseases, age.

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Introduction

COVID-19 (the new coronavirus infection, COrona-VIrus Disease 2019) has posed certain challenges to both healthcare system and individual person's health. In addition large prevalence and direct socio-economic losses, the potential impact of COVID-19 on cardiovascular morbidity and mortality is of particular concern since there is an evidence of a more severe course of the disease in both patients with cardiovascular disease (CVD) risk factors (RFs) and established CVDs. The results of numerous studies indicate the mutual aggravation of the COVID-19 course and cardiovascular pathology. It has been shown that from15 % to 70 % of deaths are registered in patients with cardiovascular pathology accompanying the COVID-19. The pathogenesis of cardiovascular damage in the background of inflammation are complex and include the effects of hypoxia, systemic proinflammatory effects, direct myocardial and vascular endothelial damage [1]. Currently, more and more data are being collected on the consequences of this infection — specifically, that the acute phase of COVID-19 is the beginning of the continuum on the way to recovery. According to a study by O'Hearn M. et al., most admissions due to new coronavirus infection occur in patients with concomitant cardiometabolic disease [2]. The authors estimate that among 906,849 admissions, 30 % occurred in patients with obesity, 26 % with arterial hypertension (AH), 20 % with diabetes mellitus (DM) and 12 % with heart failure. The mean age of admitted patients was 63 (51–74) years, including 1678 (61.2 %) males and 1063 (38.8 %) females.

The meta-analysis of 56 studies included 159,698 patients with COVID-19 and showed that acute cardiac injury (odds ratio (OR) 13.29, 95 % CI 7.35–24.03), arterial hypertension (AH) (OR 2.60, 95 % CI 2.11–3.19), heart failure (OR 6, 72, 95 % CI 3.34–13.52), cardiac arrhythmias (OR 2.75, 95 % CI 1.43–5.25), cardiac heart disease (CHD) (OR 3.78, 95 % CI 2.42–5.90), and cardiovascular diseases (CVD) (OR 2.61, 95 % CI 1.89–3.62) were significantly associated with mortality [3]. Cardiac arrhythmias (OR 7.03, 95 % CI 2.79–17.69), acute cardiac injury (OR 15.58, 95 % CI 5.15–47.12), CHD (OR 2.61, 95 % CI 1.09–6.26), CVD (OR 3.11, 95 % CI 1.59–6.09) and AH (OR 1.95, 95 % CI 1.41–2.68) were also significantly associated with the admission to intensive care unit in patients with COVID-19.

Data from the ACTIV international registry both involved outpatients (n = 1057, men 41.91 %, women 58.09 %) and inpatients (n = 4751, men 46.39 %, women 53.61 %) of the Eurasian region with COVID-19 showed more severe clinical couse in patients with comorbidities in admitted patients who were older than outpatients. The median age was higher in those with the more severe course of COVID-19 (lower and upper quartiles: Q1-Q3) 59.0 (50–69) and 49.9 (38–60) years, respectively]. Moreover, females tended to have the severe course of COVID-19 more often than males (53.6 %). Obesity (OR 1.079, 95 % CI (0.829–1.404, p = 0.57) and AH (OR 3.123, 95 % CI 2.946–4.852, p < 0.01), along with DM, chronic kidney disease, chronic obstructive pulmonary disease and cancer substantially affected the prognosis. The unfavorable cluster of 4 diseases in terms of prognosis can be determined: AH, CHD, heart failure, DM [4].

Given the available literature data on the prevalence of cardiovascular complications and its association with the history of infection, as well as the contribution of COVID-19 to the development of cardiovascular risk (CVR), we can assume that the number of patients with the above-mentioned complications will increase. In this regard, young and middle-aged patients (both with and without cardiovascular risk

factors) should be monitored on the subject of premature cardiovascular morbidity development in the after COVID-19.

Due to of the role of carbohydrate metabolism disorders in the development of atherosclerosis, high cardiovascular morbidity and mortality, the registration of the new cases of type 2 DM, is also important for the prediction of the disease course. The literature data on COVID-19 as risk factor for CVD in young and middle-aged individuals are currently scarce and contradictory due to different methodological approaches and inclusion criteria, which led to the conduction of this study.

The aim of the study was to determine the prevalence and risk factors of new cases of CHD, AH, and diabetes mellitus in patients who underwent COVID-19.

Material and Methods

A total of 658 patients were included in an open comparative prospective study: 111 (16.8 %) men and 547 (83.2 %) women who underwent medical examination by a general practitioner. There were 432 (65.6 %) patients aged 25–44 years and 226 (34.4 %) patients aged 45–59 years. The SCORE score on the relative risk scale (RR) was 2.47 ± 2.5 % for people aged 40 years and older; 1.05 ± 0.4 for people under 40 years old. Low CVR was found in 202 (30.6 %), moderate in 389 (59.1 %), high in 48 (7.2 %), and very high in 19 (3.1 %) patients.

Inclusion criteria: men and women aged 25 to 59 years; compliance with all study procedures; signed written consent to participate in the study.

Exclusion criteria: mental disorder; alcohol dependence; participation in another study.

Patients were divided into two groups based on whether they had COVID-19 infection (between March 2020 and June 2021): the main group included 416 (63.2 %) patients aged 40 (33; 47) years after COVID-19; the comparison group included 242 (36.8 %) patients aged 41 (32.8; 47) years without COVID-19 history.The groups were comparable by age (p = 0.324) and gender: the main group had 361 (86.8 %) women and 55 (13.2 %) men, the comparison group had 197 (81.4 %) women and 45 (18.6 %) men, p = 0.083. The diagnosis of COVID-19 was confirmed by the positive oral and nasopharyngeal smear polymerase chain reaction test for SARS-CoV-2 and/or typical pattern according to chest computed tomography.Data on the history of infection and the severity of the disease were obtained from the patients' medical records.

At the first visit, all patients were assessed for demographic characteristics, the presence of risk factors (smoking, obesity, hypercholesterolemia), concomitant CVDs (AH, CHD, myocardial infarction history, DM), and laboratory data (total cholesterol, glucose). At the second visit, which took place one year after, in addition to the assessment of the above-mentioned indicators, new cases of AH, CHD, and DM diagnosed according to the existing guidelines were registered [5, 6]. The presence of CHD was performed by the history of myocardial infarction, revascularization or confirmed coronary atherosclerosis by coronary angiography (CAG).

All patients with new cases were advised to limit salt intake (less than 5 g/day), alcohol, to quit smoking if present, to control body weight, to exercise regularly (at least 30 minutes of moderate-intensity dynamic activity for 5–7 days a week) and to receive appropriate medication therapy.

The period from recovery after COVID-19 to the development of outcomes lasted from 1 to 7 months [median: 3 months, interquartile range 25–75 %: 2–4 months].

Patients with body mass index (BMI) value of 25–29.9 kg/m² were considered overweight and obese — with BMI over 30 kg/m². CVR was calculated using Systematic Coronary Risk Estimation (SCORE) scale at the age of 40 years and over, and under 40 years — using OR scale [7].

