ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

РОССИЙСКИЙ КАРДИОЛОГИЧЕСКИЙ ЖУРНАЛ

Russian Journal of Cardiology

SCIENTIFIC, PEER-REVIEWED MEDICAL JOURNAL

RUSSIAN SOCIETY OF CARDIOLOGY

IN ISSUE:

IN FOCUS:
Hypertension

№ 4 | 2021

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

Russian Society of Cardiology

Scientific peer-reviewed medical journal

Mass media registration certificate № 017388 dated 06.04.1998

Periodicity — 12 issues per year
Circulation — 7 000 copies

The Journal is in the List of the leading scientific journals and publications of the Supreme Examination Board (VAK)

The Journal is included in Scopus, EBSCO, DOAJ

Russian Citation Index:
SCIENCE INDEX (2019) 2,710
Impact-factor (2019) 1,668

Complete versions of all issues are published: *www.elibrary.ru*

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Printed: OneBook, Sam Poligraphist, Ltd. 129090, Moscow, Protopopovsky per., 6. www.onebook.ru

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RUSSIAN JOURNAL OF CARDIOLOGY

№ 26 (4) 2021
founded in 1996

Editorial office:
119049, Moscow,
ul. Shabolovka, 23-254
e-mail: cardiojournal@yandex.ru
Tel. +7 (985) 768 43 18

Publisher:
Silicea-Poligraf
e-mail: cardio.nauka@yandex.ru

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2021-4

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

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MANUSCRIPT PUBLICATION RULES (2019)
http://russjcardiol.elpub.ru/jour/about/submissions#authorGuidelines

Dear colleagues,

Zhanna D. Kobalava

Sergey V. Nedogoda

For more than a year, we have been living in a next normal due to the coronavirus disease 2019 (COVID-19) pandemic, which largely specifies the routine practice in various medical specialties, including cardiology. Offline medical conferences are still being canceled, while online communication has become commonplace. In this regard, the importance of telemedicine is increasing. We have yet to assess the COVID-19 consequences, but its ability to induce long-term stable symptoms of both general and specific nature is already generally recognized, which served as the basis for the term "long COVID". We have witnessed the rapid increase in a number of studies, which has become, on the one hand, an advantage in the form of vaccine development, and on the other, a disadvantage in the form of denials and wrongful observational studies. From the evidence-based medicine, we have largely returned to a pathophysiological approach in the choice of treatment strategy. Burnout syndrome among doctors is increasing everywhere. In the pandemic, a decrease in hospitalization rate of cardiovascular patients was recorded with an increase in infarction-related mortality and incidence of decompensated heart failure. It became apparent that the withdrawal of cardiovascular drugs, which improve the prognosis, is associated with higher mortality in the acute and post-acute phase. The section "Methodological aspects" of this journal issue analyzes the one-year publication activity during the COVID-19 pandemic in medical specialties in Russian. This issue of the journal is mainly devoted to hypertension (HTN), but also contains interesting materials on related problems, in particular, heart failure and myocardial infarction. The original studies highlight the problems of treating resistant HTN and management of patients of different age groups. Of great practical interest is the material on the quality of outpatient follow-up of the hypertensive adults in Russia.

We would like to present you the current issue of the Russian Journal of Cardiology, which is largely devoted to HTN. It is noteworthy that a significant part of papers is devoted to the problems of high blood pressure (BP) in obesity, overweight, apnea and comorbidities. These works will be very useful for practitioners for more effective BP control in these clinical situations.

Publications on resistant HTN are of great practical interest, since they describe not only the globality and importance of the problem, but also suggest ways to solve it, which can already be applied in actual clinical practice.

Undoubtedly, one of the most interesting publications is devoted to the Retrospective analysis of clinical decision support system use in patients with hypertension and atrial fibrillation (INTELLECT). In fact, this is one of the first works on the practical application of artificial intelligence, which is increasingly used in the routine practice of a doctor.

Traditionally, the current clinical guidelines of the Russian Society of Cardiology are of great interest – "Non-ST elevation acute coronary syndrome" and "Bradyarrhythmias and conduction disorders".

We would especially like to note the Dynamics analysis of comorbidities in SARS-CoV-2 survivors (AKTIV SARS-CoV-2), with an assessment of unfavorable prognostic factors. This work is not only very timely and necessary, but is also largely based on data from Russian centers, which is especially important for planning further strategies to combat the COVID-19 epidemic.

Best regards, on behalf of the editorial staff

Zhanna D. Kobalava, Doctor of Medical Science,
Professor, Corresponding Member of Russian Academy of Sciences
Sergey V. Nedogoda, Doctor of Medical Science, Professor

Russian Journal of Cardiology 2021;26(4):4466
doi:10.15829/1560-4071-2021-4466
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Effect of visceral obesity on main artery elasticity and vascular age in patients with hypertension, obesity, and type 2 diabetes

Statsenko M. E., Derevianchenko M. V.

Aim. To assess the effect of visceral obesity on main artery elasticity and vascular age in patients with hypertension (HTN), obesity, and type 2 diabetes (T2D).

Material and methods. A total of 320 patients with stage II-III HTN aged 45-70 years were divided into 4 groups: isolated HTN (group 1), HTN and obesity (group 2), HTN, obesity and T2D (group 3), HTN and T2D without obesity (group 4). We assessed the clinical status, parameters of visceral obesity, main artery elasticity, and vascular age. We used nonparametric statistics, Spearman correlation analysis.

Results. At least 50% of all patients had visceral obesity, despite no BMI-estimated obesity in groups 1 and 4: 57,5 vs 100,0 vs 100,0 vs 50,0% in groups 1, 2, 3 and 4, respectively ($p<0,0001$).

In the groups where hypertension was combined with obesity and T2D, the proportion of patients with leptin content above 32,7 ng/ml significantly increased to 80% (in total for groups 2 and 3) compared with 25,0% among HTN people without obesity (in total for groups 1 and 4). There was a significant increase in proportion of patients with a adiponectin decrease <14,6 ng/ml among patients with a combination of HTN and T2D ± obesity (45% in total for groups 3 and 4) in comparison with those with HTN and without T2D ± obesity (22,5% in total for groups 1 and 2). The visceral adiposity index (VAI) was significantly higher among patients with HTN, obesity and T2D compared with those with isolated HTN and HTN in combination with T2D only (2,96 [2,36; 3,98] vs 1,87 [1,40; 2,67] vs 2,22 [1,61; 3,26], respectively). A higher proportion of subjects with adipose tissue dysfunction was noted in groups 2 and 3 compared to groups 1 and 4 (75 vs 81,1 vs 41,5 vs 53,4%, respectively, $p_{1-2}<0,001$, $p_{1-3}<0,001$, $p_{2-4}=0,023$, $p_{3-4}=0,002$). The proportion of patients with a pulse wave velocity >10 m/s was consistently more common among patients of group 3 compared with patients in groups 1 and 2 (77,0 vs 57,9 and 55,3%, respectively, $p_{1-3}=0,004$, $p_{2-3}=0,006$).

Vascular age was significantly lower in group 1 compared with groups 3 and 4 (64,0 [57,8; 71,0] vs 69,0 [62,0; 73,0] and 69,5 [66,0; 74,3] years, respectively), as well as in group 2 compared with group 4 (64,0 [56,5; 70,5] vs 69,5 [66,0; 74,3] years). The 5-year risk of cardiovascular events was significantly higher among patients with hypertension, obesity and T2D and those with HTN and T2D without obesity, compared with patients with isolated HTN, and with those with HTN and obesity (5,9 [3,9; 7,9] and 6,5 [4,7; 8,7] vs 4,4 [2,7; 6,8] and 3,6 [2,4; 5,8], respectively).

Correlation analysis revealed the relationship between the visceral obesity parameters, main artery elasticity, vascular age and the 5-year risk of cardiovascular events, demonstrating the special aspects of HTN course in each of the studied groups.

Conclusion. The paper showed peculiarities of the effect of visceral obesity on main artery elasticity and vascular age in patients with HTN in combination with obesity and T2D.

Keywords: hypertension, visceral obesity, diabetes, vascular age.

Relationships and Activities. The study was performed at the expense of scientists' grant of Volgograd State Medical University (order 29-KO dated June 2, 2020).

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Received: 15.04.2021
Revision Received: 22.04.2021
Accepted: 23.04.2021

For citation: Statsenko M. E., Derevianchenko M. V. Effect of visceral obesity on main artery elasticity and vascular age in patients with hypertension, obesity, and type 2 diabetes. *Russian Journal of Cardiology*. 2021;26(4):4466. (In Russ.) doi:10.15829/1560-4071-2021-4466

Currently, there is a tendency towards an increase in the prevalence of obesity [1] and a understandable increase in the number of persons with type 2 diabetes (T2D) [2]. Both diseases increase the risks of cardiovascular diseases and events. Thus, the presence of hypertension (HTN) in a patient with T2D additionally quadruples the risk [3].

The pathogenesis of vascular involvement in patients with HTN combined with obesity, T2D are not only endothelial dysfunction, hyperuricemia, activation of the sympathoadrenal and renin-angiotensin-aldosterone systems, secretion of pro-inflammatory cytokines, microcirculation disorders, decreased elasticity of major vessels, but also additional ones inherent in obesity and T2D — visceral obesity, carbohydrate and lipid metabolism disorders, insulin resistance. In earlier papers, we have already considered the role of low-grade chronic inflammation, endothelial dysfunction, insulin resistance in target organ damage in hypertensive persons with obesity, T2D, as well as the importance of leptin and adiponectin in increasing the vascular stiffness in hypertensive people with obesity [4-9].

The aim was assess the effect of visceral obesity on main artery elasticity and vascular age in patients with hypertension (HTN), obesity, and T2D.

Material and methods

This open-label, comparative, prospective, parallel group study included 320 patients with stage II-III HTN aged 45-70 years with unreached target blood pressure (BP). Patients were randomized into 4 groups, matched by sex, age, smoking, history of HTN, office systolic BP (SBP) and heart rate (HR), depending on the presence/absence of obesity and/or T2D. The first group consisted of 102 patients with isolated HTN (without obesity and T2D), the second — 90 patients with HTN and obesity, the third — 96 patients with HTN, obesity and T2D, the fourth — 32 patients with HTN and T2D without obesity (Table 1). Patients with T2D (groups 3 and 4) were also comparable in disease duration and dosages of hypoglycemic medications. The 1st and 4th groups were control. There were following exclusion criteria: uncontrolled malignant hypertension, prior acute coronary syndrome and stroke within last 6 months, hemodynamically relevant heart defects and arrhythmias, type 1 diabetes, class III obesity, manifested liver failure, stage >C3b chronic disease kidney, alcohol abuse, any other diseases that could affect the study results. The nature of the study is an in parallel groups.

In all patients, we assessed their clinical status (complaints, medical and life history, risk factors for hypertension, overall health status, office BP, heart rate), anthropometric data (height, weight, body mass index (BMI), level of subcutaneous and visceral fat analyzed by bioelectrical impedance analysis using the Omron BF-508 system, waist circumference (WC), hip circumference (HC). Abdominal obesity was considered to be a waist-to-hip ratio (WHR) >0,9 for men and WHR >0,85 for women; WC ⩾102 cm for men and WC ⩾88 cm for women [1]; visceral obesity — visceral fat ⩾9% [1].

To determine obesity laboratory markers, the serum concentration of leptin (Diagnostics Biochem, Canada) and adiponectin (Mediagnost, GmbH, Germany) by sandwich enzyme-linked immunosorbent assay using a Uniplan analyzer, Russia. There were following reference values: for leptin — 3,7-11,1 ng/ml (for women ⩽27,6 ng/ml, for men ⩽13,8 ng/ml), for adiponectin — 8,2-19,1 ng/ml.

Visceral obesity index (VAI) was estimated. The severity of adipose tissue dysfunction (ATD) was assessed taking into account the patient age [10].

To analyze the main artery elasticity, the pulse wave velocity (PWV) was measured using a Poly-Spectr-8/E sphygmographic system (Russia). PWV in elastic (PWVe) and muscular (PWVm) arteries was assessed in the carotid-femoral and carotid-radial segments, respectively. The normal values of PWVm and PWVe were interpreted individually using the software, taking into account the sex and age of the patients.

Vascular age and 5-year cardiovascular risk were assessed using the ADVANT'AGE calculator for smartphones (version 2021).

Statistical analysis was performed using the Microsoft Excel 2010 and Statistica 10.0 software package. The normality of the distributions was assessed using the Shapiro-Wilk test. In non-normal distribution, nonparametric statistical methods were used. Quantitative data are presented as Me [Q25; Q75], where Me is the median, Q25 and Q75 are the 25th and 75th percentiles, respectively; qualitative variables are presented as prevalence (%). Multiple comparison of four independent samples was performed using the Kruskal-Wallis test. The differences were considered significant at $p<0,05$. When significant differences were identified according to the Kruskal-Wallis test, a subsequent Bonferroni-Dunn comparisons were carried out. In the case of dichotomous variables, the significance of the differences was analyzed using Fisher's exact test. To assess the relationship statistics, a Spearman correlation was used.

This study was performed in accordance with the Helsinki declaration, Good Clinical Practice, World Medical Association (2008), and the Constitution of the Russian Federation. The study was approved by the Regional Ethics Committee. All patients signed written informed consent.

Table 1

Clinical and demographic parameters in studied patients (Me [25%; 75%])

Parameter	Group 1 HTN without obesity and T2D	Group 2 HTN + obesity without T2D	Group 3 HTN + obesity + T2D	Group 4 HTN + T2D without obesity
Number of patients, n	102	90	96	32
Men/women, %	34,4/65,6	37,8/62,2	32,3/67,7	34,4/65,6
Age, years	62,0 [55,0; 66,0]	62,0 [55,3; 65,8]	62,0 [58,0; 65,0]	63,0 [60,0; 66,0]
BMI, kg/m^2	26,7*,† [25,4; 28,7]	32,9†† [31,1; 36,0]	34,7§§ [32,5; 37,5]	27,2 [25,9; 28,5]
WC, cm	94,0*,† [83,0; 100,0]	105,0†† [99,3; 111,8]	107,0§§ [102,0; 116,0]	93,5 [88,3; 99,3]
HC, cm	102,0*,† [99,0; 105,0]	115,0†† [110,0; 125,0]	116,0§§ [108,0; 122,0]	103,5 [98,0; 105,3]
WHR	0,91 [0,82; 0,96]	0,91 [0,85; 0,99]	0,94 [0,88; 1,00]	0,91 [0,87; 0,96]
Patients with abdominal obesity assessed by WHR,%	51,2*,†,§	73,7**	86,3	71,9
Patients with abdominal obesity assessed by WC,%	61,0*,†,§	100,0††	100,0§§	90,6
Subcutaneous fat, %	30,7*,† [26,0; 39,2]	45,1†† [39,3; 49,4]	44,7§§ [38,1; 50,0]	35,2 [27,0; 40,1]
Visceral fat, %	10,5*,† [8,0; 13,0]	14,0†† [11,0; 16,0]	14,0§§ [13,0; 17,0]	9,5 [8,0; 11,0]
Prevalence of visceral obesity, %	57,5*,†	100,0††	100,0§§	50,0
Smokers, %	21,6	21,1	20,8	21,9
Duration of HTN, years	12,0 [8,0; 19,0]	12,0 [7,0; 20,0]	15,0 [9,5; 20,0]	12,0 [7,0; 20,0]
Prevalence of statin therapy, %	8,8†,§	7,8**,††	50,0	59,4
Duration of T2D, years	0†,§	0**,††	7,0 [3,0; 10,0]	7,0 [4,5; 10,0]
Office SBP, mm Hg	160 [150; 170]	160 [150; 170]	159 [150; 170]	160 [150; 164]
Office DBP, mm Hg	100†,§ [91; 103]	100**,†† [94; 108]	93 [90; 100]	90 [83; 100]
Office PP, mm Hg	60†,§ [50; 70]	60 [55; 70]	62 [60; 77]	70 [60; 75]
Heart rate, bpm	70 [65; 75]	73 [64; 78]	70 [64; 76]	70 [65; 80]

Note: * — significance of differences between groups 1 and 2, † — significance of differences between groups 1 and 3, § — significance of differences between groups 1 and 4, ** — significance of differences between groups 2 and 3, †† — significance of differences between groups 2 and 4 groups, §§ — significance of differences between 3 and 4 groups.

Abbreviations: HTN — hypertension, DBP — diastolic blood pressure, BMI — body mass index, HC — hip circumference, WC — waist circumference, WHR — waist–to–hip ratio, PP — pulse pressure, SBP — systolic blood pressure, T2D — type 2 diabetes.

Results

There were significant differences in BMI between 1 and 2, 1 and 3, 2 and 4, 3 and 4 groups: BMI was higher in groups 2 and 3 (p<0,0001).

WC and HC were also significantly higher in the groups of patients with HTN and obesity, as well as with HTN, obesity and T2D in comparison with those with HTN and HTN + T2D without obesity (p<0,0001). There was a tendency towards higher values of WHR among persons with HTN, obesity and T2D. However, the differences were not significant.

Noteworthy is the high percentage of patients with abdominal obesity determined by WC, WHR, and visceral fat in all studied groups. As for proportion of obese (assessed by WC) patients, significant differences were noted between 1 and 2, 1 and 3 groups. In group 1, the proportion of patients with abdominal obesity assessed by WHR was significantly lower in comparison with groups 2, 3 and 4 (Table 1).

Subcutaneous and visceral fat levels were lower in groups 1 and 4 compared to groups 2 and 3 (p<0,0001 for both). At the same time, at least 50% of patients in all groups had visceral obesity, despite the absence of obesity assessed by BMI in groups 1 and 4: 57,5 vs 100,0 vs 100,0 vs 50,0% in 1, 2, 3 and 4 groups, respectively (p<0,0001).

The proportion of statin therapy was significantly higher among patients with HTN, obesity and T2D, as well as among those with HTN and T2D without obesity, which is due to compliance with national guidelines and standards for the management of T2D patients. Statin dosages was comparable in all 4 groups.

Differences were noted between groups 1 and 2 in comparison with groups 3 and 4 in terms of office diastolic BP (DBP) — p<0,0001: lower DBP values

Table 2

Laboratory markers of obesity in studied patients (Me [25%; 75%])

Parameter	Group 1 HTN without obesity and T2D	Group 2 HTN + obesity without T2D	Group 3 HTN + obesity + T2D	Group 4 HTN + T2D without obesity
Leptin, ng/ml	15,2* [6,6; 32,7]	53,8 [38,4; 75,8]	42,8 [25,1; 54,0]	13,2 [9,9; 18,2]
Adiponectin, ng/ml	21,7 [14,6; 32,9]	18,6 [15,3; 22,4]	16,5 [11,2; 20,5]	17,5 [7,1; 27,6]

Note: * — significance of differences between groups 1 and 2.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes.

Table 3

Elasticity parameters of the main arteries in studied patients (Me [25%; 75%])

Parameter	Group 1 HTN without obesity and T2D	Group 2 HTN + obesity without T2D	Group 3 HTN + obesity + T2D	Group 4 HTN + T2D without obesity
PWVm, m/s	8,2 [7,4; 10,0]	8,4 [7,7; 9,2]	9,0 [8,1; 10,3]	8,9 [7,0; 10,8]
PWVm >10 m/s, % of patients	44,7	34,2**	55,2	44,8
PWVe, m/s	8,9† [8,2; 10,2]	8,8** [7,7; 10,6]	10,4 [9,1; 12,4]	9,2 [8,3; 11,4]
PWVe >10 m/s, % of patients	57,9†	55,3**	77,0	62,1
PWVm/PWVe	0,93 [0,77; 1,03]	0,92 [0,83; 1,03]	0,87 [0,80; 0,97]	0,91 [0,80; 1,03]

Note: † — significance of differences between groups 1 and 3, ** — significance of differences between groups 2 and 3.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes, PWVm — pulse wave velocity in muscular arteries, PWVe — pulse wave velocity in elastic arteries.

Table 4

Assessment of vascular age and 5-year cardiovascular risk in studied patients (Me [25%; 75%])

Parameter	Group 1 HTN without obesity and T2D	Group 2 HTN + obesity without T2D	Group 3 HTN + obesity + T2D	Group 4 HTN + T2D without obesity
Vascular age, years	64,0†,§ [57,8; 71,0]	64,0†† [56,5; 70,5]	69,0 [62,0; 73,0]	69,5 [66,0; 74,3]
5-year risk.	4,4†,§ [2,7; 6,8]	3,6**,†† [2,4; 5,8]	5,9 [3,9; 7,9]	6,5 [4,7; 8,7]
5-year risk grade				
Low, % of patients	16,9†,§	17,5**,††	3,1	0,0
Moderate, % of patients	46,5§	44,4	33,3	25,0
High, % of patients	36,6†,§	33,3**,††	61,5	75,0
Very high, % of patients	0,0*	4,8	2,1	0,0

Note: * — significance of differences between groups 1 and 2, † — significance of differences between groups 1 and 3, § — significance of differences between groups 1 and 4, ** — significance of differences between groups 2 and 3, †† — significance of differences between groups 2 and 4 groups, §§ — significance of differences between 3 and 4 groups.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes.

are characteristic of patients with T2D. An increase in office pulse pressure (PP) was naturally revealed in persons of groups 3 and 4 compared with groups 1 and 2 (p=0,0009 for both).