The study was performed at the Internal Medicine Outpatient Department of the Faculty of Medicine of the Pirogov Russian State Medical University and the Outpatient Department of the City Clinical Hospital № 13. The study protocol was approved by the local Ethics committee of the Pirogov Russian State Medical University. The study was performed in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Data were presented as medians with interquartile range for quantitative variables that significantly deviated from normal distribution. Mann-Whitney U-test was used to analyze the differences between the groups; Spearman correlation analysis was used to study the relationship between the studied parameters. To assess the risk factors for cardiovascular events we used

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logistic regression model thatincluded: sex, age, body mass index (BMI), systolic and diastolic blood pressure (BP) (SBP and DBP) levels, absolute and relative CVR according to SCORE scale, presence or absence of AH, CHD, DM, COVID-19. Differences were considered statistically significant at $p < 0.05$.

Results

In total, 343 (82.5%) patients had a mild course of COVID-19, 56 (13.5%) had a moderate-to-severe course, and 17 (4.0%) had severe course followed by hospital admission. Characteristics of patients before and after COVID-19 are shown in Table 1.

Table 1. **Characteristics of study participants before and after COVID-19**

Parameter	Before COVID-19, n = 416	After COVID -19, n = 416	p
SBP, mmHg	127 (110;148)	129 (125;136)	0,006
DBP, mmHg	85 (81;93)	85 (75;87)	0,866
HR, bpm	76 (68;93)	77 (75;85)	0,001
Smoking, n (%)	102 (24,5)	48 (11,5)	< 0,001
Hypercholestero-lemia, n (%)	28 (6,7)	201 (48,3)	< 0,001
Cholesterol, mmol/l	5 (5;5)	5 (5;6)	< 0,001
Glucose, mmol/l	5 (3;8)	4 (4;6)	0,038
Hyperglycemia, n (%)	21 (5)	33 (7,9)	0,121
BMI, kg/m^2	23 (23;32)	25 (22;34)	0,003
Excessive body weight, n (%)	167 (40,1)	316 (75,9)	< 0,001
Obesity, n (%)	18 (4,3)	13 (3,1)	0,464
CHD, n (%)	9 (2,1)	23 (5,5)	0,019
DM, (%)	9 (2,1)	26 (6,25)	0,005
AH, n (%)	36 (8,6)	73 (17,5)	< 0,001
SCORE CVR, %	1 (1;13)	6 (1;13)	0,086
CVR low, n (%)	145 (34,8)	62 (14,9)	< 0,001
CVR moderate, n (%)	230 (52,2)	256 (61,5)	0,078
CVR high, n (%)	31 (6)	35(8,4)	0,700
CVR very high, n (%)	10 (7)	63 (15,2)	< 0,001
CVR relative, score	1 (1;7)	2 (1;7)	0,606

Study outcomes developed in 97 (23,3%) people after COVID-19; 40 (16,5%) — in comparison group, $p = 0,050$. New cases of confirmed AH in the comparison group were registered in 29 (11.9%) patients, DM — in 9 (3.7%) patients, CHD — in 9 (3.7%) patients (5 patients had acute coronary syndrome, coronary atherosclerosis was confirmed in 4 patients according to CAG). In the main group 36 patients (8.6%) had new cases of AH, 26 (6.3%) — DM, 23 (5.5%) — CHD (15 patients had myocardial infarction, 8 — percutaneous coronary intervention, i.e. stent placement) (Table 2).

Table 2. **Characteristics of patients afterCOVID-19 with (group 1) and without(group 1) (group 2) the development of the new cases of AH, CHD and DM**

Parameter	Group 1, n = 97	Group 2, n = 319	p
Age, years	44 (42;46)	39 (39;41)	0,000
Aged 18–44 years, n (%)	49 (50,5)	217 (68)	0,002
Aged 45–59 years, n (%)	48 (49,4)	102 (31,9)	0,002
Males, n (%)	17 (17,5)	38 (11,9)	0,116
Mild course of COVID-19, n (%)	52 (53,6%)	291 (91,2%)	< 0,001
Moderately severe course of COVID-19, n (%)	35 (36,1%)	21 (6,6%)	< 0,001
Severe course of COVID-19, n (%)	10 (10,3%)	7 (2,2%)	0,002
SBP, mmHg	127 (130;134)	127 (128;131)	0,090
DBP, mmHg	76 (86;87)	75 (85;86)	0,035
HR, bpm	76 (75;77)	75 (75;77)	0,985
Smoking, n (%)	16 (16,4)	32 (10)	0,479
Hypercholesterolemia, n (%)	31 (31,9)	170 (53,2)	0,000
Cholesterol, mmol/l	5 (5,1;5,3)	5 (5,02;5,08)	0,000
Glucose, mmol/l	5 (5,0;5,3)	5 (5,0;5,1)	0,102
Hyperglycemia, n (%)	3 (3)	30 (9,4)	0,004
BMI, kg/m^2	27 (25,5;26,5)	23 (24,4;24,9)	0,000
Excessive body weight, n (%)	83 (85,5)	248 (77,7)	0,126
Obesity, n (%)	1 (1)	13 (4)	0,256
CHD, n (%)	21 (21,6)	2 (0,6)	0,000
DM, (%)	26 (26,8)	0	0,000
AH, n (%)	73 (75,2)	0	0,000
SCORE CVR, %	2,7 (2,5;3,9)	2,0 (2,1;2,6)	0,004
CVR low, n (%)	8 (8,2)	54 (16,9)	0,052
CVR moderate, n (%)	23 (23,7)	233 (73)	0,000
CVR high, n (%)	3 (3)	32 (10)	0,051
CVR very high, n (%)	63 (64,9)	0	0,000
CVR relative, score	1 (0,89;1,29)	1 (0,96;1,11)	0,526

The data of correlation analysis between new cases of AH, CHD, and studied parameters are presented in Table 3.

The above-mentioned data were used for a more detailed assessment by logistic regression analysis (Table 4).

Discussion

In most cases, COVID-19 manifests with respiratory and general symptoms, which persist for a certain period after recovery that is named "postcovid period/syndrome" in the literature. However, some patients of any age can develop changes in the cardiovascular system (vascular thrombosis, acute myocardial damage, acute coronary syndrome, new cases of CVD etc.), including in the long-term [8, 9].

While evaluating patients' characteristics after COVID-19, we paid attention to statistically signifi-

Table 3. **The data of the correlation analysis between new cases of AH, CHD, and studied parameters**

Parameter	r	p
New cases of AH, CHD, DM		
Smoking	0,20	< 0,001
Sleep disorder	0,15	< 0,001
Three or more RFs	0,16	< 0,001
SBP	0,15	< 0,001
DBP	0,17	< 0,001
Moderate CVR	0,19	< 0,001
High CVR	0,45	< 0,001
COVID-19	0,25	< 0,001
Development of AH		
High CVR	0,35	< 0,001
Aged 45–59	0,16	< 0,001
Hypercholesterolemia	0,14	< 0,001
DM	0,15	< 0,001
Development of CHD		
DM	0,53	< 0,001
Smoking	0,16	< 0,001
Hypercholesterolemia	0,37	< 0,001
Excessive body weight	0,17	< 0,001
High CVR	0,28	< 0,001
Three or more RFs	0,28	< 0,001
Development of DM		
Smoking	0,16	< 0,001
Hypercholesterolemia	0,37	< 0,001
Excessive body weight	0,22	< 0,001
Three or more RFs	0,29	< 0,001

Table 4. **Factors, associated with the development of cardiovascular events after COVID-19. The results of logistic regression analysis**

Parameter	OR	(95% CI)	p
Any cardiovascular events			
Sleep disorder	2,48	1,51–4,07	< 0,001
Smoking	3,09	1,89–5,06	< 0,001
Three or more RFs	11,01	6,54–18,55	< 0,001
COVID-19	1,74	1,14–2,65	0,010
High CVR	42,7	12,6–144,6	0,001
Development of AH			
High CVR	11,3	5,99–21,04	0,001
Aged 45–59	3,16	1,88–5,31	< 0,001
Hypercholesterolemia	3,59	2,01–6,41	< 0,001
Development of CHD			
DM	14,33	5,19–39,51	0,001
Three or more RFs	13,03	4,33–39,18	< 0,001
Smoking	3,67	1,56–8,60	0,003
Hypercholesterolemia	8,63	4,36–17,06	< 0,001
Excessive body weight	3,67	1,47–9,11	0,005
Development of DM			
Smoking	4,75	2,11–10,72	< 0,001
Hypercholesterolemia	6,04	3,121–11,38	< 0,001
Excessive body weight	7,02	2,59–19,02	< 0,001
Three or more RFs	11,70	4,30–31,84	< 0,001

cant increase of BP level (from 127 to 129 mm Hg, p = 0.006); increase of patients with hypercholesterolemia (from 6.7% to 48.3%, p < 0.001); overweight (from 40.1% to 75.9%, p < 0.001); very high CVR (from 7 to 15.2%, p < 0.001) and, correspondingly, decrease of patients with low CVR (from 34.8% to 14.9%, p < 0.001).

The fact of decrease of the number of smokers should be highlighted: from 24,5% to 11,5%, p < 0,001. It should be noted that patients included in the above study who suffered from COVID-19 had a median age of 40 (33; 47) years, predominately females (86,8%), and every fourth person (24,5%) smoked. Excessive body weight was present in 40,1% of patients. Mean score by the SCORE scale was 2.62 ± 2.6%, relative SCORE was 1.04 ± 0.48. Only 34.8% of patients from low-risk group, 52.2%, from moderate risk group, 6% from high-risk group and 7% of patients from very high-risk group had a low score by the SCORE scale

The registration of new cases of AH and CHD after COVID-19 can be mainly explained by the morbidity of elderly people, especially of those with initial cardiovascular pathology. Prediction of the consequences of this infection based on the degree of CVR in order to prevent the development of adverse outcomes at younger age is also relevant, since the delayed development of cardiovascular complications is considered to be one of the features of COVID-19 [10–12]. In this regard, prevention of life-threatening cardiovascular events by reducing the risk of CVD and identifying associated risk factors is the highest priority [13].

Between 1st and 7th months [median 3 (2; 4)] after COVID-19, one in four (23.3%) young and middle-aged subjects developed the study endpoints: 8.6% had AH, 6.3% had DM, and 5.5% had CHD. The estimated risk of premature cardiovascular events after COVID-19 was 74% higher than in the population of similar age and sex represented by the comparison group. In the group of patients who developed new cases of AH, CHD and DM, a moderately severe (p < 0.001) and severe course (p = 0.002) of COVID-19 followed by admission was registered more frequently; in the group of patients who did not develop CV events — a mild course (p < 0.001) of COVID-19.

Our findings are similar to those of other researchers. The study by Stefan N. et al. showed that comorbidities also increased the risk of COVID-19-related death among young adults (n = 3163). These findings come from the March 2020 Lean European Open Survey on SARS-CoV-2 (LEOSS) aimed to examine the prevalence and clinical course of SARS-CoV-2 in-

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fection. It revealed an additional influence of obesity, DM and AH on the increased risk of adverse outcomes in young and middle-aged patients. Compared to patients aged 18 to 55 years without obesity, DM and AH (n = 593), the adjusted risk of death (OR 7.42, 95% CI 1.55–27.3) in similar age group of patients with these pathologies was comparable with mortality risk in patients aged 56–75 years but without obesity, DM and AH (OR 8.21, 95% CI 4.10–18.3) [14].

The results of the retrospective study also confirmed that excess weight and AH contribute to the development of adverse outcomes of COVID-19 in young and middle-aged individuals [15].

While analyzing the group of patients who developed study outcomes, we noted that the age of these patients was higher compared with those without remote events. Patients in the main group were more likely to have CHD, AH and DM; baseline CVR, BP and BMI were higher than in the comparison group, which is consistent with data from other studies [16].

A systematic review by Harrison S et al. that included data from 84 clinical trials conducted between January 1, 2020, and November 5, 2020 showed that chronic kidney disease (OR 3.07, 95% CI 2.43–3.88), DM (OR 2.09, 95% CI 1.80–2.42) were the RF of fatal outcome and severe COVID-19. AH (OR 2.50, 95% CI 2.02–3.11), smoking history (OR 1.26, 95% CI 1.20–1.32), cerebrovascular disease (OR 2.75, 95% CI 1.54–4.89), and CVD (OR 2.65, 95% CI 1.86–3.78) contributed to more severe outcomes. Liver disease was associated with higher odds of death (OR 2.81, 95% CI 1.31–6.01), but not with the severe course of COVID-19. Smoking was associated with a higher risk of severe COVID-19 (OR 1.80, 95% CI 1.14–2.85), but not with mortality. Obesity was associated with a higher risk of death (OR 2.18, 95% CI 1.10–4.34), but there was no evidence of the association with more severe COVID-19 course. Patients admitted with COVID-19 were diagnosed acute heart failure (2%), myocardial infarction (4%), deep vein thrombosis (7%), myocardial damage (10%), angina pectoris (10%), cardiac arrhythmias (18%), pulmonary embolism (19%) and venous thromboembolism (25%) [17].

It is pivotal for the practicing physician, especially in the outpatient setting, to identify the group of patients who need earlier additional examination in order to prescribe rational preventive therapy. According to the results of our study, the presence of factors such as sleep disturbance (OR 2.48), smoking (OR 3.09), three or more of any CVD RF (OR 11.01), high CVR (OR 42.7), the very fact of COVID-19 was associated with higher probability of cardiovascular events and could be considered as possible risk factors in clinical practice.

The likelihood of developing AH increased by 11.3-fold those with high CVR, 3.59-fold in hypercholesterolemic patients, and 3.16-fold in middle-aged patients. DM (OR 14.33), three or more CHD RF (OR 13.03), smoking (OR 3.67), hypercholesterolemia (OR 8.63), and excess body weight (OR 3.67) were significantly associated with the development of CHD after COVID-19. The development of DM in young and middle-aged patients was associated with smoking (OR 4.75), hypercholesterolemia (OR 6.04), excess body weight (OR 7.02) and the presence of three or more RFs (OR 11.70). All of the above-mentioned parameters are proven components of high CVR, are easily identified in routine practice, and are modifiable [18].