In all studied groups, a relationship was found between the level of visceral fat and WC (r=0,74 vs r=0,61 vs r=0,55 vs r=0,59 in groups 1, 2, 3 and 4, respectively, p<0,05).

There were significant correlations between BMI and WC (r=0,79), HC (r=0,79), subcutaneous (r=0,64) and visceral fat (r=0,67) extent, and leptin level (r=0,55).

Of all the revealed relationships with the WHR, the most clinically and pathogenetically important are correlations with the levels of visceral fat (r=0,52, p<0,05) and adiponectin (r=-0,34, p<0,05).

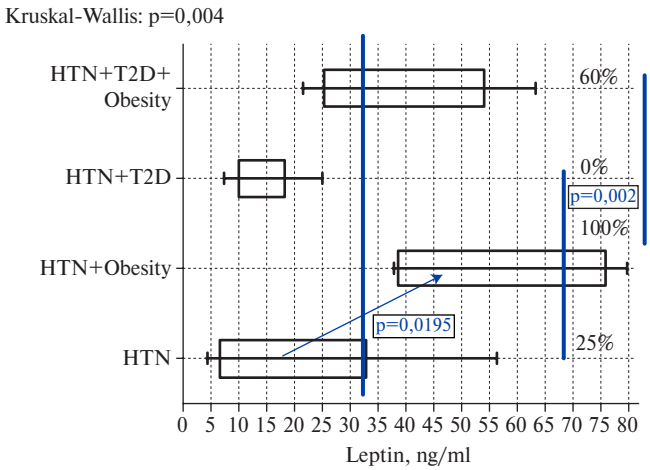

Figure 1. Distribution of patients by leptin level and proportion of subjects with analyte >32,7 ng/ml.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes.

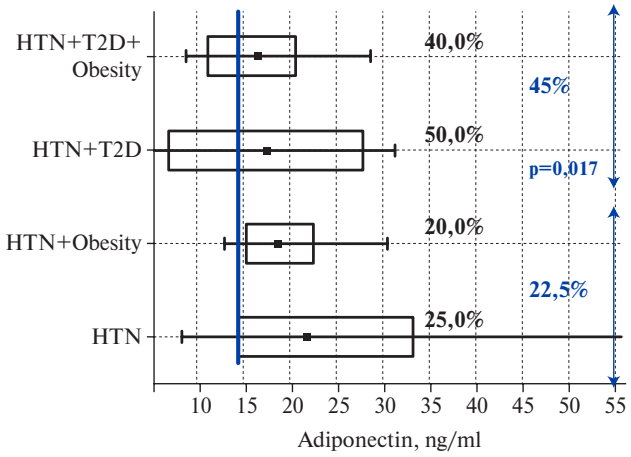

Figure 2. Distribution of patients by adiponectin level and proportion of patients with analyte <14,6 ng/ml.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes.

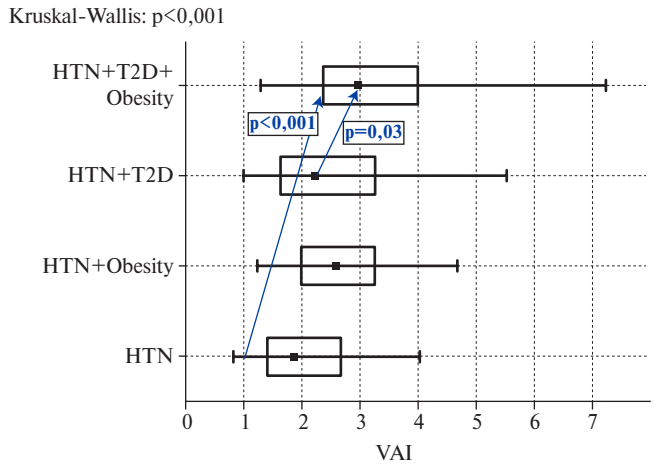

Figure 3. Distribution of patients by VAI.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes, VAI — visceral adiposity index.

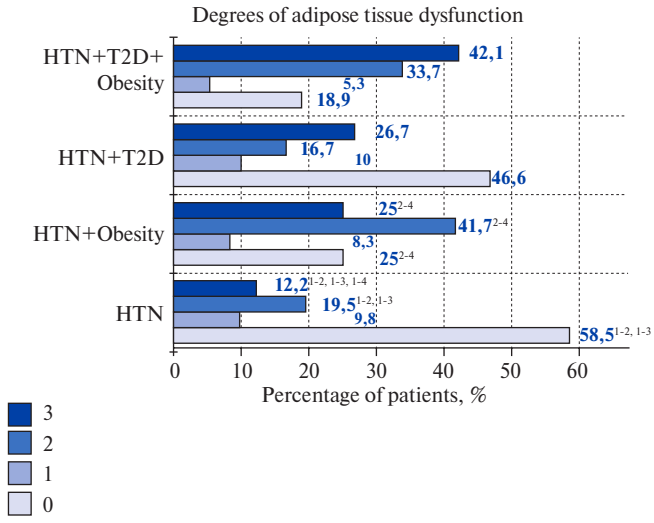

Figure 4. Distribution of patients by the severity of adipose tissue dysfunction.
Note: 0 — no dysfunction, 1 — mild dysfunction, 2 — moderate dysfunction, 3 — severe dysfunction, 1-2, 1-3, 1-4, 2-4 — significant differences between 1 and 2, 1 and 3, 1 and 4, 2 and 4 groups.
Abbreviations: HTN — hypertension, T2D — type 2 diabetes.

The analysis of obesity markers revealed an increase in the serum concentration of leptin in patients with HTN, obesity and those with hypertension, obesity, and T2D (Table 2). However, the differences reached the significance level only when comparing groups 1 and 2 (15,2 [6,6; 32,7] vs 53,8 [38,4; 75,8] ng/ml, p=0,02), which is probably associated with a large variation. At the same time, in the groups where HTN was combined with obesity ± T2D, the proportion of patients with leptin >32,7 ng/ml significantly increased to 80% (total for 2 and 3 groups) compared with 25,0% among hypertensive patients without obesity (total for groups 1 and 4) — Figure 1.

Correlation analysis showed the presence of significant relationships between the concentration of leptin and PWVe (r=0,58) in the group of isolated HTN, as well as between leptin levels and PP (r=0,99), ATD (r=0,59) in those with HTN and obesity.

Noteworthy is the decrease in serum adiponectin levels when obesity, T2D, and especially the combination of obesity and T2D are combines with HTN, but no significant differences were found between the groups (Table 2). According to interquartile intervals, adiponectin level of 14,6-22,5 ng/ml was in the majority of studied patients. However, there was a significant increase in the prevalence of adiponectin <14,6 ng/ml among

patients with a combination of HTN and T2D ± obesity (45% for groups 3 and 4) in comparison with hypertensive patients without T2D ± obesity (22,5% for groups 1 and 2) (Figure 2).

In group 4, the adiponectin level correlated with office (r=-0,76), office DBP (r=-0,85), PWVe (r=-0,97) — p<0,05 for all.

VAI was significantly higher among patients with HTN, obesity and T2D compared with those with isolated HTN and HTN in combination with T2D without obesity (2,96 [2,36; 3,98] vs 1,87 [1,40; 2,67] vs 2,22 [1,61; 3,26], respectively) (Figure 3).

A higher proportion of patients with adipose tissue dysfunction was noted in groups 2 and 3 compared to groups 1 and 4 (75 vs 81,1 vs 41,5 vs 53,4%, respectively, p_{1-2}<0,001, p_{1-3}<0,001, p_{2-4}=0,023, p_{3-4}=0,002). The distribution of patients depending on ATD is shown in Figure 4.

When HTN combined with obesity and T2D, there is an increase in PWVm but the differences between the groups did not reach the significance level (Table 3).

PWVe was significantly higher among patients with HTN, obesity and T2D in comparison with both subjects with isolated HTN and those with HTN and obesity (10,4 [9,1; 12,4] vs 8,9 [8,2; 10,2] and 8,8 [7,7; 10,6] m/s, respectively). The proportion of patients with PWVe >10 m/s was consistently more common among group 3 patients compared with groups 1 and 2 (77,0 vs 57,9 and 55,3%, respectively, p_{1-3}=0,004, p_{2-3}=0,006). The correlation was established between PWVe and leptin concentration (r=0,58), ATD (r=0,53) in group 1, as well as between PWVe and adiponectin concentration (r=-0,96) in group 4 (p<0,05 for all).

Vascular age was significantly lower in group 1 in comparison with groups 3 and 4 (64,0 [57,8; 71,0] vs 69,0 [62,0; 73,0] and 69,5 [66,0; 74,3] years, respectively), as well as in group 2 in comparison with 4 (64,0 [56,5; 70,5] vs 69,5 [66,0; 74,3] years) (Table 4).

The five-year risk of CVE was significantly higher among patients with HTN, obesity and T2D and those with HTN and T2D without obesity compared with subjects with isolated HTN and HTN + obesity (5,9 [3, 9; 7,9] and 6,5 [4,7; 8,7] vs 4,4 [2,7; 6,8] and 3,6 [2,4; 5,8], respectively). Risk stratification showed that the total percentage of persons with high and very high risk was significantly higher among groups 3 and 4 compared to groups 1 and 2.

Intragroup correlation analysis revealed significant correlations between visceral fat level and BMI (r=0,79), heart rate (r=0,55), 5-year cardiovascular risk (r=0,64) among patients with isolated HTN, as well as significant relationships between the visceral fat level and adiponectin (r=-0,80), vascular age (r=0,58), 5-year cardiovascular risk (r=0,72) in patients with HTN and obesity without T2D.

Correlation analysis in all groups revealed a significant relationship of age with vascular age (r=0,78) and 5-year CVD risk (r=0,54).

Discussion

Significant differences in BMI between groups 1 and 2, 1 and 3, 2 and 4, 3 and 4 are due to the study design. With an increase in BMI, the percentage of subcutaneous and visceral fat, as well as WHR naturally increased.

Identified high prevalence of abdominal obesity in the patients with isolated HTN and HTN in combination with T2D without obesity (with normal or overweight), as well as of visceral obesity in people with normal and overweight (according to BMI) has an important practical significance. So, for the diagnosis of obesity, it is advisable to assess not only BMI, but also WC, WHR, as well as the visceral fat proportion.

Significantly higher numbers of office PP in patients with a combination of HTN and T2D are associated with a decrease in office DBP and indicate an increase in arterial stiffness and subclinical target organ damage [11].

Revealing significant correlations between BMI, WC, HC, WHR, levels of subcutaneous and visceral fat and laboratory markers of obesity confirms the pathogenetic role of obesity in the progression of target organ damage. Different nature of interrelations in each of the studied groups indicates a different degree of significance of pathogenetic links as obesity and T2D join the HTN.

A significant increase in PWVe among patients with HTN, obesity and T2D in comparison with both individuals with isolated HTN and those with HN and obesity (10,4 [9,1; 12,4] vs 8,9 [8,2; 10,2] and 8,8 [7,7; 10,6] m/s, respectively) is associated with early main artery remodeling in patients with HTN and comorbidities. Apparently, both obesity and T2D potentiate the negative effect on the vascular wall.

The highest percentage of patients with PWVe >10 m/s, which is a sign of asymptomatic vascular involvement and an independent prognostic marker for fatal and non-fatal cardiovascular events, was naturally more common among patients in group 3 compared with groups 1 and 2 (77,0 vs 57,9 and 55,3%, respectively, p_{1-3}=0,004, p_{2-3}=0,006). This indicates an increase in stiffness and allow assessing the true arterial wall damage [12].

The concept of main artery stiffness is associated with the concept of vascular age. Currently, a new risk stratification algorithm in hypertensive patients receiving antihypertensive therapy is being

used — the ADVANT'AGE vascular age calculator for smartphones (version 2021). Demographic parameters, smoking status, SBP, previous antihypertensive therapy and diabetes, total cholesterol, high-density lipoprotein cholesterol, glucose and creatinine are taken into account.

A significant increase in vascular age in groups 3 and 4 compared with group 1, as well as in group 2 compared with group 4, was associated with an increase in the 5-year cardiovascular risk among patients with HTN, obesity and T2D and those with HTN and T2D without obesity in comparison with patients with isolated HTN, as well as with HNT and obesity. Risk stratification revealed that the total proportion of patients with high and very high risk was significantly higher among patients of groups 3 and 4 compared with those in groups 1 and 2. This justifies a high cardiovascular mortality among patients with a combination of HTN and T2D and/or obesity.

It is acknowledged that adipokines can not only affect vascular function, but also contribute to the strengthening of the relationship between obesity and HTN [13].

In parallel with a decrease in the main artery elasticity, there was an increase in the concentration of leptin and a decrease of adiponectin level with an increase in BMI in hypertensive patients. One of the pathogenetic mechanisms of increasing the large vessel stiffness is associated with the production of hormones and cytokines by metabolically active adipose tissue, including angiotensinogen and angiotensin II. The protective role of adiponectin and the negative role of leptin in main artery damage are discussed. The obtained data are comparable with foreign studies, which indicate that the serum concentration of adipokines can be a predictor of arterial stiffness in patients with HTN [14]. There are publications on leptin activation by the sympathetic nervous system in obesity [15]. In addition to chronic hyperleptinemia due to tissue resistance to leptin, local synthesis of angiotensinogen by adipocytes and hyperinsulinemia contribute to the development and progression of HTN in obese patients.

Adiponectin is an anti-inflammatory adipokine and insulin sensitizer [16]. Vascular adiponectin protection may be associated with an improvement in endothelial dysfunction, a decrease in oxidative stress, and an increase in endothelial nitric oxide synthase expression due to the activation of adenosine 5'-monophosphate-activated protein kinase by AdipoR1 and the action of a peroxisome proliferator-activated receptor (PPAR)-α2 signaling [16].

Established correlations of PWVe with leptin concentration and ATD in group 1, as well as of PWVe and adiponectin concentration in group 4 indicate a pathogenetic relationship between the main artery elasticity and adipokine status in the studied groups of hypertensive patients.

Conclusion

Thus, the data obtained showed peculiarities of the effect of visceral obesity on main artery elasticity and vascular age in patients with HTN in combination with obesity and T2D.

Relationships and Activities: none.

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Russian Journal of Cardiology 2021;26(4):4290
doi:10.15829/1560-4071-2021-4290
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Sleep disorders — risk factors and hypertension markers in young people with normal body weight

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Aim. To assess the relationship between different types of sleep disorders, sleep-related symptoms and hypertension (HTN).

Material and methods. This cross-sectional study based on the online survey of persons aged 18-39 years with a body mass index of 18-25 kg/m^2.

Results. According to the res ults, the HTN risk in persons aged 18-39 years with normal body mass index increases 2 or more times in the presence of various types of sleep disorders and related symptoms. The prevalence of HTGN depends on the patient's phenotype, i.e. from a combination of different types of sleep disorders and sleep-related symptoms.

Conclusion. Given the widespread prevalence of various sleep disorders, as well as the relationship between sleep disorders and hypertension in young people, it is necessary to develop preventive measures aimed at reducing the HTN risk by restoring healthy sleep. We also suggest that various sleep disorders may be the primary link in the development of essential HTN.

Keywords: hypertension, sleep disorders, snoring, sleep apnea, insomnia, restless legs syndrome.

Relationships and Activities. The work (data analysis) was carried out within the state assignment of the Lomonosov Moscow State University.

Acknowledgments. The authors are grateful to N. V. Rubinsky for help in data collection and analysis.

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Received: 14.01.2021
Revision Received: 16.02.2021
Accepted: 14.03.2021

For citation: Kalinkin A. L., Sorokin A. S. Sleep disorders — risk factors and hypertension markers in young people with normal body weight. *Russian Journal of Cardiology*. 2021;26(4):4290. (In Russ.) doi:10.15829/1560-4071-2021-4290

Hypertension (HTN), despite hundreds of thousands of related studies and a wide range of antihypertensive drugs, remains the leading cause of death both in Russia [1] and in many countries of the world [2]. From 1998 to 2017, the prevalence of HTN in European Russia increased from 35,5 to 43,3% [3]. Due to wide prevalence of HTN, its prior probability is very high, while high predictive value of a positive result of routine blood pressure (BP) measurement makes its diagnosis perhaps one of the simplest ones. Despite this, the multifactorial nature of the problem, the complexity and long-term pathogenetic mechanisms do not allow to comprehensively solve it, often reducing the doctor's actions only to the appointment of antihypertensive therapy. It is well known that this problem is largely due reduced awareness among people with HTN, ignoring the problem by patients themselves, and their unwillingness to regularly take antihypertensive therapy. The situation is aggravated by the fact that factors contributing to HTN at an early age are often not considered. By the age of 40, when many people begin to think about maintaining health, hypertension may have already reached the stage where the correction of modifiable risk factors (RF) will no longer be as effective as before, and from secondary hypertension it can transform into essential or, more precisely, acquire its traits. This means that despite the cause elimination, BP may remain elevated. And in this case, the question arises whether this is a consequence of target organ, the presence of true essential hypertension, or is it still unrecognized one or several causes of the disease. There is also the gradient of essential HTN equal to 0, if the elimination of BP increase cause will lead to its complete normalization. Unfortunately, the theory by Yu. V. Postnov and S. N. Orlov "primary hypertension as the pathology of cell membranes" [4] did not on the march, but the question of the essential nature of HTN remains relevant to this day.

In 1997, we showed that obstructive sleep apnea (OSA) affects the HTN course, while the relief of OSA led to BP decrease, primarily at night. However, sleep disorders, in addition to respiratory ones, are represented by a wide range of insomnia and movement disorders, etc. Therefore, the analysis of sleep disorders in clinical practice is extremely important for identifying the causes of increased BP not only during sleep, but also during wakefulness. The pathogenetic mechanisms underlying this process are of fundamental importance for management of patients.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The research included data from an impersonal survey of visitors to somnology websites www.somnolog.ru and www.sleeplab.ru. In the period from June 2015 to June 2020, 5179 respondents responded to the survey. The survey included 42 questions to assess the presence of various sleep disorders and sleep-related symptoms (snoring, sleep apnea, insomnia, narcolepsy, restless legs syndrome (RLS), depression, anxiety) on a 5-point scale (0 — never, 1 — rarely, 2 — sometimes, 3 — often, 4 — almost always). All questions needed to be answered. The respondents also noted their age, sex, height, weight and place of residence. Before statistical analysis, duplicate data were removed, and respondents aged 18-39 years with a body mass index (BMI) of 18-25 kg/m^2 were selected. These categories are of interest due to absence of the effect of increased body weight and comorbidities, which are HTN RFs. As a result, for the statistical processing, the data of 2094 respondents were used.

The aim was to assess the relationship between different types of sleep disorders, sleep-related symptoms and HTN.

Statistical analysis was performed using IBM SPSS Statistics 25 software.

Results

The clinical characteristics of participants are presented in Table 1.

The dependent variable "I have high BP" was converted into a binary variable: 0 — never and 1 — all other answers (1-4).

All independent variables indicating the sleep disorders and sleep-related symptoms were transformed as follows. As already noted, the assessment of sleep disorders in the questionnaire was initially carried out using 5-point scale (0-4). Such a scale ranks the response categories well among themselves, but does not allow measuring how the category values differ among themselves. It is a well-known fact that when using such a scale, different respondents tend to overestimate or underestimate values.

To solve this problem, we calculated the average score for all questions for each respondent. Further, for each question, the difference between the answer score and this average was calculated. For further statistical analysis, we used the deviation for each question from the typical answer of a respondent [5, 6]. This made it possible to solve the abovementioned problem.

Further, to assess the effect of independent variables, the optimized categorization algorithms in the SPSS package was applied, which was based on the following optimization criteria: maximization of the relationship measure between the created

Table 1

Clinical characteristics of participants (n=2094)

Parameter	Value
Sex	m — 553 (26,4%); f — 1541 (73,6%)
Age, years	25,8±6,0
Height, cm	169,3±8,7
Weight, kg	61,0±8,9
BMI, kg/m^2	21,2±1,9

Abbreviation: BMI — body mass index.

Table 3

Prevalence of HTN in clusters

Cluster number	Sample		Presence of HTN, %
	n	%	
I	334	16,0	35,6
II	1345	64,3	38,6
III	412	19,7	46,1
Total	2091	100,0	39,6

Abbreviation: HTN — hypertension.