Our results highlighted the effect of COVID-19 pandemic on human health and allow to consider a new coronavirus infection as a possible cardiovascular RF. This fact confirms the necessity of following the principles of prevention of non-infectious diseases as a priority of the health care system, starting at young age [20].

In the Russian Federation databases of COVID-19 patients were created, one of which named TARGET-VIP, studying clinical and medical history parameters, multimorbidity structure, treatment outcomes at hospital and outpatient setting in patients aged 58.0 ± 14.8 years, of 51.3% which are males. It was shown that higher mortality was observed during the first months after the disease (31.4%), especially in persons with severe course, indicating the need to improve the continuity between different health care units, as well as long-term complex, including outpatient follow-up of such patients [21].

This study allowed to identify risk factors associated with the development of AH, CHD and DM after the infection, which could be used for the development of multifactorial approach for timely detection and correction of cardiometabolic risk in young and middle-aged individuals that shouldinclude the healthy lifestyle principles.

Study limitations

The young and middle-aged patients included into the study underwent annual prophylactic examina-

tions, which defined set of necessary tests that limit the extrapolation of the results obtained. Due to the course of COVID-19, it is not possible to completely exclude the fact that some of the study participants in the comparison group did not have this infection asymptomatically. Therefore, it is difficult to argue that the new cases of AH, CHD, and DM are the direct consequence of the infection and are not due to the risk factors and concomitant pathology that existed before COVID-19.

Conclusion

One in four people aged from 18 to 59 years may develop a cardiovascular event after COVID-19, with a 74% higher risk those without the history of COVID-19. This probability was associated with initial high CVR, the presence of 3 or more of any CVD RFs, smoking, and sleep disorders. High CVR and hypercholesterolemia may be useful to identify the most vulnerable group of patients to develop AH, especially those aged 45–59 years; smoking, hypercholesterolemia, excess body weight, and three or more CVD RFs may be used to stratify patients for the risk of CHD or DM. Further inveatigation of factors associated with adverse cardiometabolic events and the formation of the phenotype of the most vulnerable young and middle-aged patient is necessary.

Conflict of interest. None declared.

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Impact of omega-3 polyunsaturated fatty acids on cardiovascular system

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Abstract. Long-term prospective cohort studies showed the association between high fish and omega-3 polyunsaturated fatty acids intake and lower risk of cardiovascular disease (CVD), especially coronary heart disease and myocardial infarction, as well as cardiovascular mortality in the general population. This review article analyses some of the key studies that have investigated the use of eicosapentaenoic and docosahexaenoic acids for primary and secondary prevention of CVD, discuss the mechanisms of its potential cardioprotective effects, and evaluates recently published randomized clinical trials in the context of existing scientific literature data.

Keywords: omega-3 polyunsaturated fatty acids, cardiovascular disease prevention, cardiovascular risk.

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Introduction

For the first time, the benefit of omega-3 polyunsaturated fatty acids (PUFAs) has been established in the 70s of the XX century, when the study among the Greenlandic Inuit was published. The Inuit practically did not have cardiovascular diseases (CVD), atherosclerosis and type 2 diabetes mellitus, unlike Europeans. This phenomenon was associated with their diet that include the consumption of large amount of oily fish rich in omega-3 PUFAs. Subsequently, ep-

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idemiological studies among the indigenous populations of Arctic and among the Japanese confirmed the data obtained among the Greenlandic Inuit. Since then, scientists focused on PUFAs as the factor for CVD prevention and mortality reduction.

The omega-3 PUFAs are the building molecules and are incorporated into cell membranes, and also are involved into such mechanisms as fluidity, permeability, activity of membrane enzymes and receptors and intracellular signal transduction pathways [1]. In addition, PUFAs are involved into metabolic processes and the production of biologically active substances [2, 3].

In this study we aimed to assess the effectiveness of omega-3 PUFAs for primary and secondary CVD prevention. We performed the analysis of scientific literature data according to PubMed and e-library databases. The articles were included only if they were published no more than 10 years ago. The following keywords were used: omega-3 polyunsaturated fatty acids, cardiovascular disease prevention, cardiovascular risk.

Cardioprotective effect of omega-3 polysaturated fatty acids

Cardioprotective effect of omega-3 PUFAs is mainly explained by its the ability to modify CVD risk factors. They are well studied and include: high blood pressure, high triglycerides (TG) levels and low high-density lipoprotein (HDL) cholesterol, endothelial dysfunction, arrhythmias, heart rate, heart rate variability, hypercoagulation and inflammation.

Biological mechanisms for cardioprotective effect of omega-3 PUFAs are associated with alteration of cell membranes properties due to eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) incorporation, as well as modulation of protein membrane receptors response. Direct modulation of ion channels by omega-3 PUFAs underlies their anti-arrhythmic effect. They also prevent cytosolic calcium fluctuations in cardiomyocytes by influencing calcium channels of the cytoplasmic reticulum. Omega-3 PUFAs prevent the development of spontaneous depolarization and life-threatening arrhythmias by blocking voltage-gated sodium channels. This effect is mostly pronounced in ischemic cells [4, 5].

EPA and DHA are involved into the synthesis of eicosanoids. Cyclooxygenase contributes to the synthesis of thromboxane A3 and prostaglandin I3 as well as the reduction of thromboxane A2 and prostaglandin I2 formation from arachidonic acid. The ratio between thromboxane A2 and prostaglandin I2 is of greater importance, since prostaglandin I2 decreases to a greater extent. This shift has antiarrhythmic effect, reduces the risk of ventricular fibrillation and sudden cardiac death. In addition, omega-3 PUFAs reduce the amount of arachidonic acid in the membranes of cardiomyocytes, and, therefore, provide anti-arrhythmic and anti-inflammatory effect [4, 6].

Anti-arrhythmic of omega-3 PUFAs is not only associated with the metabolism of eicosanoids. The incorporation of EPA and DHA into the lipid bilayer of cardiomyocyte's membrane alters its properties and, therefore, affects function of ion channels and enzymes that are incorporated into the cell membrane. The possibility to affect the cellular inositol cycle and modulate calcium release from the endoplasmic reticulum is another mechanism that prevents the development of arrythmias into the ischemic cell.

In addition, PUFAs affect cellular signal pathways. EPA and DHA can impair the initiation of toll-like receptors [1] that decreases the activation of the transcription of nuclear factor kappa, the level of pro-inflammatory cytokines (tumor necrosis factor, interleukin-1ß, interleukin-6 and interleukin-8) as well as pro-inflammatory metalloproteinases [3, 6, 7]. In addition, anti-inflammatory effect of omega-3 PUFAs can be explained by the decrease of cell adhesion molecules expression (E-selectin, P-selectin, etc.) that increases stability of atherosclerotic plaques into the arteries. Omega-3 PUFAs can regulate protein expression through peroxisome proliferator-activated receptors (PPARs), α, β, δ, γ, and thereby contribute to anti-inflammatory effect. Activation of PPAR-γ increases insulin sensitivity and enhances glucose metabolism, while activation of PPAR-β, δ enhances fatty acid metabolism. Thus, the peroxisome-activated nuclear receptors play a pivotal regulatory role into lipid metabolism and carbohydrate metabolism [8]. Several studies have described the reduction of blood triglyceride (TG) levels by 20-30% [9, 10] after high daily intake (over 4 g) of EPA and DHA. The pathophysiology of TG reduction is associated with the reduction of its hepatic synthesis and secretion into the blood. In addition, omega-3 PUFAs contribute to the elimination of very low-density lipoproteins by the liver, and the excretion of cholesterol catabolism products along with bile acids [11]. Omega-3 PUFAs

affect the level of total cholesterol, and can reduce it by 8-12%. It is also noteworthy that DHA and EPA have different effects on blood lipids. DHA primary increases HDL cholesterol level [12]. At the same time, DHA also increases low-density lipoprotein (LDL) cholesterol levels to a greater extent compared with EPA. The researchers noted that this effect is more pronounced in men compared with women [3, 13].

The hypotensive effect of omega-3 PUFAs for both normotonic and hypertensive patients has been mentioned. EPA and DHA reduce arterial stiffness and, therefore, decrease vascular resistance and pulse wave velocity. Activation of NO synthetase causes the increase of the NO production that is the main relaxing factor [14].

Omega-3 PUFAs can influence intracardiac hemodynamics and reduce myocardial remodeling. This effect can be explained by the decrease of diastolic and systolic volumes of the left ventricle, an increase of the ejection fraction and exercise tolerance [15].

The prescription of omega-3 PUFAs reduces platelet aggregation, and, considering the reduction of intracellular adhesion molecules production, can lead to the stabilization of atherosclerotic plaque and provide pleiotropic effect [16].

The effect on myocardial remodeling in patients after acute myocardial infarction has been shown into the OMEGA-REMODEL study, where the use of omega-3 PUFAs was associated with the reduction of negative left ventricular myocardial remodeling, primarily due to the decrease of the end-systolic volume index. The study also established the reduction of the fibrosis degree in the non-infarcted myocardium [17].

Omega-3 index and its interpretation

The consumption of omega-3 PUFAs dietary supplements or food rich in omega-3 is not equivalent to the content of omega-3 PUFAs in the human body, therefore, it is necessary to evaluate the level of EPA and DHA in the human body. The omega-3 index can serve as an objective biomarker for omega-3 PUFAs intake that is the total percentage of EPA and DHA from all measured fatty acids within erythrocyte membranes. This indicator does not depend on diet and correlates with the content of omega-3 PUFAs into the erythrocyte membrane. The omega-3 index ranges from 2% to 20% [18].

Several studies investigated the use of the omega-3 index for cardiovascular risk stratification. The data obtained indicate that omega-3 index level over 8% is associated with minimal cardiovascular risk, and omega-3 index less than 4% can be interpretated as risk factor for cardiovascular events (fatal and non-fatal myocardial infarction, sudden cardiac death) [19]. It has been shown that high omega-3 index is associated with the decrease of not only cardiovascular mortality, but also all-cause mortality. Thus, in patients with omega-3 index over 6.8%, all-cause mortality was 34% lower compared with those who had omega-3 index less than 4.2%, and the risk of CVD was lower by 39% [18].

Average level of omega-3 index differs between various countries. Regions with high blood levels of EPA+DHA (>8%) include the Sea of Japan, Scandinavia, and areas with indigenous populations not influenced by Westernized dietary habits. Very low blood levels (⩽4%) have been observed in North, Central and South America, Europe, the Middle East, Southeast Asia and Africa [20, 21].

Omega-3 PUFAs and cardiovascular disease prevention

Over the past 50 years large number of studies assessed the effectiveness of omega-3 PUFAs for primary and secondary CVD prevention. However, the results on the association between omega-3 fatty acid and clinical outcomes for cardiovascular events remain controversial.

For the first time, the possibility to influence recurrent cardiovascular events have been demonstrated in the DART (Diet and reinfarction trial) that showed the reduction in mortality during the 2 years after myocardial infarction among men who were advised to eat about 300 g of oily fish per week, or who took fish oil supplements giving an equivalent amount of n-3 fatty acids. The GISSI Prevenzione study confirmed the results of DART and showed that people who after myocardial infarction took omega-3 PUFAs had 15% lower risk of cardiovascular events, 30% lower relative risk of death from CVD as well as 45% lower risk of sudden cardiac death.

The GISSI-HF study (Studio della Sopravvivenza nell'Insufficienza cardiac — Heart Failure trial) evaluated the impact of PUFAs intake in patients suffering from heart failure. As a result, omega-3 intake was associated with the reduction of all-cause mortality in patients with chronic heart failure by 9% and the

frequency of admissions for ventricular tachyarrhythmia by 28%.

Subsequently, several observational studies examined the relationship between the intake of omega-3 PUFAs and cardiovascular outcomes. However, there is still lack of randomized controlled trials of sufficient duration that have shown cardioprotective effects in healthy people. The open-label JELIS study conducted by the Japan Environmental Protection Agency (Japan EPA) assessed the effect of EPA 1.8 g/day (as ethyl ester) in combination with statins versus statin alone in 18,645 hypercholesterolaemic patients. The primary endpoint was any major coronary event. The study showed that EPA and statin treatment was not superior to statin monotherapy for the primary prevention of major coronary events.

By the end of 2018 another two large randomized controlled trials on primary prevention were published. In the ASCEND (A Study of Cardiovascular Events in Diabetes) 15,480 people with diabetes mellitus without CVD were randomized to receive either marine n-3 fatty acids (840 mg/day EPA + DHA) versus olive oil (placebo) [22]. Two groups did not differ significantly by the incidence of the primary outcome (serious cardiovascular event) during 7-year follow-up.

In the VITAL study, conducted in 25,000 healthy subjects over the 50 (men) and 55 years (women) years old, participants were divided into two groups: group 1 took omega-3 fatty acids (840 mg/day EPA + DHA) and vitamin D (2000 IU/day), group 2 — placebo [23]. The follow-up period was 5 years. As a result, there were no significant differences in the primary outcomes of major cardiovascular events (combined myocardial infarction, stroke, or death from any cardiovascular cause) between the study groups.

The studies OMEGA, Supplementation en Folates et Omega-3 (SU.FOL.OM3), ORIGIN, Risk and Prevention Study evaluated the effectiveness of PUFAs for secondary prevention of recurrent fatal and non-fatal cardiovascular events. All these studies did not show any benefits of omega-3 PUFAs.