Table 2

Characteristics of the relationship between HTN and sleep disorders*

Variable/wording in the questionnaire	Cramer coefficient	Information Value (IV)	OR (95% CI)
Snoring — "I was told that I snore"	0,13	0,07	1,97 (1,56-2,49)
Apnea — "I was told that I have sleep apnea"	0,17	0,12	2,23 (1,84-2,77)
Insomnia — "I wake up earlier in the morning than I would like"	0,11	0,05	2,34 (1,68-3,27)
Cataplexy — "When I am angry or surprised, I feel muscle weakness"	0,11	0,05	0,62 (0,51-0,75)
Daytime sleepiness — "I can fall asleep while driving"	0,19	0,14	2,43 (1,97-2,98)
Cough — "I wake up at night coughing and wheezing"	0,16	0,10	2,11 (1,71-2,60)
Heartburn — "I feel heartburn"	0,12	0,06	2,14 (1,64-2,80)
Choking — "At night I wake up unexpectedly with a feeling of choking"	0,16	0,10	2,03 (1,67-2,46)
Cramps — "I have cramps or pain in my legs at night"	0,14	0,07	2,66 (1,93-3,67)

Note: * — all parameters have a significant effect on HTN (p<0,001, Pearson chi-squared test).
Abbreviations: HTN — hypertension, CI — confidence interval, OR — odds ratio.

categorical independent variable and the created binary dependent variable (entropy was used as the relationship measure) and minimization of created intervals' number. As a result, the effect of the following variables on HTN was found (Table 2). For the created categorical variables, the chi-squared test and the Cramer's coefficient were used, as well as the Information value and the odds ratio were calculated.

The average predictive power was noted for the following predictor variables: apnea, excessive daytime sleepiness, cough at night, shortness of breath at night. Other predictor variables has low predictive power. It should be noted that of the predictor variables indicated in Table 2, only 'cataplexy' had an inverse relationship with HTN (odds ratio, <1). However, in our opinion, this symptom was associated not with cataplexy as such, but with BP decrease and more closely resembles vasovagal syncope in hypertensive people. In this case, it becomes clear why this symptom had a feedback with hypertension.

Next, we created a logistic regression model predicting the HTN in respondents using the independent variables shown in Table 2. However, we did not receive a model with a sufficient number of significant independent variables in the equation and a high predictive power (Gini coefficient >0,3). Apparently, this is due to the fact that the above predictor variables are a manifestation of various diseases, which, on the one hand, can affect the quality of sleep, on the other hand, are observed in different phenotypes or clusters of patients. Therefore, they do not merge into a common model.

In this regard, we decided to conduct a cluster analysis for 19 quantitative independent variables, calculated on a deviation scale.

Hierarchical agglomerative clustering was applied, while the squared Euclidean distance was chosen as a relationship measure of objects. The clusters were divided according to the Ward method.

Clustering revealed 3 clusters of respondents (Table 3). We have arranged the clusters in the order of increasing HTN prevalence. The prevalence of HTN in the first (n=334, 16,0%), second (n=1345, 64,3%) and third (n=412, 19,7%) clusters was 35,6%, 38,58% and 46,1%, respectively. The relationship between the HTN presence and belonging to the resulting

Table 4

Clinical characteristics and relative score of answers in deviations from the total mean depending on clusters

Parameter	Me [Q1; Q3]			p-value (Kruskal-Wallis test)
	Cluster I	Cluster II	Cluster III	
Age, years	25 [21; 30]	26 [21; 31]	22 [19; 27]	<0,001
BMI, kg/m^2	20,95 [19,72; 22,53]	21,08 [19,71; 22,58]	20,81 [19,61; 22,53]	0,78
Snore	-0,61 [-1,26; 0,26]	-0,93 [-1,30; 0,11]	-1,26 [-1,67; 0,67]	<0,001
Apnea	-1,04 [-1,41; -0,70]	-1,19 [-1,48; -0,89]	-1,48 [-1,78; -1,19]	<0,001
Insomnia	0,16 [-0,32; 0,72]	1,34 [0,88; 1,83]	0,84 [0,43; 1,20]	<0,001
Daytime sleepiness	0,57 [0,19; 0,91]	-0,11 [-0,37; 0,17]	0,57 [0,33; 0,85]	<0,001
RLS	-0,15 [-0,81; 0,85]	0,04 [-0,89; 1,07]	0,41 [-0,67; 1,15]	0,008
Depression	0,85 [0,19; 1,52]	1,07 [0,48; 1,74]	1,56 [0,93; 2,00]	<0,001
Anxiety	0,52 [-0,19; 1,26]	1,67 [0,96; 2,22]	1,48 [0,74; 2,04]	<0,001

Note: insomnia — all symptoms of the questionnaire characterizing insomnia are grouped; daytime sleepiness — all the symptoms of the questionnaire characterizing daytime sleepiness are grouped; RLS — "Sometimes at night I cannot find a place for my legs, I want to move them all the time in order to feel comfortable"; depression — "I often feel sad and depressed"; anxiety — "I am constantly worried about different things and cannot relax".
Abbreviations: BMI — body mass index, RLS — restless legs syndrome.

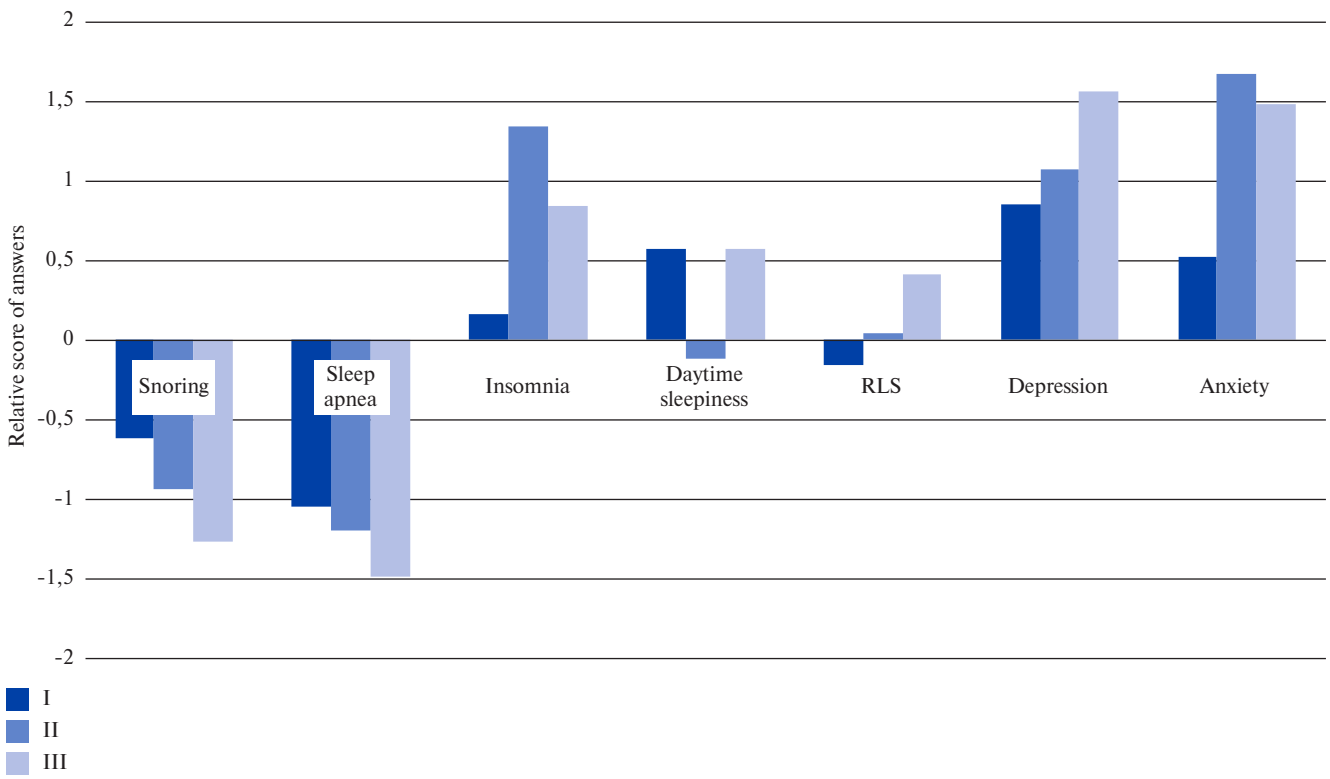

Figure 1. Distribution of the relative score* of answers depending on clusters for snoring, sleep apnea, insomnia, daytime sleepiness, RLS, depression, anxiety.
Note: * — more negative values correspond to a greater severity of symptoms/conditions.
Abbreviation: RLS — restless legs syndrome.

cluster is significant (χ^2=10,09, p=0,006). Pairwise comparison of HTN proportions between clusters using the z-test yields a significant difference only in the third cluster with the highest HTN proportion (p<0,05), i.e. the proportions of 35,6% and 38,6% do not differ significantly. By sex, the categories did not differ significantly (χ^2=4,57, p=0,102).

Clinical characteristics and relative score of answers in deviations from the total average score for each cluster are presented in Table 4.

Discussion

In recent years, more and more data have appeared on the relationship of various sleep disorders with cardiovascular diseases and, above all, hypertension. Our study identified a number of sleep-related factors that are associated with hypertension. Sleep disorders such as OSA, the clinical manifestation of which is snoring, already belong to the RFs for HTN and are dominant among other sleep disorders, which was also confirmed in our study. Early, unplanned awakening is a sign of chronic insomnia and may be a manifestation of a depressive disorder. Excessive sleepiness, one of the extreme manifestations of which is drowsy driving, is most often a manifestation of disturbed sleep at night due to respiratory and movement disorders, or the presence of chronic insomnia. The night cough and heartburn may indicate the chronic obstructive pulmonary disease, asthma, gastroesophageal reflux disease and also lead to sleep fragmentation. Moreover, these conditions are often combined with OSA. Awakening with a shortness of breath is a fairly characteristic sign of panic disorder and can be a manifestation of a wide range of anxiety disorders, but it can also be observed in patients with OSA.

Clustering allowed us to characterize the phenotypes of patients.

Considering that the prevalence of HTN in cluster III is the highest (46,11%), while the age in this cluster is significantly even less than in clusters I and II, and also that BMI and sex do not significantly differ between clusters, it remains to consider the differences by the presence of sleep disorders and sleep-related symptoms. The relationship between central sleep-related disorders and symptoms is shown in Figure 1.

The differences between the clusters consist in an increase in snoring and sleep apnea from cluster I to cluster III, while the presence of RLS and depression symptoms also decreased from cluster I to cluster III. The fact is that, according to our results, sleep apnea and periodic limb movements (PLM) during sleep, which is often combined with RLS, are competing conditions. This means that, mainly with PLM manifestations, we do not observe OSA, sometimes only central sleep apnea. Moreover, OSA can transform into PLM without changing the phase and/or stage of sleep, body position and without micro-awakening. Apparently, this is due to the fact that in the brain there is a single central mechanism for the implementation of both PLM, which is well known, and OSA. However, their intermittent manifestation is probably associated with a change in conduction pathways from a common central regulator to the periphery.

The decrease in depression prevalence from cluster I to cluster III may be due to the fact that patients with snoring and sleep apnea have a more pronounced pressure for sleep. Therefore, the duration of their sleep is longer, which may contribute to a decrease in the manifestation of depression. Another possible mechanism is associated with partial deprivation of rapid eye movement (REM) sleep phase, which is often observed in patients with OSA, and it is known that sleep deprivation, especially REM phase, is used as a temporary but effective method to reduce the manifestations of depressive disorder. There is also a decrease in anxiety in clusters II and III compared to cluster I, which indicates an inverse relationship with OSA severity.

Thus, among all sleep disorders in young people with normal body weight, snoring and sleep apnea are the earliest factors determining the HTN development. And this is not surprising, since the likelihood of chronic insomnia, RLS, and other age-related sleep disorders in this age group is minimal.

When developing methods for preventing the hypertension by restoring healthy sleep, it is necessary to take into account the phenotype of a patient with snoring and sleep apnea. On the one hand, this is a 'classic' patient with snoring and sleep apnea without or with a minimal concomitant sleep disturbances and symptoms of mental disorders but with a high risk of hypertension (cluster III). On the other hand, a patient with snoring and sleep apnea in various combinations with chronic insomnia, RLS, depression, and anxiety (cluster II), in whom daytime sleepiness is most pronounced. The third group of patients with mild snoring and sleep apnea but with a predominant chronic insomnia in various combinations and without concomitant sleep and mental disorders (cluster I).

The study limitations include the use of a non-validated questionnaire. However, the data obtained will help to determine the tasks for future studies and focus on the suspected RFs of HTN.

Conclusion

Thus, the HTN risk in people aged 18-39 years with a normal BMI increases 2 or more times in the presence of various sleep disorders and sleep-related symptoms, which must be taken into account both for creating measures for HTN prevention and in clinical practice. The prevalence of hypertension depends on the patient's phenotype, i.e. from a combination of different types of sleep disorders and related symptoms. We also suggest that various sleep disorders may be the primary link in the development of essential HTN.

Acknowledgments. The authors are grateful to N.V. Rubinsky for help in data collection and analysis.

Relationships and Activities. The work (data analysis) was carried out within the state assignment of the Lomonosov Moscow State University.

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Russian Journal of Cardiology 2021;26(4):4187
doi:10.15829/1560-4071-2021-4187
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Association of vascular stiffness and geriatric syndromes in hypertensive elderly patients

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Aim. To study the relationship of vascular stiffness (cardio-ankle vascular index (CAVI)) with frailty and other geriatric syndromes in hypertensive elderly patients.

Material and methods. The study included 160 patients aged 60 to 101 years with verified stage I-III hypertension. The previous therapy was assessed. A comprehensive geriatric assessment was performed with functional and neuropsychological tests to identify geriatric syndromes. Vascular stiffness was assessed by VaSera-VS-1500 vascular screening system (FUKUDA DENSHI, Japan) with determination of the CAVI.

Results. The mean age of the patients was 77,2±8,1 years (n=160): in the group of patients without frailty — 72,4±6,9 years (n=50), with prefrailty — 76,6±8,1 years (n=50), with frailty — 81,7±6,6 (n=60). Patients with frailty had a higher CAVI than those without frailty and with prefrailty (10,3±1,6 vs 9,3±1,0 and 9,6±1,8, respectively; p=0,002).

In patients with frailty, a negative correlation was found between the vascular stiffness and body mass index (BMI) (Rs=-0,392 (p=0,002)), and a positive correlation between the CAVI and orthostatic response (Rs=0,382 (p=0,003). In patients with prefrailty, negative relationships were found with the dynamometric parameters (Rs=-0,329 (p=0,019)), BMI (Rs=-0,343 (p=0,015) and physical activity (Rs=-0,285 (p=0,047)).

In patients without frailty, the vascular stiffness was associated with an increased total cholesterol level (Rs=0,379 (p=0,009)), a low physical activity (Rs=-0,355 (p=0,015)), as well as negative correlations were found with the clock-drawing test and falls (Rs=-0,458 (p=0,011) and Rs=-0,306 (p=0,031), respectively).

Conclusion. Vascular stiffness in elderly patients with frailty is associated with a decrease in body mass index and orthostatic hypotension. At the stage of prefrailty, the relationship between the vascular stiffness and muscle strength decrease (according to dynamometry) was revealed.

Thus, the vascular stiffness is associated with frailty markers itself.

Relationships and Activities: none.

Keywords: frailty syndrome, vascular stiffness, cardio-ankle vascular index, elderly patients.

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Received: 12.11.2020
Revision Received: 19.12.2020
Accepted: 27.12.2020

For citation: Luzina A. V., Runikhina N. K., Tkacheva O. N., Kotovskaya Yu. V. Association of vascular stiffness and geriatric syndromes in hypertensive elderly patients. *Russian Journal of Cardiology*. 2021;26(4):4187. (In Russ.) doi:10.15829/1560-4071-2021-4187

Vascular stiffness parameters are a cardiovascular risk marker, which reflects the relationship with high morbidity and mortality. Due to the low number of studies on elderly patients, this relationship is less reflected in this group, as well as the relationship with geriatric syndromes.

Cardiovascular diseases (CVD) remain the leading cause of death in developed countries, and therefore necessitate novel investigations in clinical practice in high-risk patients. Slowing the vascular stiffening is a way to prevent CVD and heart failure [1].

Measuring the vascular stiffness in routine practice is important for assessing the atherosclerosis progression. So far, many parameters have been proposed for quantifying arterial stiffness. Among them, there is pulse wave velocity (PWV), however, it depends on blood pressure (BP). Therefore, PWV is not suitable for assessing the vascular stiffness in studies with patients with BP changes [2].

The cardio-ankle vascular index (CAVI) was developed on the PWV basis by Japanese scientists to assess the degree of vascular stiffness. The CAVI calculation combines the stiffness and the Bramwell-Hill equation [3]. The most important feature of this method is its independence from BP during examinations. This is important for objective reflection of atherosclerosis severity in individuals with increased BP variability, with resistant hypertension (HTN), or while taking antihypertensive drugs [4].

It is believed that the prevalence of frailty increases with age and increases the risk of adverse outcomes in older people, including mortality, falls and hospital admissions [5].

Diagnosis and assessment of frailty severity is carried out during the implementation of a comprehensive geriatric assessment (CGA). However, is there a relationship between the severity of certain geriatric syndromes and the vascular stiffness?

The vascular stiffness is interrelated with frailty in elderly patients and it can be assumed that it is a risk factor (RF) for the atherosclerosis progression and atherosclerosis-related cardiovascular events [6].

Frailty and atherosclerotic changes have a common pathogenesis and have a mutual cause, but the relationship between them remains unclear. In clinical practice, we observed that the severity of atherosclerosis is more pronounced in the elderly with limited mobility and decreased functional and cognitive status. In this connection, we assume that frailty is associated with atherosclerosis.

The aim was to study the relationship of CAVI with frailty and other geriatric syndromes in hypertensive elderly patients.

Material and methods

The study was approved by the local ethics committee of the Russian Clinical and Research Center of Gerontology in 2017.

All participants signed informed consent prior to enrollment.

We examined 160 patients from 60 to 101 years old with verified stage I-III HTN. For preliminary screening, a short questionnaire was used to identify changes indicative of probable geriatric syndromes. The screening consists of 7 questions related to the following issues: weight loss; limitations in life due to decreased vision/hearing; fall-related injuries; mood swing; memory problems; urinary incontinence; movement disorders. The patients were divided into 3 groups in accordance with the current algorithm for frailty diagnosis [7].

Patients with prior myocardial infarction, stroke, lower limb artery stenosis and occlusions, pulmonary embolism, thromboarteritis, Raynaud's disease, angiitis, permanent atrial fibrillation, acute or exacerbated diseases, severe sensory (deafness and blindness) and cognitive impairments that impede the CGA were excluded.

All patients underwent CGA with determination of functional and cognitive status. The functional status was assessed according to the following parameters: walking speed [8], Timed Up and Go test [9]; Barthel index of activities of daily living [10], Lawton instrumental activities of daily living [11]. Cognitive status was assessed using a mini-mental state examination (MMSE) [12]. To assess the quality of life, a 'Health Status' visual analog scale (VAS) for self-assessment was used [13]. Nutritional assessment was carried out using the Mini Nutritional Assessment (MNA) score [14]. The level of physical activity was assessed for each sex separately [15]. The handgrip strength was determined using a medical dynamometer DMER-120 [16]. Anthropometric measurements included assessment of height, body weight, waist circumference and calculation of body mass index (BMI).

To assess orthostatic response, BP was measured in the supine position and 1, 2, and 3 minutes after the transition to the upright one. Orthostatic hypotension (OH) was diagnosed with a decrease in blood pressure by 20/10 mm Hg and more when moving to the upright position [17].

Evaluation of vascular stiffness by CAVI was carried out using VaSera-VS-1500 vascular screening system (FUKUDA DENSHI, Japan). Determination of CAVI was carried out by simultaneous BP measurement with cuffs placed on the arms and ankles, as well as electrocardiography and phonocardiography.