Due to conflicting results of studies that evaluated the efficacy of omega-3 PUFAs for primary and secondary prevention of cardiovascular events, large meta-analysis was conducted that included 79 randomized controlled trials (112,059 adult participants with various cardiovascular risks, mainly from high-income countries) lasting from 12 to 72 months. Most studies compared DHA and EPA supplements with diet rich in omega 3 PUFAs. This meta-analysis found little or no effect of EPA and DHA on all-cause mortality [24]. However, many researchers criticized the meta-analysis, pointing out that several factors were not considered by the researchers and could bias the result. First of all, low doses of omega-3, lack of accounting for the omega-3 index among participants, concomitant lipid-lowering therapy, short follow-up period and a long period between previous cardiovascular event and omega-3 PUFAs administration.

The REDUCE-IT study, published in early 2019, rehabilitated EPA and DHA and included 8,179 participants. The study evaluated the effect of EPA ethyl ester on primary and secondary outcomes. The study participants were divided into 2 groups: the first group took 4 g of EPA (icosapent ethyl) ethyl ester, the second group - placebo with mineral oil. The follow-up period averaged 4.9 years [25]. All patients received statins and had high triglycerides serum level (1.52–5.63 mmol/l). Patients, who received icosapent ethyl, showed statistically significant reduction in the relative risk of cardiovascular events by 25% compared with placebo. Accordingly, participants from icosapent ethyl group had significant reduction of TG and LDL cholesterol compared with placebo after 1-year follow-up. It is also noteworthy that the result in icosapent ethyl group did not depend on the initial TG level or the degree of subsequent TG decrease. This study demonstrated that high dose of EPA (4 g per day) may provide an additional benefit for the reduction of cardiovascular events and mortality.

The interaction between omega-3-polyunsaturated acids

The results obtained in the REDUCE-IT study pose the question on reason for such differences between the effect of various PUFAs on endpoints. There are significant gaps in the knowledge about the interaction between of EPA and DHA, since their effects are primarily assessed together as combination of two PUFAs. Several researchers have evaluated the effects of EPA and DHA on each other. It was found that EPA and DHA may compete for residency in membrane phospholipids, and thereby differentially displace n-6 PUFAs, which are highly prevalent in the population. This influence biophysical membrane properties, affects the synthesis of eicosanoids, activation of cellular signaling pathways and nuclear

receptors. Second, EPA and DHA exert different effects on plasma membrane biophysical structure, creating an additional layer of competition between the fatty acids in controlling signaling. DHA regulates membrane EPA levels. Therefore, there is molecular competition between EPA and DHA, which would ultimately impact outcomes [26]. These data refute the conclusions of some randomized clinical trials and meta-analyses that omega-3 PUFAs (usually administered as combination of EPA and DHA) have no effect on cardiovascular pathology [27, 28].

The REDUCE-IT study confirms the effect of EPA alone. The recent STRENGTH randomized clinical trial evaluated the impact of EPA/DHA mixed carboxylic acids (EPANOVA) in addition to statins on clinical outcomes, the development of any cardiovascular event in particular, in patients with high cardiovascular risk and hypertriglyceridemia. This study was suspended due to lack of evidence of omega-3 PUFAs supplements for cardiovascular benefit [29]. There is a possibility that these results may be due to DHA negating the effects of EPA. Although the administration of EPA alone in the REDUCE-IT study demonstrated good results.

The question on the varying degrees of absorption of different forms of omega-3 PUFAs remains open. Most dietary supplements are presented in two main forms: re-esterified triglyceride form of omega-3 or omega-3-acid ethyl esters that have varying degrees of absorption and side effects [30, 31]. The esterified monoglyceride form of omega-3 is less prevalent. Although this form has shown advantages since lower dose is needed to increase the concentration of serum PUFAs compared with other forms.

Conclusion

Omega-3 PUFAs have cardioprotective effect based on several well-studied biological mechanisms. Over the past 20 years, a fairly large number of clinical studies have been conducted to investigate the potential of EPA and DHA for the primary and secondary prevention of cardiovascular events in individuals with high and very high cardiovascular risk. The conflicting data reported by different trials can be explained by the use different EPA and DPA forms, low doses, and lack of control for omega-3 index as the key indicator for omega-3 PUFAs absorption. The REDUCE-IT study have shown the effectiveness of EPA ethyl ester in combination with statins for TG levels reduction.

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Asymptomatic severe mitral regurgitation in patient with undifferentiated connective tissue dysplasia. Clinical case of timely diagnosis and successful treatment

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Abstract. The spectrum of mitral valve (MV) pathology in patients with connective tissue dysplasia (CTD) include conditions from myxomatous degeneration with excess tissue of the valve leaflets and subvalvular apparatus, which is more common among young patients, to fibroelastic deficiency of the MV leaflets that is usually diagnosed in older age groups. Mitral regurgitation (MR) in patients with dysplasia belongs to the category of primary MR that can progress and lead to surgical treatment.

It is known that surgical intervention on MV in patients with CTD is recommended in cases of symptomatic severe MR. In asymptomatic severe MR with such pathophysiological consequences as left ventricular systolic dysfunction, pulmonary hypertension, atrial fibrillation, surgical treatment is also indicated. The question of surgical treatment of asymptomatic severe MI without the mentioned above criteria remains controversial.

Using the clinical example of long-term observation of the asymptomatic severe MR we will present step-by-step algorithm for patients with severe primary MI considering the latest clinical guidelines on valvular heart disease of 2021.

Keywords: mitral valve, mitral regurgitation, mitral valve repair, mitral valve replacement, mitral valve dysplasia.

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Introduction

Primary MR is associated with pathology of the MV and/or its subvalvular structures in contrast to secondary MR due to left ventricular (LV) pathology or left atrial dilatation (LAD) in patients with atrial fibrillation (AF). The most common cause of primary MR is connective tissue dysplasia, known as MV prolapse (MVP), a degenerative MV disease. Cardiac auscultation and echocardiography are the main tools for the diagnosis of this pathology, accompanied by transesophageal echocardiography (TEE) and cardiac MRI in controversial cases.

The understanding of disease pathophysiology and timely use of effective MR surgery is essential for the management of patients with severe primary MR. The necessity of surgical treatment is assessed considering the severity of MR, size and function of LV, presence of pulmonary hypertension (PH), AF, correction possibilities by MV repair, and of course, disease symptoms. In the absence of complaints in patients with severe primary MR, it is difficult to decide whether to perform surgery or wait, and waiting will sooner or later lead to irreversible left ventricular dysfunction.

Rational management of such patients is based on the research data that are used to update the clinical guidelines for the management of valvular heart disease regularly.

Clinical case

Patient Ya., 36 years old. Heart murmur persisted since the age of 15, at the age of 18 he was diagnosed with severe MR in the background of MV prolapse. The patient had been annually observed for 10 years, but because of the absence of complaints and stable normal parameters according to echocardiography, he did not consult a physician afterwards. Over the last year he started to have increased heart rate (HR) at restthat was the urged him to cardiologist.

The patient had asthenic constitution (height 186 cm, weight 71 kg, BMI 20.5); auscultation revealed holosystolic murmur in the precardiac area within interscapular space. Cardiac rhythm was regular, apex beat was intensified. Six-minute walk test — 500 meters. ECG showed sinus rhythm.,signs of left ventricular (LV) myocardial hypertrophy.

To determine the strategy for management of MVP, it is necessary to confirm the clinical and auscultatory picture by visualization of the heart valves.

Echocardiography is a gold standard for the diagnostics of cardiac valve pathology [1, 2]; in case of MR it enables to estimate its presence and severity accurately, describe MV pathology (changes of leaflets, localization, mechanism of MR — tear or prolapse, etc), determine hemodynamic consequences of heart chambers volume overload. In controversial cases, echocardiography can be supplemented by stress echocardiography, transesophageal echocardiogram (TEE), cardiac magnetic resonance imaging (MRI) and cardiac computed tomography (CT) [3, 4].

Step-by-step follow-up of the clinical guidelines for the management of valvular heart disease helps a physician to identify MR, determine the stage of the disease and, based on the results of scientific research, improve long-term outcomes in asymptomatic patients with severe MR [5, 6], by choosing the optimal and well-timed treatment strategy.

Step 1: Assessment of MR severity is performed according to the criteria proposed by ACC/AHA [7, 8]. MR is defined by both qualitative and quantitative criteria. Criteria of MR, including severe, are presented in Table 1.

Step 2: Determination of etiology and mechanism of MR. In primary MR, the most frequent etiological cause is MVP (about 2% in the population) [9, 10]. The important point is to specify: whether one or both leaflets are affected, whether there is no rupture of subvalvular structures.

At this stage it is also essential to clarity whether the primary MR was due to fibroelastic deficiency, as in isolated MV prolapse, or is it the Barlow disease, when there is an excess of MV tissue. The later situation is considered in the case of both leaflets prolapse

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Table 1. **MR severity criteria**

	Severity	Mild	Moderate	Severe
Qualitative criteria	Assessment by coronary angiography	1+	2+	3–4+
	Color flow doppler	< 20% LA	Variable	Central > 40% LA or holosystolic eccentric flow through MV
Quantitative criteria	Vena Contracta	< 0,3 cm	0,3–0,69 cm	⩾ 0,7 cm
	Regurgitation volume, (ml/beat) RegVol	< 30	30–44 45–54	⩾ 60
	Regurgitation fraction RF (%)	< 30	30–39 40–49	⩾ 50
	Effective regurgitant orifice area ERO (cm^2)	< 0,2	0,2–0,39	⩾ 0,40

that will be important for subsequent surgical treatment of MR.

Step 3. Evaluation of cardiac chamber sizes and volumes, LV function, which change under the influence of volume overload due to severe MR [11, 12].

Step 4. Assessment of the disease stage (Table 2). At this point, it is important to determine the stage of the disease, since the patient, remaining asymptomatic in stage C (see Table 2), has compensated MR, and MV surgery can still improve patient's prognosis. In urgent stage D, MR correction is usually ineffective [13, 14].

What is known about prognosis of asymptomatic patients with severe primary MR? The chance of asymptomatic patient with severe MR not to have chronic heart failure (CHF) and AF within 5 years is 36% [15]; 30–40% of patients will need MV surgery within 5 years, and complications they will include CHF, AF, pulmonary hypertension (PH), stroke, ventricaular tachycardia/ventricular fibrillation (VT/VF), death. Non-operative mortality in asymptomatic patients with primary MR is 0–8.4% [15, 16].

There are data on outcomes and various markers in patients with asymptomatic severe primary MR:

Assessment of MR and ejection fraction (EF) has a great prognostic value. According to Enriquez-Serrano group, the more severe is the MR, the worse is the prognosis [17, 18]. In MR, left ventricular ejection fraction (LV EF) is "supernormal", i.e., EF over 60% is considered normal, and below 60% — below normal and should be a trigger for surgical intervention.

In a multi-centric study, Ling et al. demonstrated that MV subvalvular rupture is always characterized by worse prognosis than in a healthy population, and outcomes with early surgery are superior to medical treatment [19, 20].

Patients with severe primary MR accompanied by PH had worselong-term outcomes– pulmonary artery pressure (SPAP) less than 35 mm Hg did not affect the prognosis, and when it increased over 45 mm Hg, the long-term prognosis worsened [21, 22].

Additional markers in patients with severe MR — LV Strain and brain natriuretic peptide (BNP) [23, 24]. In the study of 548 asymptomatic patients with severe MR and preserved LV EFwithout indications for MR surgery, these markers were informative in a regard to the prognosis [18, 25].

According to the results of the study published in 2014, the stress test has prognostic value: 884 patients with severe MR and preserved LV EF were examined. Those patients who did not reach 85% of necessary load had worse prognosis. In 576 pa-

Table 2. **Primary MR disease stages**

Stage	Definition	Hemodynamic changes	Symptoms
A	Risk of MR	No	No data
B	MR progression	• Moderate enlargement of LA • No LV enlargement • Normal pressure in lung artery	No data
C	Asymptomatic severe MR	• Moderate or severe LA enlargement • LV enlargement • PH is present in resting state or during: physical activity — C1: LV EF > 60% and LVID < 40 mm — C2: LV EF ⩽ 60% and LVID ⩾ 40 mm	No data
D	Symptomatic severe MR	Moderate or severe LA enlargement LV enlargement PH	Reduced exercise tolerance Dyspnea during physical activity

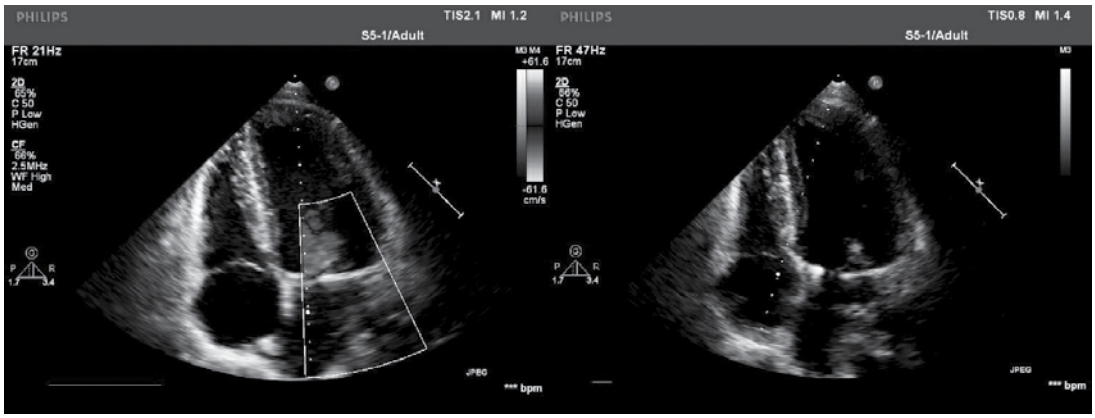

Fig. 1. Echo of the patient with severe MR before surgery

tients who performed over 100 % load, a refusal from MV surgery was not associated with a poor prognosis for at least five years [26].

Step 5. What are the indications for surgical treatment of severe primary MC in asymptomatic patients?