Statistical analysis. Results are presented as mean values (± standard deviation) or as values

Table 1

Characteristics of three patient groups: patients without frailty (n=50), with prefrailty (n=50), with frailty (n=60)

Parameter	Patients without frailty, n=50	Patients with prefrailty, n=50	Patients with frailty, n=60	p
Age, years	72,4±6,9	76,6±8,1	81,7±6,6	0,003
Women, n (%)	40 (80%)	45 (90%)	54 (90%)	0,221
Education level				0,150
Secondary, n (%)	2 (4%)	8 (16%)	9 (13,6%)	
Secondary vocational, n (%)	20 (40%)	24 (48%)	27 (45,8%)	
Higher, n (%)	28 (56%)	18 (36%)	24 (40,7%)	
Accommodation				<0,001
Alone, n (%)	23 (46,3%)	23 (46%)	32 (53,3%)	
With children, n (%)	5 (10%)	8 (16%)	22 (36,7%)	
With husband/wife, n (%)	22 (44%)	19 (38%)	6 (10%)	
Family status				
Married, n (%)	22 (44%)	21 (42,9%)	7 (11,9%)	
Widower/widow, n (%)	22 (44%)	23 (46,9%)	47 (79,7%)	
Divorced, n (%)	4 (12%)	6 (10,2%)	6 (8,4%)	

Table 2

Characteristics of anthropometric parameters of three patient groups

Anthropometric data	Patients without frailty, n=50	Patients with prefrailty, n=50	Patients with frailty, n=60	P
Height, m	1,59±7,9	1,57±8,5	1,57±7,9	0,535
Weight, kg	71,2±12,9	68,1±14,5	69,9±13,6	0,521
BMI, kg/m^2	28,2±4,6	27,4±5,0	28,7±6,4	0,816
Waist circumference, cm	92,4±13,8	93,3±13,7	94,8±19,3	0,728

Abbreviation: BMI — body mass index.

Table 3

Hemodynamic characteristics of patients in three groups

Parameter	Patients without frailty, n=50	Patients with prefrailty, n=50	Patients with frailty, n=60	P
SBP, mm Hg	142,6±22,6	147,9±22,1	142,6±22,4	0,380
DBP, mm Hg	85,9±10,6	81,6±11,5	81,3±12,9	0,084
Heart rate, bpm	70,5±8,9	70,7±8,6	72,5±10,8	0,500

Abbreviations: DBP — diastolic blood pressure, SBP — systolic blood pressure.

and percentages for qualitative traits. Quantitative variables were compared between groups using Kruskal-Wallis test. If significant differences were found, pairwise comparisons were made using Tukey's test and Dunnett's test. Qualitative variables between groups were compared using Fisher's exact test. If significant differences were found, the source was identified using Fisher's exact test with Holm correction for multiple comparisons. To identify the effect of frailty on CAVI, taking into account age, a general linear model was built with the group as a qualitative factor and with age as a covariate. Spearman's correlation coefficient was used to assess the relationship between the variables. The results were considered significant at $p<0,05$.

Table 4

Prescription rate of antihypertensive drugs in three patient groups

Parameter	Patients without frailty, n=50	Patients with prefrailty, n=50	Patients with frailty, n=60	P
ACE inhibitors	30%	38%	46,7%	0,208
ABR	36%	42%	21,7%	0,060
CCB	26%	26%	31,7%	0,777
Beta-blockers	36%	38%	40%	0,897
Diuretics	26%	26%	33,3%	0,638

Abbreviations: CCB — calcium channel blockers, ARB — angiotensin II receptor blockers, ACE inhibitors — angiotensin-converting enzyme.

Table 5

Prevalence of noncommunicable diseases and geriatric syndromes in three groups of patients

Parameter	Patients without frailty, n=50	Patients with prefrailty, n=50	Patients with frailty, n=60	p	p_1	p_2	p_3
CAD	24%	38%	42%		0,136		
HF	16%	26%	30%		0,215		
Diabetes	8%	16%	15%		0,449		
Knee/hip osteoarthritis	20%	52%	32%		0,200	0,068	0,004
Asthma	6%	2%	5%		0,708		
COPD	8%	2%	5%		0,438		
Cancer	18%	26%	17%		0,482		
Peptic and duodenal ulcer	6%	14%	8,3%		0,385		
Hearing loss	20%	58%	58,3%		<0,001	1	<0,001
Decreased vision	42%	70%	72%		0,006	1	0,016
Prior falls	30%	58%	66,2%	<0,001	0,001	0,431	0,017
Orthostatic hypotension	20%	44%	32%	0,033	0,185	0,433	0,053

Note: p-values are shown for comparing three groups (p) and, if they are significant, p-values for pairwise comparisons: p_1 — comparing groups of patients with frailty and without frailty, p_2 — comparing groups of patients with frailty and with prefrailty, p_3 — comparing groups of patients without frailty and with prefrailty.

Abbreviations: CAD — coronary artery disease, COPD — chronic obstructive pulmonary disease, HF — heart failure.

Results

The age of patients was 77,2±8,1 years (n=160; women, 139 (87%)).

In accordance with the current algorithm for frailty diagnosis, there were no frailty in 50 patients, prefrailty — in 50, and frailty — in 60. Comparative characteristics of patients depending on frailty are shown in Table 1.

All 3 groups significantly differed from each other in age (p=0,003): patients without frailty were younger than patients with frailty. In all three groups, women predominated among the study participants.

There were no significant differences in anthropometric parameters between the three groups of patients (Table 2).

Systolic BP, diastolic BP and heart rate in patients at the inclusion time are shown in Table 3. There were no significant differences in hemodynamic characteristics.

All study participants received antihypertensive therapy. The following main classes of antihypertensive drugs were used: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β-blockers and diuretics (Table 4). There were no significant differences in the prescription rate of antihypertensives between the groups.

The prevalence of noncommunicable disease is presented in Table 5. There was a high prevalence of morbidity in the surveyed groups, generally typical

Table 6

Parameters of CHA in three groups of patients

Parameter	Patients without frailty, n=50	Patients with prefrailty, n=50	Patients with frailty, n=60	P
Barthel index, points	98,3±3,4a	94,8±7,8a	86,3±4,9b	0,005
Lawton scale, points	7,7±0,7a	7,6±0,8a	6,3±1,8b	<0,0001
Mini nutritional assessment, points	24,3±3,7a	23,7±2,2a	22,6±2,5b	<0,0001
Self-reported health status scale, %	66,4±14,6a	57,5±14,5b	47,8±16,8c	<0,0001
Brief mental health assessment scale, points	27,8±2,1a	27,1±1,9ab	25±4,9b	0,0001
Clock drawing test, points	8,7±1,1a	8,2±1,1ab	7,7±1,6b	0,024
Geriatric depression scale, points	1,6±1,5a	3,0±2,1b	3,7±2,8b	<0,001
Dynamometry, kg	26,7±10,1a	23,9±7,2a	18,8±7,4b	0,0006
Walking speed, m/s	1,0±0,7a	0,9±1,1ab	0,6±0,7b	0,03
Timed Up and Go test, sec	9,1±2,8a	11,2±5,2a	17,2±8,8b	<0,0001

Note: groups that differ significantly in pairwise comparisons have a common letter.

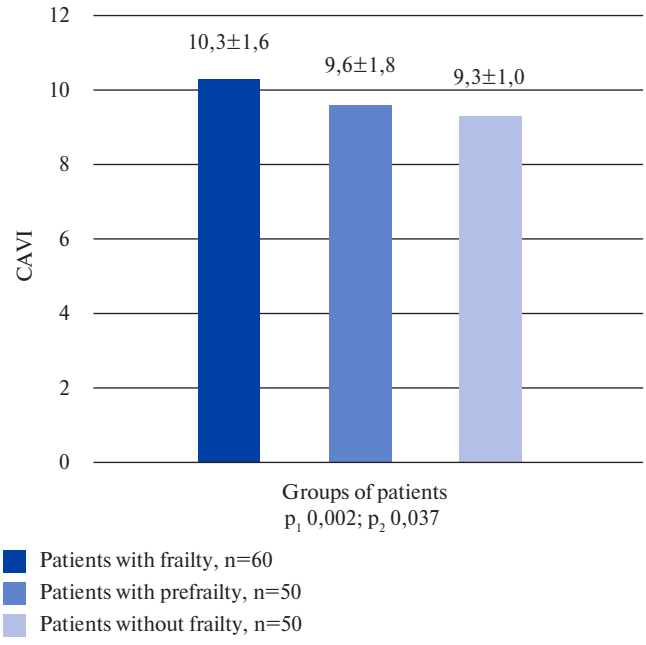

Figure 1. Vascular stiffness in three groups of patients, p=0,002.
Note: p_1 — comparing the group of patients with frailty and without, p_2 — comparing the group of patients with frailty and prefrailty.
Abbreviation: CAVI — cardio-ankle vascular index.

for elderly and senile patients. We found no significant differences in the disease prevalence in groups, with the exception of sensory deficits, the prevalence of which increased significantly with frailty progression. In addition, patients without frailty smoked more often compared to patients with prefrailty and with frailty (28% vs 8,2% and 5%, respectively, p⩽0,001).

The mean values for total cholesterol in the groups were as follows: in the group of patients with frailty, 5,3±1,2 mmol/L; in the group of patients with prefrailty, 5,3±1,5 mmol/L; in the group of patients without frailty, 5,7±1,0 mmol/L (p=0,118).

The CGA revealed significantly worse indicators in frailty group (Table 6).

As for vascular stiffness, significant differences in CAVI between the groups were revealed (p=0,002): patients with frailty had a higher CAVI than patients without frailty and with prefrailty (10,3±1,6 vs 9,3±1,0 and 9,6±1,8, respectively; p=0,002), Figure 1.

Since the groups differed significantly in age, we also performed additional analysis using the general linear model (GLM), including age as a covariate. The GLM revealed a tendency to the effect of frailty on CAVI (p=0,089): at the same age, frailty patients had higher CAVI than in patients without frailty (p=0,0004 in Tukey's test) and with prefrailty (almost reached the significance: p=0,058).

A correlation analysis of vascular stiffness with the RFs of CVD and CGA parameters was carried out (Table 7).

In patients without frailty, there were negative correlations with parameters of physical activity, clock-drawing test, and falls (Rs=-0,355 (p=0,015), Rs=-0,458 (p=0,011), and Rs=-0,306 (p=0,031)) and direct correlations with total cholesterol (Rs=0,379 (p=0,009)). In the group of patients with prefrailty: negative relationships were found with the parameters of dynamometry, BMI and physical activity (Rs=-0,329 (p=0,019), Rs=-0,343 (p=0,015) and Rs=-0,285 (p=0,047), respectively). In the

Table 7

Spearman's rank correlation coefficients between the CAVI and parameters of physical functioning, cognitive status, CVD RFs in three groups of patients

Parameter	Patients without frailty, n=50		Patients with prefrailty, n=50		Patients with frailty, n=60	
Barthel index, points	0,052	p=0,719	-0,037	p=0,799	-0,045	p=0,732
Instrumental activities of daily living, points	-0,046	p=0,747	-0,089	p=0,538	-0,113	p=0,389
Walking speed, m/s	-0,134	p=0,354	-0,209	p=0,145	-0,155	p=0,255
Timed Up and Go test, sec	0,204	p=0,154	0,091	p=0,154	0,120	p=0,379
Brief mental health assessment scale, points	-0,178	p=0,217	-0,113	p=0,433	-0,099	p=0,454
Clock drawing test, points	-0,458	p=0,011	0,016	p=0,909	-0,096	p=0,585
Dynamometry, kg	0,037	p=0,801	-0,329	p=0,019	-0,069	p=0,600
MNA, points	-0,259	p=0,069	-0,054	p=0,707	-0,192	p=0,142
Geriatric depression scale, points	0,089	p=0,539	0,043	p=0,765	0,075	p=0,569
Prior falls	-0,306	p=0,031	0,138	p=0,340	0,163	p=0,217
Orthostatic hypotension	0,173	p=0,229	0,094	p=0,518	0,382	p=0,003
Total cholesterol, mmol/LI	0,379	p=0,009	-0,143	p=0,321	-0,117	p=0,389
Glucose, mmol/L	0,221	p=0,124	0,174	p=0,226	-0,051	p=0,706
BMI, kg/m^2	0,036	p=0,811	-0,343	p=0,015	-0,392	p=0,002
Smoking	-0,002	p=0,992	-0,145	p=0,319	0,148	p=0,259
Physical activity	-0,355	p=0,015	-0,285	p=0,047	-0,206	p=0,115
Prior diabetes	0,142	p=0,345	0,182	p=0,207	0,032	p=0,806

Abbreviations: BMI — body mass index, MNA — Mini Nutritional Assessment.

group of patients with frailty, inverse correlations were found with BMI (Rs=-0,393 (p=0,002)) and direct correlations with OH (Rs=0,382 (p=0,003)).

Discussion

The relationship between vascular stiffness and severity of CVD RFs is known. The relationship with geriatric syndromes is being actively discussed. Sampaio RA, et al. (2014) suggest that muscle blood supply decreases with age, which is associated with vascular stiffness [18]. Hemodynamic dysfunction may have a predictive effect on muscle loss. This decrease leads to a decrease in body weight, strength and, as a result, to a decrease in the physical functioning of an elderly person, which leads to disability, falls and death.

Aerobic exercise reduces vascular stiffness by increasing nitric oxide levels and decreasing endothelin-1 levels. The study by Son WM, et al. (2017) revealed a positive effect of aerobic exercise on vascular stiffness [19].

Physical activity and improved vascular stiffness are important factors in slowing cognitive decline in older patients.

We found significant differences in CAVI between the groups, as well as different correlations of CAVI with CGA data.

In the group of patients without frailty, the revealed correlations indicate that high vascular stiffness is associated with a decrease in cognitive function and fall rate. Patients in this group require careful analysis and correction of factors associated with these geriatric syndromes, including decrease of total cholesterol levels and increase of exercise.

In patients with prefrailty, an association of high vascular stiffness with sarcopenia signs was revealed — a decrease in muscle strength and, indirectly, a decrease in body weight. Patients in this group should be advised of a protein-rich diet combined with adequate exercise. Weight loss is associated with a decrease in muscle strength and, as a consequence, with a decrease in physical functioning, which contributes to weakness progression [5], which we found in groups of patients with prefrailty and frailty.

In the group of patients with frailty, the association of vascular stiffness with OH was revealed. The

relationship between OH and outcomes in the elderly is poorly understood. However, there are works confirming the relationship between orthostatic response and frailty [20].

HTN is a key factor in vascular stiffening. It is necessary to adequately control BP at an earlier age to reduce the risk of OH in the elderly group of patients, when OH becomes a factor that complicates the management of these patients and potentially aggravates the prognosis.

Conclusion

Vascular stiffness in elderly patients with frailty is associated with a decrease in body mass index and orthostatic hypotension. At the stage of prefrailty, the relationship between the vascular stiffness and muscle strength decrease was revealed.

Thus, the vascular stiffness is associated with frailty markers itself.

Relationships and Activities: none.

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Russian Journal of Cardiology 2021;26(4):4406
doi:10.15829/1560-4071-2021-4406
https://russjcardiol.elpub.ru

ORIGINAL ARTICLES
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Retrospective analysis of clinical decision support system use in patients with hypertension and atrial fibrillation (INTELLECT)

Losik D.V.[1], Kozlova S.N.[2], Krivosheev Yu.S.[1], Ponomarenko A.V.[1], Ponomarev D.N.[1], Pokushalov E.A.[1], Bolshakova O.O.[2], Zhabina E.S.[2], Lyasnikova E.A.[2], Korelskaya N.A.[2], Trukshina M.A.[2], Tulintseva T.E.[2], Konradi A.O.[2]

Aim. To evaluate the relationship between the clinical decision support system use (CDSS) and adherence to clinical guidelines.

Material and methods. Medical records of 300 patients with atrial fibrillation and hypertension from the electronic medical database of the Almazov National Medical Research Center were analyzed. Demographic and clinical data, as well as information on anticoagulant, antiarrhythmic and antihypertensive prescriptions were analyzed. The primary endpoint was adherence of prescribed treatment to current clinical guidelines for each of the three therapies. Firstly, a group of independent clinical experts assessed primary endpoint for retrospective prescriptions. Secondly, new prescriptions were simulated by another group of clinical experts using CDSS and blinded to previous therapy. Primary endpoint at the second step was analysed by independent experts. We compared adherence to relevant clinical guidelines with and without use of CDSS. Additionally, we analyzed predictors of failing to meet the current recommendations in the retrospective records.

Results. Out of 300 patients, only 291 (97%) had all characteristics and were included in the analysis. In 26 patients (18%), all three treatment strategies were in accordance with current clinical guidelines. Anticoagulant therapy was adherent to the guidelines in 92% of cases. Experts who used CDSS were 15% (95% confidence interval [CI], 10-21%) more likely to prescribe novel oral anticoagulants and 14% (95% CI, 10-19%) less likely to prescribe warfarin compared to baseline. Antiarrhythmic therapy was adherent to the guidelines in 69% of cases. When the CDSS platform was applied, experts were 14% (95% CI 4-19%) more likely to prefer antiarrhythmic drug (AAD) monotherapy and 32% (95% CI 26-37%) more often prescribed radiofrequency ablation (RFA) of left atrium. At baseline, antihypertensive therapy combinations were adherent clinical guidelines in 28% of cases. The use of the CDSS platform by experts was significantly associated with an increase in the frequency of prescribing dual and triple antihypertensive therapy.

Conclusion. CDSS use is associated with improved adherence to current clinical guidelines. Prospective randomized trials are needed to evaluate the CDSS effectiveness in the prevention of cardiovascular events.

Keywords: artificial intelligence, atrial fibrillation, hypertension, clinical guidelines, clinical decision support system.

Relationships and Activities. The work was financially supported by OOO MedicBook.

Trial ID: NCT04564118 (www.clinicaltrials.gov).

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Received: 16.03.2021
Revision Received: 31.03.2021
Accepted: 15.04.2021

For citation: Losik D.V., Kozlova S.N., Krivosheev Yu.S., Ponomarenko A.V., Ponomarev D.N., Pokushalov E.A., Bolshakova O.O., Zhabina E.S., Lyasnikova E.A., Korelskaya N.A., Trukshina M.A., Tulintseva T.E., Konradi A.O. Retrospective analysis of clinical decision support system use in patients with hypertension and atrial fibrillation (INTELLECT). *Russian Journal of Cardiology*. 2021;26(4):4406. (In Russ.) doi:10.15829/1560-4071-2021-4406

Atrial fibrillation (AF) and hypertension (HTN) are socially significant diseases and are often combined with each other. HTN occurs in 60-80% of patients with AF. In patients with HTN and AF, the risk of cardiovascular diseases, such as stroke and myocardial infarction, is several times higher [1].

Clinical guidelines attempts to integrate up-to-date information about treatments and allows a physician to help guide decisions about which drug group or treatment is appropriate for a patient. A number of studies have shown that decision-making algorithms, according to clinical guidelines, help to reduce the number of adverse events in patients and improve the effectiveness of treatment [2-8].

There is a large time gap between the daily update of patient care data and the current guidelines, which are updated every 3-6 years.

Currently, there are no convenient algorithms for clinical guidelines for physicians, nurses, pharmacists that could improve the prognosis of patients and help healthcare in general. In some countries, for example, in the USA, clinical decision support systems (CDSSs) are being developed and actively introduced into clinical practice, which can improve the quality of care for the population and reduce healthcare costs.

Modern CDSSs have evidence-based proven efficacy, which has been demonstrated in a number of publications [2-8].

The MedicBK is a CDSS computer program that allows the analysis of published clinical data and suggests therapy options in accordance with the latest guidelines, data from the latest clinical studies, and individual patient characteristics.

The aim was to assess the compliance of the prescribed therapy with current published data [9, 10], as well as to assess the relationship between MedicBK use and the compliance of treatment with clinical guidelines.

Material and methods

The study included data from 300 patients over 18 years of age with nonvalvular AF and HTN who underwent out- or inpatient treatment at the Almazov National Medical Research Center in the period from 2019 to 2020. The protocol is registered at www.clinicaltrials.gov: NCT04564118.

The study did not include patients with secondary HTN, AF due to thyroid disease, acute coronary syndrome within prior 6 months, active liver disease, glomerular filtration rate <30 ml/min.

After entering the main characteristics of patients into the CDSS database, 7 expert cardiologists from the Federal Almazov National Medical Research Center appointed therapy for these patients using this program. This CDSS allows selecting a therapy based on its efficacy and safety in accordance with the current clinical guidelines for management of HTN and AF, as well as up-to-date data from the latest publications. During analysis, experts assessed the compliance of the proposed therapy for AF and HTN with clinical guidelines [11, 12]. Each of the included patients was simulated with CDSS treatment assignment. The primary endpoint was the assessment of the compliance of prescribed therapy in medical records with the current guidelines on AF and HTN, as well as a comparison of the previous prescriptions with the therapy selected using CDSS.

Operational concept of CDSS. CDSS based on data from modern clinical studies, which are subjected to statistical processing. The choice of CDSS characteristics is due to a set of features that have proven their influence on cardiovascular events and are included in various risk stratification scores. On the other hand, the CDSS takes into account the signs that are absolute contraindications for some drugs. The indirect comparison using network meta-analysis is used as the main tool for assessing the effectiveness and safety of therapy. The network meta-analysis results are presented as an intervention effectiveness/safety measure for each pairwise comparison, followed by a forest plot. In addition, P-scores are calculated, demonstrating that a specific intervention has an advantage over all other interventions [13]. For visualization, the P-scores are presented as a scatterplot. The content was evaluated by experts of the Almazov National Medical Research Center and showed compliance with modern guidelines on AF and HTN. Detailed information on the CDSS methodology is available at http://medicbk.com.

Statistical processing. The sample was formed from a total of 2560 electronic health records (EHR) for 2019. To form the sample, we used the sample command for R language, which generated a sequence of 300 random numbers without replacement. The resulting sequence was applied to numbered list of patients in such a way that patients were randomly included in the sample.

Quantitative and qualitative variables are presented as mean±standard deviation and as absolute and (in parentheses) relative values, respectively. The McNemar's test was used to compare the qualitative traits (type of therapy) between the register data and expert prescriptions, and in some cases the difference in absolute risks and related 95% confidence interval (CI) were calculated. If the latter rules out zero, the intergroup difference is considered significant.

All analyzes were performed using the R programming language (R Core Team (2020). R: A language and environment for statistical computing.

R Foundation for Statistical Computing, Austria. URL https://www.R-project.org/).

Results

Due to insufficient EHR data necessary for treatment decision-making, 9 patients were excluded from the analysis. The characteristics of 291 included patients are presented in Table 1. The study included men and women aged 32 to 90 years (mean age, 67,3±10,3 years).

Table 1

Patient characteristics. Qualitative traits are presented as absolute and relative values. Quantitative traits are presented as mean ± standard deviation

Parameter	
n	291
Hospitalization	66 (22,7%)
Outpatient visit	225 (77,3%)
Men	134 (46,0%)
Age, years	67,3±10,3
Height, cm	169,8±10,0*
Weight, kg	87,5±18,6†
Prior antihypertensive therapy	220 (75,6%)
Uncomplicated hypertension	191 (65,6%)
Coronary artery disease	124 (42,6%)
Prior percutaneous coronary intervention	4 (5,2%)
Hypercholesterolemia	176 (60,4%)
Bradycardia	90 (30,9%)
Atrioventricular block	33 (11,3%)
Hypertrophic cardiomyopathy	94 (32,3%)
Heart failure	188 (64,6%)
Cerebrovascular disease	55 (18,9%)
Diabetes	62 (21,3%)
Chronic kidney disease	72 (24,7%)
Hyperkalemia	35 (12,0%)
Hypokalemia	31 (10,6%)
Gout	11 (3,8%)
Severe COPD	12 (4,1%)
Bilateral renal artery stenosis	2 (0,7%)
Prior major bleeding	0 (0,0%)
Liver disease	32 (11,0%)
Prior angioedema	13 (4,4%)
Constipation	5 (1,7%)
Smoking	33 (11,3%)
Alcohol abuse†	6 (7,8%)
Regular exercise	8 (2,7%)

Note: * — no data in 62 (21,3%) patients, † — no data in 64 (22,0%) patients.

Abbreviation: COPD — chronic obstructive pulmonary disease.

A significant proportion of patients (77%) were treated on an outpatient basis. Most of them took antihypertensive therapy before seeking help.

The study design is shown in Figure 1.

Anticoagulant therapy did not meet the guidelines in 8% of patients, mainly due to the appointment of low molecular weight heparins and antiplatelet agents. Experts who used CDSS were 15% (95% CI, 10-21%) more likely to prescribe new oral anticoagulants and 14% (95% CI, 10-19%) less likely to prescribe warfarin compared to the EHR data.

Antiarrhythmic therapy did not meet the guidelines in 31% of cases. Experts who used CDSS 14% (95% CI, 4-19%) more often preferred antiarrhythmic monotherapy and 32% (95% CI 26-37%) more often prescribed pulmonary vein ablation (Table 2).

According to EHR data, combined antihypertensive therapy did not formally meet clinical guidelines in 72,5% of cases (Table 3). The most common inappropriate prescription was monotherapy. Perhaps this was due to patients' preferences due to fear of polypharmacy. At the same time, the CDSS use by experts was significantly associated with an increase in prescription rate of dual and triple therapy: the experts worked with a patient model without taking into account psychosocial factors.

Only in 18% of the 291 included patients, all three therapies complied with current clinical guidelines (Tables 2 and 3). Specifically, three out of four antihypertensive therapy prescriptions did not meet recommendations.

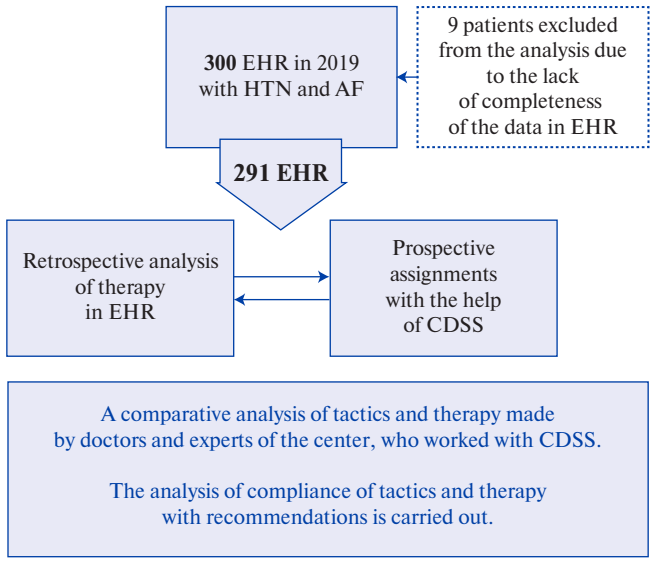

Figure 1. Study design.

Abbreviations: HTN — arterial hypertension, AF — atrial fibrillation, CDSS — clinical decision support system, DSS — decision support system, EHR — electronic health record.

Table 2

Anticoagulant and antiarrhythmic therapy

Therapy	EHR appointments, N (%)		Experts + CDSS, N (%)	
	Total	Adequate	Total	Adequate
Anticoagulant	291 (100,0%)	268 (92,1%)	291 (100,0%)	291 (100,0%)†
Novel oral anticoagulants	224 (79,7%)	224 (79,7%)	277 (95,2%)*	277 (95,2%)
Rivaroxaban	96 (34,1%)	96 (34,1%)	8 (2,7%)*	8 (2,7%)
Apixaban	109 (38,8%)	109 (38,8%)	202 (69,4%)*	202 (69,4%)
Dabigatran	19 (6,7%)	19 (6,7%)	67 (23,8%)*	67 (23,8%)
Warfarin	47 (16,1%)	43 (15,3%)	5 (1,7%)*,#	5 (1,7%)#
Therapy is not indicated	10 (3,6%)	0 (0,0%)	4 (1,3%)	4 (1,3%)
Left atrial appendage occlusion	0 (0,0%)	0 (0,0%)	8 (2,7%)*	8 (2,7%)
Other therapy	10 (3,4%)	0 (0,0%)	0 (0,0%)*	0 (0,0%)
Antiarrhythmic†	291 (100,0%)	201 (69,1%)	291 (100,0%)§	291 (100,0%)§
Rhythm control				
Antiarrhythmic drugs	71 (24,4%)	66 (22,6%)	112 (38,4%)*	112 (38,4%)
Pulmonary vein RFA	2 (0,7%)	0 (0,0%)	93 (32,0%)*	93 (32,0%)
Therapy is not indicated	3 (1,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)
Other therapy	6 (2,1%)	6 (2,1%)	0 (0,0%)	0 (0,0%)
Rate control				
Antiarrhythmic drugs	3 (1,0%)	3 (1,0%)	0 (0,0%)	0 (0,0%)
Beta Blocker‡	56 (19,2%)‡	56 (19,2%)	71 (24,4%)*	71 (24,4%)
Atrioventricular nodal RFA	1 (0,4%)	0 (0,0%)	6 (2,0%)	6 (2,0%)
Non-dihydropyridine calcium channel blocker	2 (0,7%)	2 (0,7%)	4 (1,3%)	4 (1,3%)
Beta-blocker + non-dihydropyridine calcium channel blocker	1 (0,4%)	1 (0,4%)	1 (0,4%)	1 (0,4%)
Digoxin	1 (0,4%)	1 (0,4%)	3 (1,0%)	3 (1,0%)
Beta-blocker + digoxin	15 (5,1%)	15 (5,1%)	1 (0,4%)*	1 (0,4%)
Therapy is not indicated	3 (1,0%)	0 (0,0%)	0 (0,0%)	0 (0,0%)
Other therapy	2 (0,7%)	2 (0,7%)	0 (0,0%)	0 (0,0%)

Note: * — p<0,05 (McNemar's test between the total number of appointments in the register and the number of appointments by experts using CDSS); † — in 10 cases with a CHA_2DS_2-VASc score of 1 (for men) and 2 (for women), anticoagulant therapy was recommended, which does not contradict the guidelines, since the final decision remains with the doctor; ‡ — 74 patients received beta-blocker monotherapy with as a component of antihypertensive therapy; § — in 4 cases the experts prescribed allapinin, which is not supported by CDSS; # — in 3 cases, patients were prescribed combination therapy (left atrial appendage occlusion and warfarin).

Abbreviations: RFA — radiofrequency ablation, CDSS — clinical decision support system, EHR — electronic health record.

Table 3

Antihypertensive therapy

	EHR appointments, N (%)		Experts + CDSS, N (%)	
	Total	Adequate	Total	Adequate
Monotherapy	75 (25,7%)	4 (1,3%)	0 (0,0%)	0 (0,0%)
Dual therapy	79 (27,1%)	36 (12,3%)	102 (35,0%)*	102 (35,0%)
Triple therapy	67 (23,0%)	21 (7,2%)	120 (41,2%)*	120 (41,2%)
Triple boosted therapy	59 (20,2%)	19 (6,5%)	69 (23,7%)	69 (23,7%)
Therapy is not indicated	11 (3,8%)	0 (0,0%)	0 (0,0%)*	0 (0,0%)
Total	291 (100,0%)	80 (27,5%)	291 (100,0%)§	291 (100,0%)

Note: * — p<0,05 (McNemar's test between the total number of appointments in the register and the number of appointments by experts using CDSS); § — in 25 cases, the therapy offered by CDSS had absolute contraindications, which is not taken into account by current clinical guidelines.

Abbreviations: CDSS — clinical decision support system, EHR — electronic health record.

Discussion

This work demonstrates the importance and significance of CDSS in selection of optimal treatment strategy for a specific patient according to clinical guidelines in order to reduce the risk of future cardiovascular events. Currently, the main documents regulating treatments by diseases are clinical guidelines [11, 12], created based on evidence-based clinical studies. Given the growing number of patients with various comorbidities and risk factors, the application of clinical trials results in everyday practice requires more time to make the right decision. In most cases, the guidelines describe the appointment of a drug group, while information on a specific drug should be read in the additional literature. The presented clinical study to assess the effect of CDSS on the choice of treatment for patients with HTN and AF is the first in Russia and suggests making a decision on the prescription of a specific drug based on clinical trials.

Comparative analysis demonstrated the compliance of anticoagulant, antiarrhythmic and antihypertensive therapy in 18% of cases. Most often, discrepancies with clinical guidelines were observed in antihypertensive therapy (72,5%). When making a decision on the appointment of antihypertensive therapy, CDSS offered more than 10-15 combinations that are difficult to remember and analyze during conventional office visit without using special software. CDSS use was associated with a significant increase in prescription rate of combined antihypertensive therapy, which may be due to the availability and objectivity of combination selection. When prescribing multiagent treatment regimens, absolute and relative contraindications for one of the drugs are not always taken into account, which is also difficult to foresee in patients with multimorbidity.

In the publications evaluating the effectiveness of antihypertensive therapy, along with assessing the accuracy of the doctor's adherence to clinical recommendations, an emphasis is placed on increasing patient adherence to treatment [5, 14]. To minimize the risk of cardiovascular events, it is necessary to take into account and analyze all available risk factors in a specific patient, based on current clinical guidelines, which CDSS allows to do.

Comparative analysis of antiarrhythmic therapy before and after CDSS use revealed a discrepancy between the initially prescribed therapy and clinical guidelines in 31% of cases. It is known that neither drug therapy nor catheter ablation has a significant advantage in mortality rate of AF patients [15]. However, in patients who underwent pulmonary vein ablation, there is a long-term significant decrease in arrhythmia recurrence with a lower hospitalization rate and, as a consequence, significantly better quality of life [16]. The present study showed that in case of CDSS use, experts were 32% more likely to recommend pulmonary vein isolation, which can improve quality of life.

When deciding on the anticoagulant therapy in a patient with AF, a cardiologist can use fairly simple risk scores for thromboembolic events (CHA_2DS_2-VASc) and bleeding (HAS-BLED). However, observational studies showed that only ~60% of patients with AF receive anticoagulant therapy in accordance with clinical guidelines [12]. At the same time, non-prescription, as well as insufficient or excessive anticoagulant therapy is accompanied by an increase in the risk of all-cause mortality and disability. At the same time, the use of novel oral anticoagulants demonstrates the best efficacy and safety profile (lowest risk of thromboembolic events, major cardiovascular events, and all-cause mortality) [17, 18].

Analysis of three therapy directions (antihypertensive, anticoagulant and antiarrhythmic), the anticoagulant therapy showed the lowest incidence of non-compliance with clinical guidelines (8%). In the overwhelming majority of patients, this was due to the prescription of low molecular weight heparins during bridging anticoagulation before the pulmonary vein isolation. According to current guidelines, bridge therapy has no clinical benefits and is associated with an additional bleeding risk [9]. As for outpatient stroke prevention, the use of CDSS was accompanied by an increase in prescription rate of novel oral anticoagulants by 14%. This, in turn, decrease the risk of any adverse cardiovascular events. There were also significant differences in the choice of a specific anticoagulant agent in favor of more effective and safer drugs.

Thus, this study shows that CDSS greatly facilitates a physician's work in choosing the optimal therapy that fully complies with clinical guidelines for a particular patient, which should ensure not only the clinical effect, but also, possibly, should reduce the risk of cardiovascular events.

Study limitations. This was a retrospective study, which did not allow assessing the causal relationship between the CDSS use and the endpoint. The study did not assess the CDSS impact on prognosis, since in the context of COVID-19 pandemic, it was difficult to arrange face-to-face patient visits to assess hard endpoints. Experts made decisions based on the given characteristics without taking into account the patient wishes and social factors. To assess the objective impact of CDSS on prognosis, it is necessary to conduct a study in an actual clinical practice.

Conclusion

The INTELLECT study revealed a formal discrepancy between the prescribed therapy and current clinical guidelines in 82% of cases. CDSS use is associated with improved adherence to current clinical guidelines. Prospective randomized trials are needed to evaluate the CDSS effectiveness in the prevention of cardiovascular events.

Relationships and Activities: none.

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Russian Journal of Cardiology 2021;26(4):4368
doi:10.15829/1560-4071-2021-4368
https://russjcardiol.elpub.ru

CLINICAL AND INVESTIGATIVE MEDICINE
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Pharmacoepidemiological analysis of routine management of heart failure patients in the Russian Federation. Part I

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Aim. To assess the healthcare system costs for the management of patients with heart failure (HF) based on a retrospective analysis of primary medical documentation.

Material and methods. We performed the analysis of outpatient records of 1000 patients, followed up for 1 year by a general practitioner or cardiologist in ambulatory clinic in 7 Russian regions. The study included men and women over 18 years of age with an established class II-IV HF and at least one hospitalization due to acute decompensated HF within 12-month follow-up.

Results. The final analysis included 888 patients (men, 52,9%; women, 47,1%; mean age, 69 [61; 78] years). The preserved ejection fraction (EF) was detected in 47,86% of patients, mid-range — in 40,54%, reduced — in 11,6%. Only in 16% of patients, there was improved by 1 or more HF. Hypertension and coronary artery disease were predominant in etiology pattern of HF. Preserved EF was more often detected in women over 60 years of age, with HTN and obesity, as well as with HF with mid-range and reduced EF in men in the same age group. There was sufficient follow-up rate, but the extent examinations do not correspond to the recommended one. The prescription rate of renin-angiotensin-aldosterone system (RAAS) inhibitors corresponds to the recommended one, but there is a high frequency of prescribing angiotensin II receptor blockers (ARBs). The prescription rate of β-blockers and loop diuretics (mainly torasemide) increased in comparison with previous studies, while thiazide diuretics — decreased. In patients with reduced EF, the prescription rate of sacubitril/valsartan was only 14,7%, β-blockers — 83,3%, mineralocorticoid receptor antagonists (MCRA) — 72,5%. In patients with mid-range EF, there was a sharp decrease in prescription rate of RAAS inhibitors, β-blockers, MCRA.

Conclusion. The practical follow-up of patients with HF differs significantly from clinical guidelines. Due to inadequate pharmacotherapy, as well as insufficient noncompliance with the recommended extent of investigations, 1-year HF therapy does not lead to a pronounced improvement in the patients' class.

Keywords: pharmacoepidemiology, heart failure, left ventricular ejection fraction, functional class.

Relationships and Activities: none.

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Received: 26.02.2021
Revision Received: 27.03.2021
Accepted: 15.04.2021

For citation: Lopatin Yu. M., Nedogoda S. V., Arkhipov M. V., Galyavich A. S., Koziolova N. A., Lozhkina N. G., Reznik E. V., Salasyuk A. S., Frolov M. Yu., Chesnikova A. I., Chumachek E. V., Shpagina L. A. Pharmacoepidemiological analysis of routine management of heart failure patients in the Russian Federation. Part I. *Russian Journal of Cardiology*. 2021;26(4):4368. (In Russ.) doi:10.15829/1560-4071-2021-4368

Heart failure (HF) has a widespread prevalence and poor prognosis, which leads to a high burden on the healthcare system in any country in the world. The prevalence of HF in different Russian regions varies within 7-10% [1]. At the same time, in recent years, the proportion of patients with severe HF has increased most significantly. Thus, the number of patients with HF of any class increased 2 times (from 7,18 million to 14,92 million), and patients with severe HF (class III-IV) — 3,4 times (from 1,76 million to 6,0 million) [1]. In the Russian Federation, the mean annual mortality among patients with class I-IV HF is 6%, and among patients with severe HF — 12% [2], and this is despite the great progress achieved in the treatment of this disease [3]. Decompensated HF is the cause of every second case of hospitalization in the cardiology department [4]. In the Russian Federation, the main causes of HF are hypertension (HTN) and coronary artery disease (CAD) [5]. Approximately half of patients with HF have preserved ejection fraction (EF) (HFpEF). Its prevalence in relation to HF with reduced EF (HFrEF) continues to increase with a frequency of 1% per year [2]. With the isolation of another HF type (HF with mid-range ejection fraction (HFmrEF), 40-49%), attention to the prevalence of this category of patients, their management and prognosis has increased significantly [6].

Despite the obvious fact of HF burden for the healthcare system, data on the compliance of actual practice with clinical guidelines and accepted standards of patient management in Russia, the specifics of prescribed therapy, and the effect of treatment on disease outcomes are very limited [1, 7, 8].

Therefore, the aim of our study was to assess the healthcare system costs for the management of HF patients based on a retrospective analysis of primary medical documentation of patients under general and cardiology outpatient supervision.

In this work, the first part of the study results is presented, including the epidemiological characteristics of patients and the specifics of therapy. Pharmacoeconomic data on the management of patients with HF in Russia will be presented in the second part of the work.

Material and methods

The study used data obtained from the outpatient records of 1000 patients followed up for 1 year by a general practitioner or cardiologist in an outpatient clinic in 7 Russian regions.

Research centers: 9 in 7 cities of Russia (Volgograd, Yekaterinburg, Kazan, Moscow, Novosibirsk, Perm, Rostov-on-Don).

The study included men and women over 18 years old with established class II-IV HF for at least 1 year. The inclusion criterion was the presence of at least one hospitalization (cardiology or therapy department) with acute decompensated HF within 12-month follow-up. All patients agreed to participate in the study and signed an informed consent. The starting point for 12-month period was any case of seeking medical help due to HF at the in- or outpatient stage in the period from January 01, 2018 to March 31, 2019.

Collection of primary data from a random sample. Demographic and clinical information, as well as data on investigations and pharmacotherapy were obtained from the primary medical documentation (outpatient records, discharge summary, UMIAS).

For a more detailed analysis, as well as for verifying and validating the data, a questionnaire was developed that includes, in addition to the information included in outpatient records, data on social status, disability and its cause, the source of payment for pharmacotherapy and rights for medicine assistance program.

Pharmacoepidemiological analysis was carried out in accordance with the international ATC/DDD methodology [9].