The latest 2021 Clinical Guidelines for the Management of Valvular Heart Disease of the European Society of Cardiology and Cardiothoracic Surgeons state that if the probability of successful MV repair is over 95 % and the estimated mortality of planned surgery is less than 1 %, surgical treatment should be performed in patients severe MR. It is especially important in the presence of PH, LV enlargement, LV EF decrease less than 60 % [27, 28]. According to above-mentioned guidelines, there should be very strong reasons not to perform surgery in these patients. One of such reasons can be insufficient experience of the surgical team, inability to guarantee the success of MV repair.

Summarizing the information above, the patient should undergo surgical treatment in case when severe MR is detected and there is no need to wait for the development of LV dysfunction and progression of clinical symptoms, and it is important to have an experienced surgical team that can offer wide range of surgeries on MV [29, 30].

Step 6. Cardiologist and the cardiac surgeon should inform patient on which MV surgery is and surgical incisions are planned.

Possible surgical approach options for surgical treatment of MR include total sternotomy, partial sternotomy, and anterolateral thoracotomy. There are many variants of MV repair and its combinations, and implantation of artificial heart valves is performed using both biological and mechanical prostheses. MV repair is preferable to mitral prosthesis in patients with isolated primary MR [4, 18], especially when using a mini-access.

Step 7. The key one, concerning the residual (return) MR and LV EF. Residual MR occurs infrequently, mainly after anterior MV leaflet repair, or the repair without using MM ring. The lower postoperative EF is, the worse are the outcomes [28].

Discussion

In the presented clinical case the patient underwent an echocardiography (Echo) (Fig. 1): the MV leaflets hadmyxomatous degeneration, there were anterior and posterior MV leaflets prolapse, dilation of the left LA, LV, MV fibrous ring. LV EF was 58 %, systolic pulmonary artery pressure (SPAP) was 39 mm Hg. Color flow doppler indicated the presence of eccentrically directed heavy MR flow. ERO — 0.45 cm^2, RV — 70 ml were calculated, which quantitatively confirmed the severity of the detected pathology.

According to the Echo results, the patient had severe asymptomatic MR in the background of Barlow disease, with hemodynamic overload of the left heart chambers, which has been going on all these years without affecting the patient's quality of life. Obviously, the had stage C, progressing MR, waiting for the appearance of clinical manifestation of the disease (stage D) is unacceptable, as it will worsen the patient's life prognosis and will not lead to the improvement of the condition after MV surgery, if it is postponed again (see Table 1).

On this basis, the patient was recommended to undergo MV repair with the installation of the support ring and it was explained that in case of unsatisfactory results, a prosthetic MV will be needed. Effective correction of the defect is evaluated intraoperatively, and if the MR persists, the patient is reoperated.

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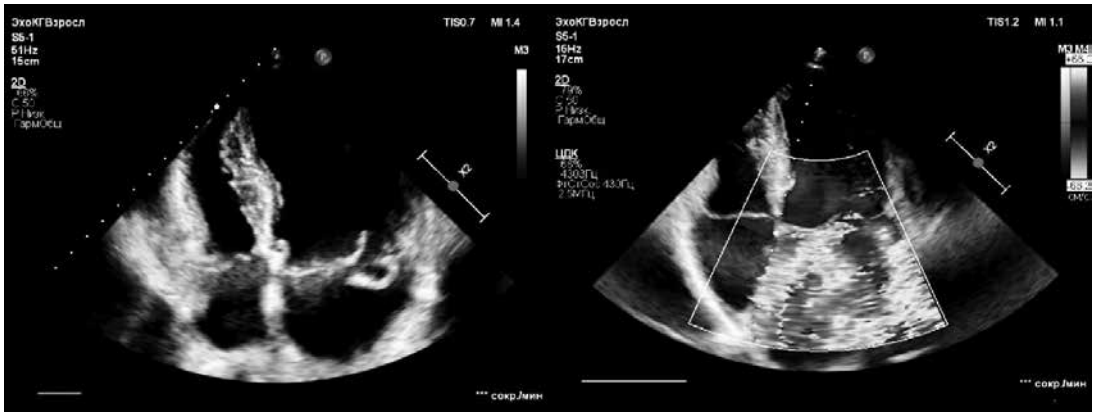

Fig. 2. ECHO of the patient after the surgery

In this clinical case the dilated MV fibrous ring was narrowed, it resulted in optimal coaptation of excess MV leaflet surfaces, providing an extended zone of contact between the anterior and posterior leaflets. One week after, by the time of discharge, due to the absence of volume overload, the size of LV and LV decreased, there were no residual MR, systolic anterior motion (SAM)-syndrome, EF was normal (Fig. 2). The patient was discharged in good condition.

Conclusion

The management of patients with severe primary MR should be performed in accordance with the current guidelines on valve diseases.

It is simple and clear to follow the algorithm when there are clinical manifestations of the disease and LV dysfunction; more difficult — when there are no symptoms. However, according to the 2021 guidelines, the earlier surgery is associated with better results.

The key point of the diagnosis is accurate Echo data. In addition, the role of biomarkers, stress test, and LV Strain is important.

The decision-making team regarding surgical treatment of MR should discuss all cases of severe primary MR, recommend the best time for surgery, suggest advanced valve repair techniques, and present their own experience and success in this direction.

Conflict of interest: None declared.

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Author Guidelines

Manuscript publication rules
in the International heart and vascular disease journal

Edit from December, 2021

Disclaimer: The rules came into effect from December 2021. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

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International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

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2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5.000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

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[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

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2. The author is sent a notification letter of receipt of the manuscript with the number (ID), which will be used in subsequent correspondence. The author can track the stages of work on his manuscript through the site. Since the process of bringing the manuscript to the necessary standards takes enough expert time, the payment for the initial review of the article was introduced, which the author (s) are required to carry out after the article is posted on the site.

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— Manuscripts are checked in the "Antiplagiat" system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

4. All manuscripts submitted to the journal are sent to one of the permanent reviewers or an independent expert according to the profile of the research.

5. The review process is anonymous both for the Author and for the reviewers. The manuscript is sent to the reviewer without the names of the authors and the name of the institution.

6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the ar-

ticle or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

9. If the reviewer makes a conclusion about the impossibility of publication of the article. The author of the reviewed work is given the opportunity to read the text of the review, if he does not agree with the conclusions of the reviewer. In case of disagreement with the opinion of the reviewer, the Author has the right to provide a reasoned response to the Editor. The article can be sent for re-review or for approval to the editorial Board. The editorial Board or its authorized editor shall send its response to the Author.

10. All manuscripts that have been reviewed and evaluated by an expert in statistics are submitted to the editorial Board, which decides on the publication. After the decision on the admission of article for publication, the Editorial office inserts the publication of the article in terms of publications. Information about the annual (thematic) plan of publications is placed on the website of the journal.

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X. After the publication in the journal

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XII. Position E-log backup (if journal is no longer published)

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All this information is publicly available in The system of the Russian citation index on the website of the Electronic library www.elibrary.ru

XIII. Journal subscription

Information on subscriptions is available on the journal website in the section "Subscription":

XIV. Journal subscription

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http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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