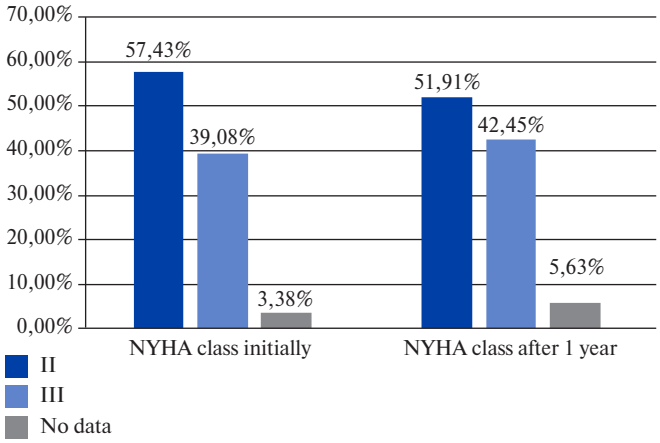

Figure 1. Distribution of patients by NYHA class.
Abbreviation: NYHA — New York Heart Association.

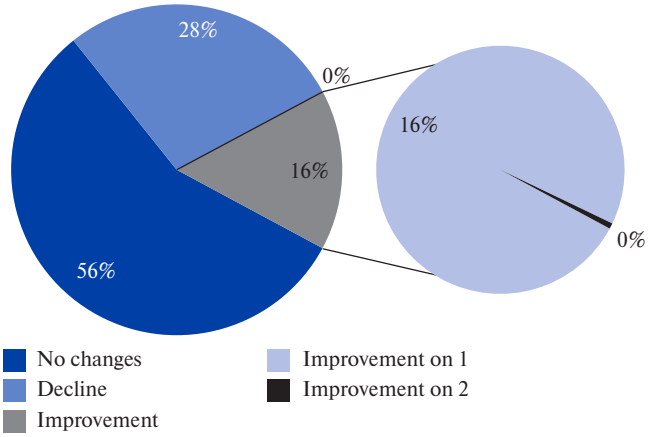

Figure 2. Changes in NYHA class in HF patients during follow-up.
Abbreviation: NYHA — New York Heart Association.

Table 1

Characteristics of the included patients

Parameter		Value	Sample (n)
Working-age patients, N (%)		181 (20,4%)	888
Patients included in medicine assistance program, N (%)		92 (10,4%)	888
Pensioners, N (%)		690 (78%)	888
Disability, N (%)	Total	311 (35%)	888
	Group I, N (%)	10 (3,2%)	311
	Group II, N (%)	192 (61,7%)	311
	Group III, N (%)	109 (35%)	311
Total number of working patients with HF		165 (18,6%)	888

Abbreviation: HF — heart failure.

Table 2

HF control parameters depending on the baseline LVEF

Parameter	Whole cohort, n=888		HFrEF LVEF <40%, n=103		HFmrEF LVEF ⩾40% ⩽49%, n=360		HFpEF LVEF ⩾50%, n=425	
	Baseline	After 1 year	Baseline	After 1 year	Baseline	After 1 year	Baseline	After 1 year
LVEF (%)	50,4±11,1	48,3±11,1	31,5±5,9	33,3±9,0	45,5±2,8	43,8±6,2	60,6±7,0	57,2±8,0
GFR (ml/min/1,73 m^2)	64,4±15,8	62,0±25,6	60,7±16,2	59,2±15,9	64,3±12,5	61,5±12,8	64,9±18,4	62,9±36,7
Weight (kg)	84,4±15,3	84,1±14,7	88,2±15,9	86,7±15	85,7±13,4	85,7±13,0	82,1±16,7	82,2±16,5
6 minute walk test, m	235,8±143,2	214,0±129,7	149,7±113,7	160,2±122,1	218,5±144,8	195,6±132,7	290,4±122,9	264,4±110,2
SBP, mm Hg	142,3±48,9	129,1±15,2	131,5±23,6	115,8±13,3	146,4±75,8	127,6±12,2	141,4±14,9	134,3±16,2
Heart rate, bpm	77,4±11,4	71,4±11,1	83,1±15,6	72±14,4	78,3±10,6	70,0±9,4	74,8±10,5	72,1±12,0

Abbreviations: SBP — systolic blood pressure, GFR — glomerular filtration rate, HFrEF — heart failure with reduced ejection fraction, HFmrEF — heart failure with mid-range ejection fraction, HFpEF — heart failure with preserved ejection fraction, LVEF — left ventricular ejection fraction, HR — heart rate.

Table 3

Number of investigations per patient year in patients with HF

Procedure	Mean ± Standard deviation	Median [95% CI, 0,25; 0,75]
ECG	1,87±1,27	2 [1; 2]
Echocardiography	0,84±0,61	1 [0; 1]
Chest X-ray	0,87±0,53	1 [1; 1]
NT-proBNP	0,02±0,19	0 [0; 0]
CBC	1,6±0,76	2 [1; 2]
Hemoglobin	1,61±0,76	2 [1; 2]
Potassium	1,25±0,79	1 [1; 2]
Sodium	1,23±0,81	1 [1; 2]
Creatinine	1,44±0,77	1 [1; 2]
GFR	1,2±0,87	1 [0; 2]
AST	1,41±0,75	1 [1; 2]
ALT	1,41±0,75	1 [1; 2]
Plasma glucose	1,59±1,95	1 [1; 2]
Clinical urine tests	1,19±0,65	1 [1; 2]
BBA	1,46±0,73	1 [1; 2]
6 minute walk test	It was initially performed in 65,3% of patients	

Abbreviations: ALT — alanine aminotransferase, AST — aspartate aminotransferase, CI — confidence interval, CBC — complete blood count, GFR — glomerular filtration rate, ECG — electrocardiography, NTproBNP — N-terminal pro-brain natriuretic peptide.

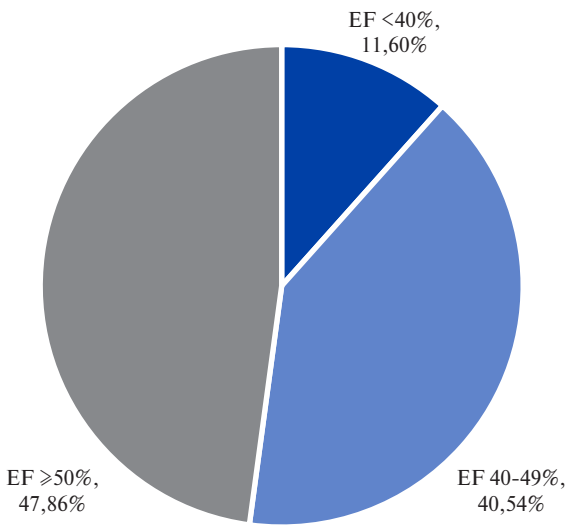

Figure 3. Distribution of patients by EF.
Abbreviation: EF — ejection fraction.

Statistical analysis. Statistical processing was carried out using STATISTICA 10.0, Stat Soft, Inc, and Microsoft Excel 2016. The normality of distribution in quantitative variables was tested using the Shapiro-Wilk, Kolmogorov-Smirnov, Cramer von Mises and Anderson-Darling tests.

Continuous quantitative data are presented as the mean and its standard deviation: M (SD). Non-normally distributed quantitative traits are presented as the median and its interquartile range: Me (25-75 percentiles). Dichotomous and ordinal qualitative data are presented as the number (n) and proportions (%).

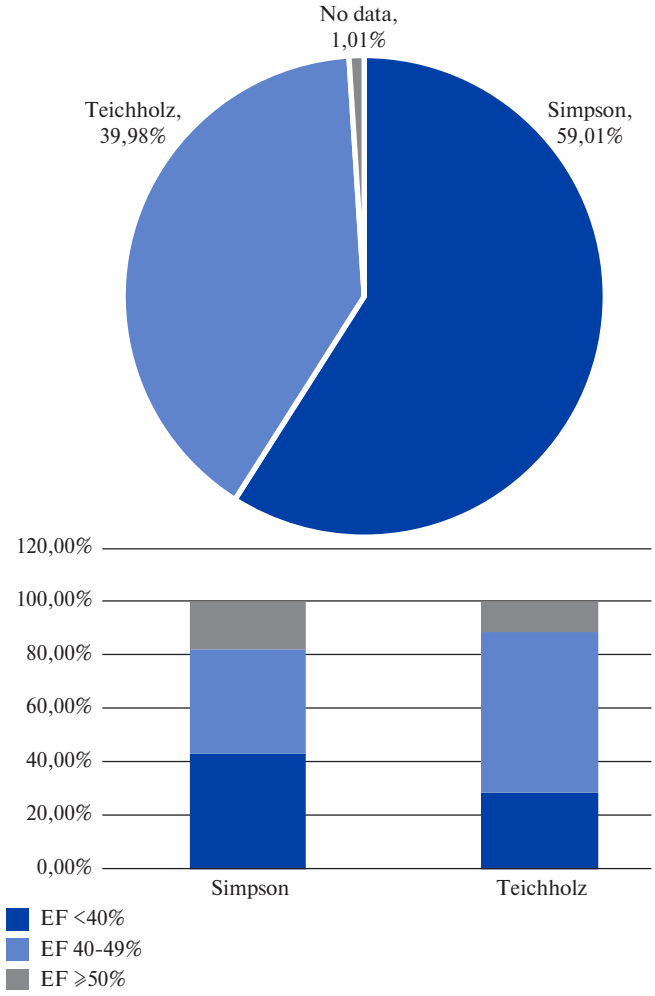

Figure 4. LVEF assessment technique and distribution of LVEF depending on the technique.
Abbreviation: EF — ejection fraction.

Results

Of the 1000 patients included in the study, 888 patients were included in the analysis. In 112 patients, the quality of primary medical documentation after filling out the questionnaire was insufficient for processing. Of the patients included, men accounted for 52,9%, while women — 47,1%. The mean age of patients was 69 years (95% confidence interval, 61-78 years); 24% of patients were of working age, and 35% of patients had persistent disability (Table 1).

Analysis of the patient distribution by NYHA classes showed that most of the patients at the start of follow-up and after 1 year had class II HF (Figure 1).

At the same time, in most cases, NYHA class did not change over 1 year of follow-up, and only in 16% of patients, as a result of therapy, it improved by 1 or more classes (Figure 2).

Most of the patients with HF, when included in the study, had preserved (47,86%) or mid-range ejection fraction (40,54%), while HFrEF was observed in 11,6% of cases (Figure 3).

It should be noted that, taking into account the clinical guidelines since 2016 [4, 6], the level of the N-terminal pro-brain natriuretic peptide (NT-proBNP) should be indicated in patients with HFpEF and HFmrEF. However, in actual clinical practice, NT-proBNP was determined only in 1% of patients. LVEF was more often determined by the Simpson method, which is consistent with modern guidelines [2], but the high frequency of using Teichholz method should be noted (Figure 4).

As shown in Figure 4, when determining LVEF by the Teichholz method, patients were more frequently assigned to the group with mid-range EF. In 15% of cases, patients with HFrEF were not detected when using this diagnostic method. This discrepancy is due to the fact that the Teichholz method is based on measuring linear dimensions, which can give inaccurate results, especially in patients with

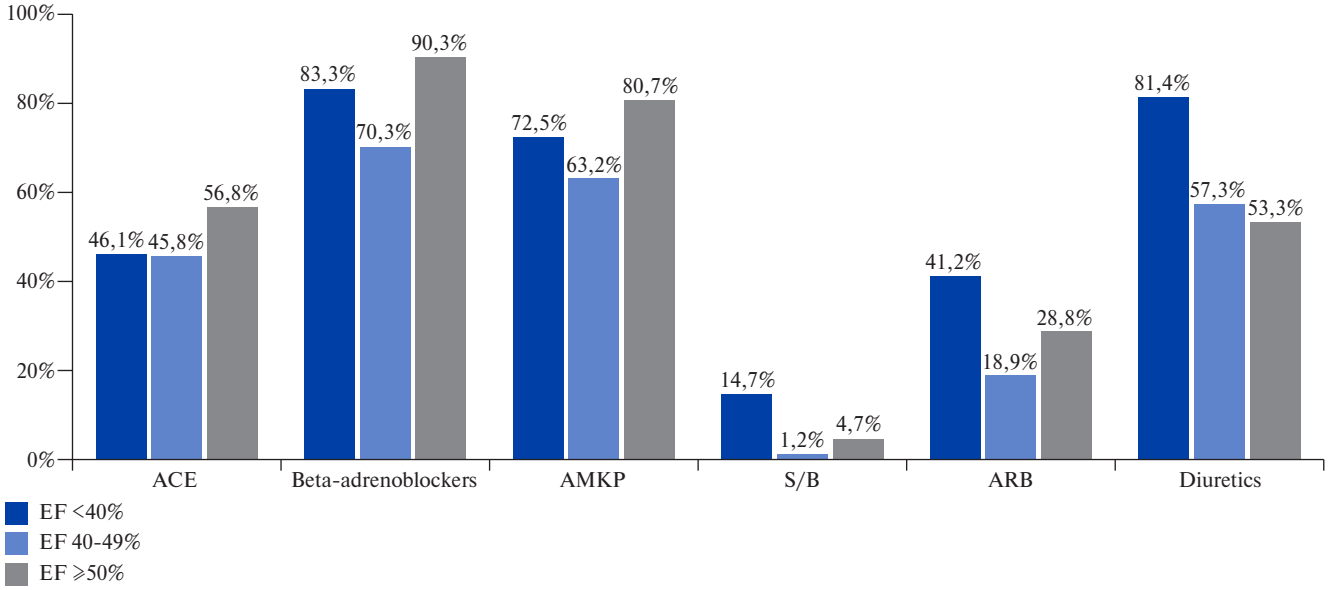

Figure 5. Compliance of the prescribed therapy with clinical guidelines.
Abbreviations: AMKR — mineralocorticoid receptor antagonists, ACE — angiotensin-converting enzyme, ARB — angiotensin II receptor blockers, S/B — sacubitril/valsartan, EF — ejection fraction.

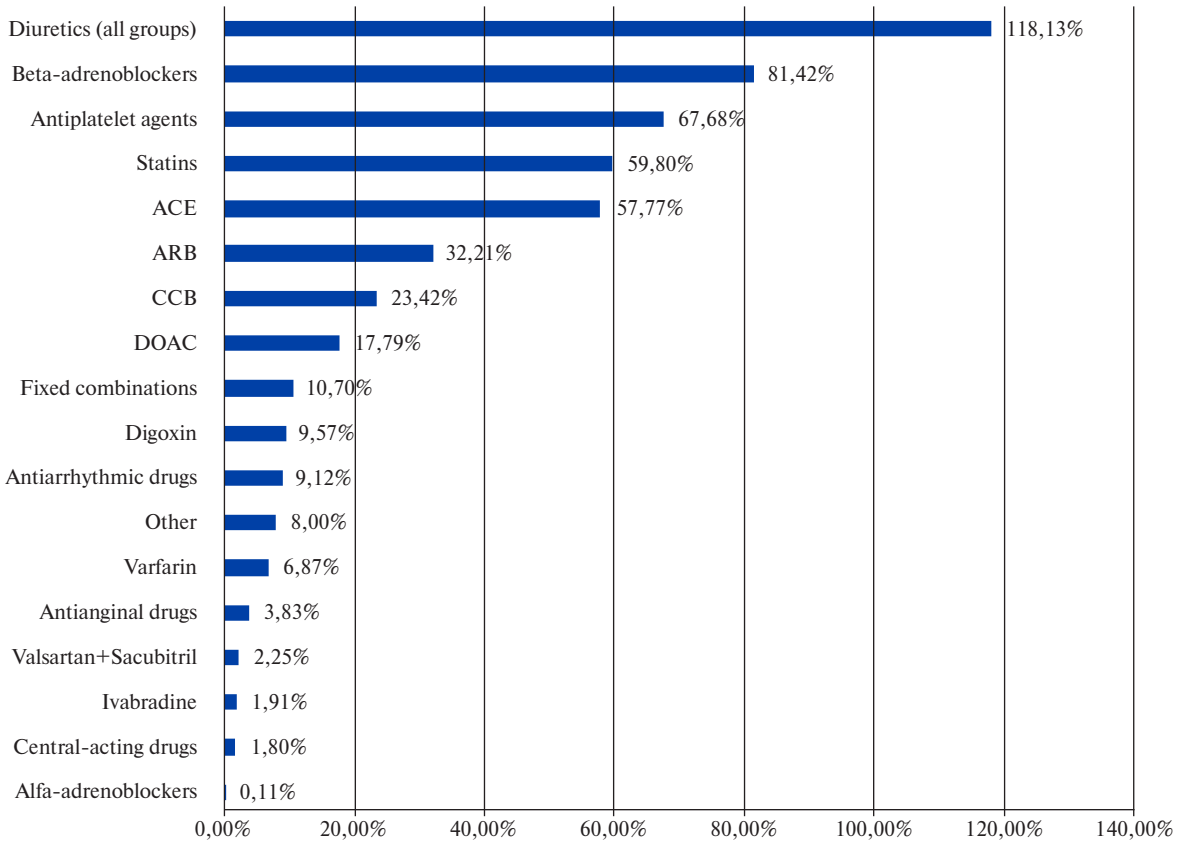

Figure 6. Distribution of prescribed therapy.
Abbreviations: ACE — angiotensin-converting enzyme inhibitors, ARB — angiotensin II receptor blockers, CCB — calcium channel blockers, DOAC — direct oral anticoagulants.

impaired local LV contractility. Therefore, this method is currently not recommended for clinical use [2].

In the majority of patients, there were data on comorbidities in the outpatient records. As for the etiology of HF, HTN and CAD prevailed — 94%

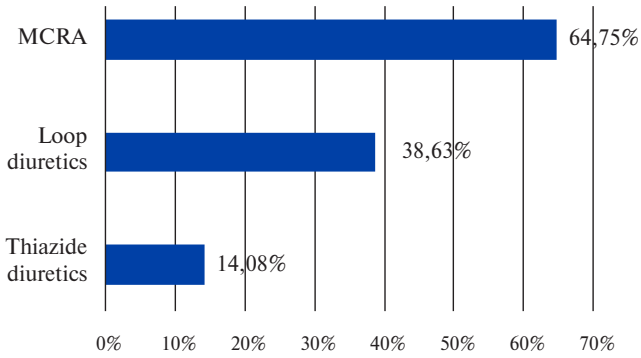

Figure 7. Distribution of diuretic prescriptions.
Abbreviation: MCRA — mineralocorticoid receptor antagonists.

and 75%, respectively. Their combination was found in 67% of patients. Valvular heart disease occurred in 0,6% of cases, dilated cardiomyopathy (DCM) — in 3,5%, type 2 diabetes — in 28,5%, atrial fibrillation, in most cases permanent one — in 38,7%.

Among patients with HFpEF, women over 60 years old, with a combination of HTN and obesity, were more common, and HF with mid-range and reduced EF was more common in men in the same age group.

The mean values of HF control at baseline and after 1 year are presented in Table 2.

As for diagnostic investigation rates, a pronounced discrepancy was found between the re-

Table 4

Therapy in patients with HF by INN

Groupe	INN	Total number of subscriptions	% total number of subscriptions	% receiving patients (total/in INN group)
ACE inhibitors		**513**	**11,51%**	**57,77%**
Captopril	7			1,4%
Lisinopril	60			11,7%
Perindopril	164			32,0%
Ramipril	20			3,9%
Fosinopril	23			4,5%
Enalapril	239			46,6%
ARB		**286**	**6,42%**	**32,21%**
Azilsartan	13			4,5%
Valsartan	66			23,1%
Candesartan	14			4,9%
Losartan	187			65,4%
Telmisartan	6			2,1%
β-blockers		**723**	**16,22%**	**81,42%**
Atenolol	2			0,3%
Bisoprolol	454			62,8%
Carvedilol	36			5,0%
Metoprolol	155			21,4%
Nebivolol	76			10,5%
α-blockers, Doxazosin	**1**	**1**	**0,02%**	**0,11%**
Centrally-acting drugs, Moxonidine	**16**	**16**	**0,36%**	**1,80%**
Diuretics, total		**984**	**22,08%**	**110,81%**
CAI, Acetazolamide	6			0,6%
Thiazide diuretics		125	2,80%	14,08%
Hydrochlorothiazide	45			36%
Indapamide	80			64%
Loop diuretics		343	7,70%	38,63%
Torasemide	300			87,46%
Furosemide	43			12,54%
MCRA		575	12,90%	64,75%
Spironolactone	416			72,35%
Eplerenone	159			27,65%

Table 4. Continuation

Groupe	INN	Total number of subscriptions	% total number of subscriptions	% receiving patients (total/in INN group)
CCB		**208**	**4,67%**	**23,42%**
Amlodipine	190			91,35%
Verapamil*	1			0,48%
Diltiazem*	1			0,48%
Lercanidipine	10			4,81%
Nifedipine	6			2,88%
Statins		**531**	**11,91%**	**59,80%**
Atorvastatin	338			63,65%
Pitavastatin	1			0,19%
Rosuvastatin	173			32,58%
Simvastatin	19			3,58%
DOAC		**158**	**3,54%**	**17,79%**
Apixaban	44			27,85%
Dabigatran	35			22,15%
Rivaroxaban	79			50,00%
Warfarin		**61**	**1,37%**	**6,87%**
Antiarrhythmic agents		**81**	**1,82%**	**9,12%**
Amiodarone	60			74,07%
Sotalol	21			25,93%
Antianginal drugs		**34**	**0,76%**	**3,83%**
Isosorbide mono/dinitrate	31			91,18%
Molsidomin	1			2,94%
Nicorandil	2			5,88%
Ivabradin	**17**	**17**	**0,38%**	**1,91%**
Antiplatelet agents		**601**	**13,48%**	**67,68%**
Acetylsalicylic acid	502			83,53%
Clopidogrel	93			15,47%
Ticagrelor	6			1,00%
Digoxin		**85**	**1,91%**	**9,57%**

Note: * — in accordance with the indications.

Abbreviations: MCRA — mineralocorticoid receptor antagonists, ARB — angiotensin II receptor blockers, carbonic anhydrase inhibitors — CAI, CCB — calcium channel blockers, ACE — angiotensin-converting enzyme, INN — international non-proprietary name, DOAC — direct oral anticoagulants.

commended [2, 4] and the actual prevalence of their appointment and implementation (Table 3).

Analysis of follow-up monitoring of outpatients with HF revealed compliance with the clinical guidelines [2, 4]. The average number of outpatient visits per patient year to a primary care physician was 3,64±2,37 visits, to a cardiologist — 1,5±1,47 visits (in total — 5,14 outpatient visits per year). The number of visits to the cardiologist was directly related to the deterioration of a patient's condition and the increase in NYHA class of HF. The average hospitalization rate per patient year was 1,21, of which according to ICD I50 — 0,67 hospitalizations.

The analysis of therapy revealed its pronounced inconsistency with the current clinical guidelines [2, 4], both in the management of patients with HFrEF, as well as with HFpEF and HFmrEF (Figure 5).

A total of 888 patients with HF received 4457 prescriptions of the medication. The distribution of prescribed drug therapy is shown in Figure 6.

The distribution of diuretic prescriptions is shown in Figure 7.

The distribution of drugs by INN is shown in Table 4.

Discussion

Taking into account the steady aging of the population and the increase in the number of patients with

Table 5

Prescriprion rate of various drugs in the population of HF patients. Adapted from the study by I. V. Fomin (2016) with additions [1]

% of intake	1998 Nizhny Novgorod Oblast	2000 Nizhny Novgorod Oblast	EPOCHA 2002	EPOCHA-Hospit.	EPOCHA 2007	EPOCHA 2014	2020 Reznik E. V., et al. [18]	Current study
ACE inhibitors	24,3	33,5	53,2	78,9	64,9	69,3	63,7	57,77
ARB	0	0	0		1,9	16,5	4,8	32,21
β-blockers	15,3	20,0	20,3	58,7	30,5	43,3	90,9	81,42
Thiazide/loop diuretic	8,3/5,6	16,9/4,3	21,8/2,4	43,6/10,8	43,7/2,2	30,1/3,9	0/96,1	14,08/38,63
Glycosides	0	2,4	7,9	9,0	7,1	3,9	22,2	9,57
Spironolactone	0	0	1,3	11,4	2,3	11,0	79,7	64,75*
Antiplatelet agents	0	4,7	11,1	50,5	21,1	58,3	71,5	83,53
Anticoagulants	0	0	0,3	5,4	0,4	0,8	47,3	16,47
Lipid-lowering drugs	0	0	0	27,7	1,9	3,6	29,5	no data
CCB	5,0	4,7	14,9	24,7	14,9	18,5	no data	23,42
Antiarrhythmic agents	NA	0	0,7	2,4	0,4	0,8	no data	3,83
Nitrates	2,0	10,6	34,2	36,3	28,6	28,3	no data	9,12
Other	74,3	74,7	56,0	17,0	30,8	15,5	no data	no data

Note: * — including eplerenone.

Abbreviations: ARB — angiotensin II receptor blockers, CCB — calcium channel blockers, ACE — angiotensin-converting enzyme, NA — not available.

HF [1], medical tariffs, and costs of drug therapy, the cost of managing patients with HF will progressively increase. Back in 2014, the burden of HF in Russia amounted to over 520 billion rubles and there was a significant increase in costs compared to 2008-2010 [10]. At the same time, in developed countries, the costs of treating HF patients amount to 1-2% of the total health care costs and up to 10% of the total spending on the therapy of cardiovascular diseases, of which 62-75% is spent on inpatient treatment [11, 12]. In addition, in the period from 2012 to 2030, costs are expected to increase by 127% [13]. Back in 2010, the healthcare reform in the United States identified the reduction in the number of HF-related readmissions as a key area to achieve a potential decrease in the cost of managing HF patients [14]. This makes important to study the HF in Russia to improve the management of such patients and meet the clinical guidelines [2], which will reduce the healthcare costs of treating patients and improve clinical outcomes.

In accordance with the aim of the paper, at the first stage, we analyzed the epidemiological characteristics of patients with class II-IV HF in actual clinical practice. The average age of studied HF patients reflected some stabilization and was 69 years (95% confidence interval, 61-78 years), after the growth in previous years: 64,0±11,9 (1998), 67,0±11,0 (2000), 68,3±11,7 (2007) and 69,9±12,2 (2014) [1]. The distribution by NYHA class also corresponded to the hospital stage of the EPOCH-CHF study [8] with a tendency to an increase in the number of patients with class III-IV HF, which are characterized by frequent readmissions [13].

The etiology of HF, demonstrated in our study, reflect the national trends [1]. The overwhelming majority of patients had comorbidities. HTN and CAD prevailed as the etiological cause of HF. Their combination was found in 67% of patients, which coincides with the available data [2]. Various heart defects occurred in 0,6% of cases, which reflects a tendency towards a decrease in the contribution of this factor to HF etiology [1]. DCM, on the contrary, was more common — in 3,5% of cases vs 0,8% in the hospital stage of the EPOCH-CHF study [15]. However, the prevalence of DCM as an etiology in our study correlates with the EuroHeart Survey data (Russian sample), where the prevalence of DCM as a cause of the disease in patients with class III-IV HF was 5% [16]. Type 2 diabetes (28,5%) and atrial fibrillation (38,7%) were also, as expected, identified as common comorbidities.

In our study, sex differences were shown — HFpEF was more often diagnosed in women over 60 years old with a combination of HTN and obesity, while HF with mid-range and reduced EF — in men in the same age group. Similar data were obtained by Dushina A. G. et al. (2019) in the in-depth examination of patients with HF depending on EF [17].

The analysis of follow-up monitoring of patients with HF showed that with a sufficient frequency of visits, the extent of diagnostic investigations, determined by clinical guidelines [2], is not observed in actual clinical practice. Thus, echocardiography and chest x-ray were performed at half the rate recommended. The six-minute walk test was initially performed in only 63% of patients, while NT-proBNP was measured in 10 patients (1%) from the cohort.

The analysis of drug therapy shows a lower prescription rate of angiotensin-converting enzyme inhibitors (mainly enalapril (47%) and perindopril (32%)) and, on the contrary, a higher prescription rate of angiotensin II receptor blockers in all patients with HF in comparison with previous studies, and also an increase in prescribing β-blockers. In addition, there is a pronounced increase in prescribing loop diuretics (mainly, torasemide) and a decrease — thiazide diuretics, which is associated both with an increase in the availability of torasemide in recent years, and with the characteristics of patients observed in large federal centers. The prescription rate of mineralocorticoid receptor antagonists (MCRA) also increased, with about a quarter of patients taking eplerenone (Table 5).

In patients with HFrEF, the prescription rate of sacubitril/valsartan is only 14,7%, β-blockers — 83,3%, MCRA — 72,5%. At the same time, the prevalence of prescribing renin-angiotensin-aldosterone system (RAAS) inhibitors generally corresponds to the recommended [2], but there is a high prescription rate of angiotensin II receptor blockers. As for patients with HFmrEF, there is a sharp decrease in the prescription rate of RAAS inhibitors, β-blockers, and mineralocorticoid receptor antagonists (MCRA).

It has been shown that the HF therapy received by patients for 1 year in actual clinical practice does not lead to a pronounced improvement in NYHA class.

Conclusion

The practical follow-up of patients with HF differs significantly from clinical guidelines:

- One-year HF therapy in actual clinical practice does not lead to a pronounced improvement in NYHA class;
- With a sufficient frequency of visits, the extent of diagnostic investigations, determined by clinical guidelines, is not observed in actual clinical practice.

Relationships and Activities: none.

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Russian Journal of Cardiology 2021;26(4):4470
doi:10.15829/1560-4071-2021-4470
https://russjcardiol.elpub.ru

CLINICAL AND INVESTIGATIVE MEDICINE
ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

International register "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV SARS-CoV-2): analysis of predictors of short-term adverse outcomes in COVID-19

Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G., Belenkov Y. N., Konradi A. O., Lopatin Y. M., Rebrov A. P., Tereshchenko S. N., Chesnikova A. I., Hayrapetyan H. G., Babin A. P., Bakulin I. G., Bakulina N. V., Balykova L. A., Blagonravova A. S., Boldina M. V., Vaisberg A. R., Galyavich A. S., Gomonova V. V., Grigorieva N. U., Gubareva I. V., Demko I. V., Evzerikhina A. V., Zharkov A. V., Kamilova U. K., Kim Z. F., Kuznetsova T. Yu., Lareva N. V., Makarova E. V., Malchikova S. V., Nedogoda S. V., Petrova M. M., Pochinka I. G., Protasov K. V., Protsenko D. N., Ruzanov D. Yu., Sayganov S. A., Sarybaev A. Sh., Selezneva N. M., Sugraliev A. B., Fomin I. V., Khlynova O. V., Chizhova O. Yu., Shaposhnik I. I., Schukarev D. A., Abdrahmanova A. K., Avetisian S. A., Avoyan H. G., Azarian K. K., Aimakhanova G. T., Ayipova D. A., Akunov A. Ch., Alieva M. K., Aparkina A. V., Aruslanova O. R., Ashina E. Yu., Badina O. Y., Barisheva O. Yu., Batchayeva A. S., Bitieva A. M., Bikhteyev I. U., Borodulina N. A., Bragin M. V., Budu A. M., Burygina L. A., Bykova G. A., Varlamova D. D., Vezikova N. N., Verbitskaya E. A., Vilkova O. E., Vinnikova E. A., Vustina V. V., Galova E. A., Genkel V. V., Gorshenina E. I., Gostishev R. V., Grigorieva E. V., Gubareva E. Yu., Dabylova G. M., Demchenko A. I., Dolgikh O. Yu., Duvanov I. A., Duyshobayev M. Y., Evdokimov D. S., Egorova K. E., Ermilova A. N., Zheldybayeva A. E., Zarechnova N. V., Ivanova S. Yu., Ivanchenko E. Yu., Ilina M. V., Kazakovtseva M. V., Kazymova E. V., Kalinina Yu. S., Kamardina N. A., Karachenova A. M., Karetnikov I. A., Karoli N. A., Karpov O. V., Karsiev M. Kh., Kaskaeva D. S., Kasymova K. F., Kerimbekova Zh. B., Kerimova A. Sh., Kim E. S., Kiseleva N. V., Klimenko D. A., Klimova A. V., Kovalishena O. V., Kolmakova E. V., Kolchinskaya T. P., Kolyadich M. I., Kondriakova O. V., Konoval M. P., Konstantinov D. Yu., Konstantinova E. A., Kordukova V. A., Koroleva E. V., Kraposhina A. Yu., Kriukova T. V., Kuznetsova A. S., Kuzmina T. Y., Kuzmichev K. V., Kulchoroeva Ch. K., Kuprina T. V., Kouranova I. M., Kurenkova L. V., Kurchugina N. Yu., Kushubakova N. A., Levankova V. I., Levin M. E., Lyubavina N. A., Magdeyeva N. A., Mazalov K. V., Majseenko V. I., Makarova A. S., Maripov A. M., Marusina A. A., Melnikov E. S., Moiseenko N. B., Muradova F. N., Muradyan R. G., Musaelian Sh. N., Nikitina N. M., Ogurlieva B. B., Odegova A. A., Omarova Yu. M., Omurzakova N. A., Ospanova Sh. O., Pahomova E. V., Petrov L. D., Plastinina S. S., Pogrebetskaya V. A., Polyakov D. S., Ponomarenko E. V., Popova L. L., Prokofeva N. A., Pudova I. A., Rakov N. A., Rakhimov A. N., Rozanova N. A., Serikbolkyzy S., Simonov A. A., Skachkova V. V., Smirnova L. A., Soloveva D. V., Soloveva I. A., Sokhova F. M., Subbotin A. K., Sukhomlinova I. M., Sushilova A. G., Tagayeva D. R., Titojkina Yu. V., Tikhonova E. P., Tokmin D. S., Torgunakova M. S., Trenogina K. V., Trostianetckaia N. A., Trofimov D. A., Tulichev A. A., Tupitsin D. I., Tursunova A. T., Ulanova N. D., Fatenkov O. V., Fedorishina O. V., Fil T. S., Fomina I. Yu., Fominova I. S., Frolova I. A., Tsvinger S. M., Tsoma V. V., Cholponbaeva M. B., Chudinovskikh T. I., Shakhgildyan L. D., Shevchenko O. A., Sheshina T. V., Shishkina E. A., Shishkov K. Yu., Sherbakov S. Y., Yausheva E. A.

The international AKTIV register presents a detailed description of out- and inpatients with COVID-19 in the Eurasian region. It was found that hospitalized patients had more comorbidities. In addition, these patients were older and there were more men than among outpatients. Among the traditional risk factors, obesity and hypertension had a significant negative effect on prognosis, which was more significant for patients 60 years of age and older. Among comorbidities, CVDs had the maximum negative effect on prognosis, and this effect was more significant for patients 60 years of age and older. Among other comorbidities, type 2 and 1 diabetes, chronic kidney disease, chronic obstructive pulmonary disease, cancer and anemia had a negative impact on the prognosis. This effect was also more significant (with the exception of type 1 diabetes) for patients 60 years and older. The death risk in patients with COVID-19 depended on the severity and type of multimorbidity. Clusters of diseases typical for deceased patients were identified and their impact on prognosis was determined. The most unfavorable was a cluster of 4 diseases, including hypertension, coronary artery disease, heart failure, and diabetes mellitus. The data obtained should be taken into account when planning measures for prevention (vaccination priority groups), treatment and rehabilitation of COVID-19 survivors.

Keywords: AKTIV register, COVID-19, multimorbidity, mortality predictors.

Relationships and Activities: none.

Trial ID: ClinicalTrials.gov: NCT04492384.

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Received: 19.04.2021
Revision Received: 24.04.2021
Accepted: 26.04.2021

For citation: Arutyunov G. P., Tarlovskaya E. I., Arutyunov A. G., Belenkov Y. N., Konradi A. O., Lopatin Y. M., Rebrov A. P., Tereshchenko S. N., Chesnikova A. I., Hayrapetyan H. G., Babin A. P., Bakulin I. G., Bakulina N. V., Balykova L. A., Blagonravova A. S., Boldina M. V., Vaisberg A. R., Galyavich A. S., Gomonova V. V., Grigorieva N. U., Gubareva I. V., Demko I. V., Evzerikhina A. V., Zharkov A. V., Kamilova U. K., Kim Z. F., Kuznetsova T. Yu., Lareva N. V., Makarova E. V., Malchikova S. V., Nedogoda S. V., Petrova M. M., Pochinka I. G., Protasov K. V., Protsenko D. N., Ruzanov D. Yu., Sayganov S. A., Sarybaev A. Sh., Selezneva N. M., Sugraliev A. B., Fomin I. V., Khlynova O. V., Chizhova O. Yu., Shaposhnik I. I., Schukarev D. A., Abdrahmanova A. K., Avetisian S. A., Avoyan H. G., Azarian K. K., Aimakhanova G. T., Ayipova D. A., Akunov A. Ch., Alieva M. K., Aparkina A. V., Aruslanova O. R., Ashina E. Yu., Badina O. Y., Barisheva O. Yu., Batchayeva A. S., Bitieva A. M., Bikhteyev I. U., Borodulina N. A., Bragin M. V., Budu A. M., Bury-

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For more than a year, the coronavirus disease 2019 (COVID-19) pandemic continues, which has covered almost all countries of the world and claimed 2978935 lives (according to the World Health Organization as of April 16, 2021) [1]. To assess the specifics of COVID-19 in the Eurasian region, an international register "Dynamics analysis of comorbidities in SARS-CoV-2 survivors" (AKTIV) was created [2], which was attended by specialists from 7 countries: Russian Federation, Republic of Armenia, Republic of Belarus, Republic of Kazakhstan, Kyrgyz Republic, Republic of Moldova, Republic of Uzbekistan.

The central aim of the register is to assess the impact of multimorbidity, various combinations of comorbidities and risk factors (RF) (obesity, smoking, hypertension (HTN), age over 60 years) on the risk of a severe COVID-19 course and death, as well as to analyze the effect of SARS-CoV-2 infection on the course of main noncommunicable diseases and cancer.

The design and statistical analysis methods of the register, as well the first data (n=1000) were presented in detail in previous publications [3-5]. It should be noted that analysis of the complete cohort of patients (n=5808) confirmed the patterns that were found in the preliminary analysis [5], and new patterns were also found.

Results

The register included 5808 patients with COVID-19: 4751 (81,8%) inpatients and 1057 (18,2%) outpatients (Table 1). The diagnosis was confirmed by polymerase chain reaction (PCR) test in 67,6%, while in the rest of the patients the diagnosis was made based on clinical performance and lung computed tomography (CT). The mean age of patients was 58 [48, 68] years: women — 53,6% (mean age, 59 [49, 68] years), men — 46,4% (mean, 57 [46, 66] years). Women were significantly older than men (p<0,0001). The distribution of patients according to the degree of lung damage according

Table 1

Characteristics of in- and outpatients included in the AKTIV register

	Inpatients (1)	Outpatients (2)	P for difference between 1 and 2	Total cohort (% of condition/outcome across the entire sample)
N	4751	1057	-	5808
Age, years	59,00 [50, 69]	49,90 [38, 60]	<0,001	58 [48, 68]
Women, %	53,61	58,09	0,01	54,42
Deceased, %	7,56	0,30	<0,01	6,17
HTN, %	60,85	30,84	<0,01	55,41
Obesity, % BMI ⩾30 kg/m^2	38,11	24,84	<0,01	35,54
Smoking, %	4,61	7,76	<0,01	5,18
CAD, %	23,10	9,43	<0,01	20,62
Prior myocardial infarction,%	6,57	1,96	<0,01	5,73
Prior history, %	4,85	1,67	<0,01	4,27
T2D, %	19,20	9,92	<0,01	17,52
HF, %	19,10	3,80	<0,01	16,30
Class I-II HF, %	12,2	3,40	<0,01	10,60
Class III-IV HF, %	6,80	0,40	<0,01	5,60
AF, %	7,83	2,06	<0,01	6,78
CKD, %	8,11	4,91	<0,01	7,53
COPD, %	5,39	1,28	<0,01	4,65
Asthma, %	3,33	3,05	0,65	3,28
Active cancer, %	2,20	1,77	0,39	2,12

Abbreviations: HTN — hypertension, CAD — coronary artery disease, MI — myocardial infarction, BMI — body mass index, T2D — type 2 diabetes, AF — atrial fibrillation, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, HF — heart failure.

to CT data was presented as follows: CT 0 (normal and absence of CT signs of viral pneumonia) — 5,2%, CT 1 (pulmonary parenchymal involvement ⩽25%) — 29,6%, CT 2 (pulmonary parenchymal involvement of 25-50%) — 34,7%, CT 3 (pulmonary parenchymal involvement of 50-75%) — 18,8% and CT 4 — 11,6% (diffuse ground glass opacities, pulmonary parenchymal involvement more than 75%). The overall mortality rate was 6,2%, while the intrahospital mortality rate — 7,6%. Non-invasive and invasive mechanical ventilation (MV) was performed in 14,3% of cases. In the group of patients receiving mechanical ventilation, the mortality rate was 36,7%.

The most common complication of COVID-19 according to the AKTIV register was a cytokine storm (23,2%), followed by bacterial pneumonia (9,7%), acute kidney injury (AKI) (9,0%), acute respiratory distress syndrome (ARDS) (5,9%), pulmonary embolism (PE) (0,61%), stroke (0,47%), deep vein thrombosis (DVT) (0,44%), and myocarditis (0,25%).

The majority of patients had several comorbidities (Table 1). Among comorbid pathologies, the most common were HTN — 55,41%, obesity — 35,54%, coronary artery disease (CAD) — 20,62%, type 2 diabetes (T2D) — 17,52%, heart failure (HF) — 16,3%, class I-II HF — 10,6%, class III-IV HF — 5,7%, chronic kidney disease (CKD) — 7,53%, atrial fibrillation (AF) — 6,78%, prior myocardial infarction (MI) — 5,73% and stroke — 4,27%, chronic obstructive pulmonary disease (COPD) — 4,65%, asthma — 3,28%, active cancer — 2,12%.

It is noteworthy that hospitalized patients were older than outpatients: 59,00 [50-69] vs 49,90 [38-60] years (p<0,0001). Among hospitalized patients compared with outpatients, there were fewer women (53,61 vs 58,09%, p=0,01), more patients with HTN (60,85 vs 30,84%, p<0,001) and obesity (38,11 vs 24,84%, p<0,001), but fewer smokers (4,61 vs 7,76%, p<0,001). Hospitalized patients more often than outpatients had CAD (23,10 vs 9,43%, p<0,001), prior MI (6,57 vs 1,96%, p<0,001) and stroke (4,85 vs 1,67%, p<0,001), T2D (19,20 vs 9,92%, p<0,001) and HF (19,10 vs 3,80%, p<0,001), both class I-II and III-IV (Table 1). In addition, hospitalized patients were more likely to have AF (7,83 vs 2,06%, p<0,001), CKD (8,11 vs 4,91%, p<0,001), and COPD (5,39 vs 1,28%, p<0,001).

Thus, hospitalized patients were more severe, older and there were more men among them than among outpatients.

Comparative analysis of surviving and deceased patients

When comparing deceased and surviving patients, predictors of intrahospital mortality were determined (Table 2). This is, first of all, the age ⩾60 years; this factor was more important for men (odds ratio (OR), 3,055 (95% confidence interval (CI), 2,418-3,86) p<0,001) than for women (OR, 1,462 (95% CI, 1,154-1,852) p<0,001). The mean age of the deceased and surviving patients was 70,24 [62, 80] and 56,65 [47, 67] years (p<0,001), respectively. Male sex was also an unfavorable prognostic factor that increased the death risk by one and a half times (OR, 1,529 (95% CI, 1,22-1,92) p<0,001). It is noteworthy that an extremely unfavorable factor is a positive PCR test at visit 3, i.e. 10-20 days after the admission. Grade 3 and 4 CT lung involvement increased the risk of death almost 4 times compared to grade 1-2. HTN increased the death risk by more than 3 times (OR, 3,123 (95% CI, 2,324-4,198) p<0,001), and this pattern was more pronounced for patients ⩾60 years of age (Table 2). Obesity was an unfavorable factor only for patients aged ⩾60 years (OR, 2,067 (95% CI, 1,558-2,743)), but a reduced body mass index (BMI) <18,5 kg/m^2 was also more often observed in deceased patients in comparison with survivors (2,79% vs 0,82%, respectively, p=0,01). Thus, among traditional RFs, obesity and HTN had a significant negative effect on prognosis, which was more pronounced for patients aged ⩾60 years.

Among comorbidities, CAD had a pronounced negative effect on the prognosis of patients, which was associated with an increase in the death risk by almost 4 times (OR, 3,829 (95% CI, 3,032-4,836) p<0,001). With age adjustment, this pattern persisted only for patients aged ⩾60 years. Prior MI also negatively affected the prognosis of patients, being associated with an increased risk of death (OR, 3,005 (95% CI, 2,165-4,170) p<0,001). Prior stroke had an even stronger negative effect on prognosis, which increased the risk by 5 times (OR, 5,02 (95% CI, 3,592-7,015) p<0,001). Any type of AF increased the mortality risk by more than 4 times (OR, 4,239 (95% CI, 3,17-5,669) p<0,001). With age

Table 2

Characteristics of survivors and deceased inpatients from the AKTIV register

Parameter	Total cohort, N=4751	Survivors, N=4390	Deceased patients, N=361	P	OR (95% CI)
Men, %	46,39	45,63	56,21	<0,01	1,529 (1,22-1,92)
Age, years	59,00 [50, 69]	56,65 [47, 67]	70,24 [62, 80]	<0,01	
Age <40 years, %		9,96	1,87	<0,01	
Age of 40-59 years, %		40,84	17,13		
Age of 60-80 years, %		42,41	52,96		
Age >80 years, %		6,79	28,04		
Male age ⩾60, %		20,20	43,61	<0,01	3,055 (2,418-3,86)
Female age ⩾60, %		29,00	37,38	<0,01	1,462 (1,154-1,852)
Positive 1st PCR test, %	63,66	62,12	74,26	<0,01	
Positive 2nd PCR test, %	18,10	16,32	35,60		
Positive 3rd PCR test, %	3,62	3,57	66,67		
CT 3-4, %	30,40	16,18	44,65	<0,01	4,178 (3,143-5,552)
HTN, %	55,41	59,88	82,33	<0,01	3,123 (2,324-4,198)
HTN ⩾60 years, %		38,78	70,57	<0,01	3,785 (2,946-4,862)
HTN <60 years, %		21,06	11,71	<0,01	0,497 (0,35-0,706)
Obesity (BMI ⩾30 kg/m^2), %	38,11	37,64	39,44	0,57	1,079 (0,829-1,404)
Obesity ⩾60 years, %		17,91	31,08	<0,01	2,067 (1,558-2,743)
Obesity <60 years, %		19,74	8,37	<0,01	0,371 (0,235-0,586)
BMI <18,5 kg/m^2, %	1,03	0,82	2,79	0,01	
BMI ⩾40 kg/m^2, %	4,78	4,51	7,57		
AF, %	7,83	6,59	23,03	<0,01	4,239 (3,17-5,669)
AF ⩾60 years, %		5,72	21,84	<0,01	4,606 (3,414-6,214)

Table 2. Continuation

Parameter	Total cohort, N=4751	Survivors, N=4390	Deceased patients, N=361	P	OR (95% CI)
AF <60 years, %		0,85	0,95	0,86	1,113 (0,339-3,649)
CAD, %	23,10	21,02	50,47	<0,01	3,829 (3,032-4,836)
CAD ⩾60 years, %		17,70	47,50	<0,01	4,195 (3,314-5,310)
CAD <60 years, %		3,20	2,80	0,71	0,877 (0,442-1,742)
Prior MI, %	6,57	6,00	16,10	<0,01	3,005 (2,165-4,170)
High Tn, %	5,85	5,05	16,33	<0,01	3,665 (1,542-8,712)
HF, %	19,10	14,50	44,00	<0,01	4,614 (3,633-5,859)
Class I-II HF, %	12,20	9,90	21,20	<0,01	2,446 (1,831-3,267)
Class III-IV HF, %	6,80	4,50	22,50	<0,01	6,124 (4,538-8,266)
Prior stroke, %	4,85	3,93	17,03	<0,01	5,02 (3,592-7,015)
T2D, %	19,20	18,43	37,54	<0,01	2,659 (2,089-3,386)
T2D ⩾60 years, %		12,08	31,33	<0,01	3,32 (2,568-4,291)
T2D <60 years, %		6,34	6,33	0,99	0,998 (0,623-1,599)
T1D, %	0,39	0,34	1,26	0,01	3,79 (1,228-11,691)
T1D ⩾60 years, %		0,05	0,32	0,09	6,132 (0,554-67,808)
T1D <60 years, %		0,28	0,95	0,05	3,358 (0,932-12,1)
CKD, %	8,11	7,01	20,19	<0,01	3,358 (2,486-4,536)
CKD ⩾60 years, %		4,92	17,09	<0,01	3,987 (2,874-5,53)
CKD <60 years, %		2,07	3,16	0,20	1,546 (0,793-3,014)
COPD, %	5,39	5,09	9,78	<0,01	2,02 (1,358-3,005)
COPD ⩾60 years, %		3,80	8,54	<0,01	2,363 (1,541-3,623)
COPD <60 years, %		1,29	1,27	0,97	0,978 (0,351-2,726)
Active cancer, %	2,20	2,07	5,05	<0,01	2,517 (1,453-4,36)
Cancer ⩾60 years, %		1,35	4,11	<0,01	3,146 (1,694-5,842)
Cancer <60 years, %		0,72	0,95	0,65	1,313 (0,397-4,344)
Anemia, % Hb in men <130 г/л Hb in women <120 г/л	18,08	16,67	35,04	<0,01	2,697 (2,073-3,508)

Abbreviations: HTN — hypertension, CI — confidence interval, CAD — coronary artery disease, MI — myocardial infarction, BMI — body mass index, CT — computed tomography, OR — odds ratio, PCR — polymerase chain reaction, T1D — type 1 diabetes, T2D — type 2 diabetes, Tn — troponin, AF — atrial fibrillation, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, HF – heart failure, Hb — hemoglobin.

adjustment, this pattern persisted only for patients aged ⩾60 years. HF of any functional class was associated with a poor prognosis, increasing the death risk by more than 4 times (OR, 4,614 (95% CI, 3,633-5,859) p<0,001). With class I-II and III-IV HF, the risk increased almost 2,5 times (OR, 2,446 (1,831-3,267) p<0,001) and 6 times (OR, 6,14 (4,538-8,266) p<0,001), respectively.

T2D was associated with a death risk (OR, 2,659 (95% CI, 2,089-3,386) p<0,001) predominantly for patients aged ⩾60 years. Type 1 diabetes (T1D) as also associated with a risk of death (OR, 3,790 (95% CI, 1,228-11,691) p<0,001), but mainly for patients under 60 years of age (Table 2). CKD was a strong risk factor for lethal outcome (OR, 3,358 (95% CI, 2,486-4,536) p<0,001), which was most significant for patients aged ⩾60 years. Among the deceased patients with CKD, the proportion of patients with a glomerular filtration rate (GFR) <45 ml/min/1,73 m^2 was 40,6%, and among survivors with CKD, the proportion of patients with a GFR <45 ml/min/1,73 m^2 was only 11,5% (p<0,001). COPD significantly increased the death risk (OR, 2,02 (CI 95% 1,358-3,005) p<0,001). With age adjustment, this pattern persisted only for patients aged ⩾60 years. Active cancer was also associated with the death risk (OR, 2,517 (1,453-4,36) p<0,001), which was most significant for patients over 60 years of age. Anemia was associated with an increased death risk by more than 2,5 times (OR, 2,697 (2,073-3,508) p<0,001). The deceased patients had a lower hemoglobin level (127,05 vs 134,51 g/l, p<0,001). Thus, among

Table 3

Characteristics of survivors and deceased inpatients from the AKTIV register, depending on the degree and type of multimorbidity

	Survivors, N=4390	Deceased patients, N=361	P	OR (95% CI)
No comorbidities, %	21,44	4,88	<0,01	-
1 comorbidity, %	26,49	10,57		-
2-3 comorbidities, %	33,98	32,52		-
⩾4 comorbidities, %	18,09	52,03		-
⩾2 comorbidities, ⩾60 years, %	34,85	71,14	<0,01	4,608 (3,462-6,132)
⩾3 comorbidities, <60 years, %	17,17	13,41	0,13	0,747 (0,512-1,091)
⩾2 comorbidities and obesity, ⩾60 years, %	11,78	27,24	<0,01	2,802 (2,072-3,79)
⩾2 comorbidities and obesity, <60 years, %	6,60	5,69	0,58	0,855 (0,489-1,494)
Diabetes + obesity + CVD*, %	9,53	19,11	<0,01	2,242 (1,595-3,151)
Diabetes + obesity + CVD* in patients aged ⩾60 years, %	5,99	13,82	<0,01	2,516 (1,699-3,725)
Diabetes + obesity + CVD* patients in patients aged <60 years, %	3,55	5,28	0,16	1,516 (0,84-2,739)
Most common combination of 2 diseases (HTN + Obesity)	26,12	36,99	<0,01	1,661 (1,266-2,178)
Most common combination of 2 diseases, 2nd place (HTN + CAD)	18,86	43,50	<0,01	3,311 (2,532-4,33)
Most common combination of 2 diseases, 3rd place (HTN + HF)	15,82	42,68	<0,01	3,963 (3,022-5,197)
Most common combination of 3 diseases (HTN + CAD + HF)	10,74	32,93	<0,01	4,082 (3,054-5,455)
Most common combination of 3 diseases, 2nd place (HTN + Obesity + Diabetes)	9,10	17,89	<0,01	2,177 (1,535-3,086)
Most common combination of 3 diseases, 3rd place (HTN + Obesity + CAD)	7,42	16,26	<0,01	2,421 (1,68-3,488)
Most common combination of 4 diseases (HTN + CAD + HF + Obesity)	3,98	13,82	<0,01	3,869 (2,578-5,806)
Most common combination of 4 diseases, 2nd place (HTN + CAD + HF + Diabetes)	3,55	13,41	<0,01	4,215 (2,784-6,382)
Most common combination of 4 diseases, 3rd place (HTN + CAD + HF + OMI)	3,65	10,16	<0,01	2,990 (1,896-4,716)

Note: * — CVD = HTN, CAD, MI, stroke, DVT, HF.

Abbreviations: HTN — hypertension, CI — confidence interval, CAD — coronary artery disease, MI — myocardial infarction, OR — odds ratio, OMI — old myocardial infarction, CVD — cardiovascular disease, DVT — deep vein thrombosis, HF — heart failure.

comorbidities, cardiovascular diseases (CVDs) had the maximum negative effect on prognosis, and this effect was more significant for patients aged ⩾60 years. Among other comorbidities, T2D, T1D, CKD, COPD, cancer and anemia had a negative impact on the prognosis. This effect was also more significant (with the exception of T1D) for patients aged ⩾60 years.

One of the most significant risk factors for lethal outcomes was the multimorbidity. So, among the deceased patients, there were only 4,88% without comorbidities, while among the surviving ones — 21,44% (p<0,001) (Table 3). Four or more comorbidities were present in 52,03% and 18,09% of deceased and surviving patients, respectively (p<0,001). With age adjustment, multimorbidity as RF was most significant for patients aged 60 years and older. For such patients, the presence of 2 or more comorbidities was associated with an increased death risk by more than 4,5 times (OR, 4,608 (95% CI, 3,462-6,132) p<0,001). We analyzed the influence of the most common combinations of comorbidities on the death risk. Among the most common combinations of two diseases, the most significant negative effect on the prognosis had a combination of HTN and HF (OR, 3,963 (95% CI, 3,022-5,197) p<0,001). This combination of two diseases occurred in 43,5% of deceased patients and only in 18,9% of survivors. Among the common combinations of three diseases, the combination of HTN, CAD and HF had a great adverse effect on the prognosis (OR, 4,082 (95% CI, 3,054-5,455) p<0,001). This cluster of diseases was observed in 32,93% and 10,74% of deceased and surviving patients, respectively. Among the common combinations of four diseases, the combination of

Table 4

Characteristics of survivors and deceased patients included in the AKTIV register

	Survivors, N=4944	Deceased patients, N=325	p
Age, years	56,65 [47, 67]	70,24 [62, 80]	<0,01
SBP, mm Hg	127,79 [120, 136]	127,96 [110, 140]	0,94
RR	19,84 [18, 21]	23,49 [20, 26]	<0,01
Heart rate	85,98 [77, 94]	92,47 [80, 100]	<0,01
SaO_2, %	94,41 [93, 97]	85,78 [82, 92]	<0,01
Hb, g/L	134,51 [125, 146]	127,05 [111, 144]	<0,01
WBC, ×10*9/L	6,64 [4,5, 7,87]	9,19 [5,8, 11,7]	<0,01
Lymphocytes, %	22,39 [12,55, 31,55]	13,31 [6, 18]	<0,01
Platelets ×10*9/L	225,36 [166, 267]	202,89 [150, 256]	<0,01
CRP, mg/L	54,24 [10, 77]	102,52 [20,5, 160]	<0,01
D-dimer, μg FEU/ml	1,62 [0,3, 1,5]	2,4 [0,6, 2,8]	<0,01
GFR, ml/min/1,73 m^2	73,08 [57,79, 89,78]	53,65 [35,32, 72,92]	<0,01
AST, U/Ll	38,38 [22, 43]	64,81 [27,6, 62,3]	<0,01
Glucose, mmol/L	6,41 [5, 6,97]	8,37 [5,5, 9,6]	<0,01
Glucose in patients with T2D, mmol/L	9,19 [6,1, 11]	10,38 [6,7, 12,85]	0,02
Glucose in patients with T1D, mmol/L	11,05 [6,9, 14,2]	12,12 [3,86, 20,38]	0,778
Fibrinogen, g/L	4,64 [3,5, 5,5]	4,50 [3,39, 5,5]	0,13
Procalcitonin, ng/ml	0,62 [0,05, 0,3]	2,09 [0,2, 1,06]	<0,01
Troponin T, ng/ml	0,01 [0, 0,02]	0,21 [0,03, 0,36]	<0,01
Troponin I, ng/ml	0,26 [0, 0,1]	0,25 [0,01, 0,14]	0,12
Total cholesterol, mmol/L	4,57 [3,63, 5,3]	3,6 [2,96, 4,08]	<0,01
LDL-C, mmol/L	2,63 [1,9, 3,2]	1,94 [1,43, 2,3]	0,02
Triglycerides, mmol/L	1,46 [1, 1,88]	1,4 [0,99, 1,69]	0,91
Potassium, mmol/L	4,11 [3,8, 4,5]	4,17 [3,6, 4,6]	0,97

Abbreviations: AST — aspartate aminotransferase, TC — total cholesterol, SBP — systolic blood pressure, T1D — type 1 diabetes, T2D — type 2 diabetes, GFR — glomerular filtration rate, CRP — C-reactive protein, RR — respiratory rate, HR — heart rate, LDL-C — low density lipoprotein cholesterol, Hb — hemoglobin, SaO_2 — blood oxygen saturation.

HTN, CAD, HF and diabetes was most associated with a negative prognosis (OR, 4,215 (2,784-6,382) p<0,001). This cluster of diseases occurred in 13,41% and 3,55% of deceased and surviving patients, respectively. Thus, the death risk in patients with COVID-19 depended on the degree and type of multimorbidity; the most unfavorable factor was the presence of 4 or more comorbidities, among which the most unfavorable cluster was a combination of HTN, CAD, HF and diabetes.

Analysis of clinical and laboratory data (Table 4) revealed that subsequently deceased patients had a higher respiratory rate (23,49 vs 19,84, p<0,001), a higher heart rate (92,47 vs 85,98, p<0,001), and lower blood oxygen level (SaO_2) (85,78 vs 94,41%, p<0,001). The deceased patients had a high level of white blood cells (9,19 vs 6,64 × 10*9/L, p<0,001), a reduced proportion of lymphocytes (13,31 vs 22,39%, p<0,001) and platelet count (202,89 vs 225,36 × 10*9/L, p<0,001).

The deceased patients had a higher level of C-reactive protein (CRP) (102,52 vs 54,24 mg/L, p<0,001), D-dimer (2,40 vs 1,62 μg FEU/ml, p<0,001), troponin (Tn) T (0,21 vs 0,01 ng/ml), and procalcitonin (2,09 vs 0,62 ng/ml, p<0,001). An increase in the Tn level was observed in 16,33% of deceased patients and was a RF for lethal outcome (OR, 3,665 (95% CI, 1,542-8,712) p<0,001).

It was noteworthy that the deceased patients had a lower GFR (53,65 vs 73,08 ml/min/1,73 m^2, p<0,001) and a high level of aspartate aminotransferase (AST) (64,81 vs 38,38 U/L, p<0,001). The deceased patients were characterized by hyperglycemia both in the general cohort of patients (8,37 vs 6,41 mmol/L, p<0,001) and in those with T2D (10,38 vs 9,19 mmol/L, p<0,02). In addition, the deceased patients had lower levels of total cholesterol (3,60 vs 4,57 mmol/L, p<0,001) and low-density lipoprotein cholesterol (1,94 vs 2,63 mmol/L, p<0,001).

Table 5

Characteristics of survivors and deceased inpatients from the AKTIV register, depending on the complications developed

	Survivors, N=4390	Deceased patients, N=361	P	OR (95% CI)
DVT, %	0,41	0,93	0,17	2,305 (0,668-7,953)
PE, %	0,33	5,59	<0,01	17,877 (8,677-36,832)
Stroke, %	0,30	3,73	<0,01	12,665 (5,643-28,425)
Bacterial pneumonia, %	11,40	14,91	0,06	1,361 (0,986-1,878)
ARDS, %	3,30	55,59	<0,01	36,667 (27,688-48,556)
Cytokine storm, %	22,45	35,97	<0,01	1,94 (1,355-2,777)
AKI, %	6,52	43,50	<0,01	11,04 (7,846-15,535)
Myocarditis, %	0,30	0,31	0,99	1,019 (0,132-7,863)
Sepsis, %	0,13	4,04	<0,01	33,093 (11,722-93,43)

Abbreviations: CI — confidence interval, AKI — acute renal injury, ARDS — acute respiratory distress syndrome, OR — odds ratio, DVT — deep vein thrombosis, PE — pulmonary embolism.

In the group of deceased patients, severe COVID-19 complications, such as PE (5,59 vs 0,33%, p<0,001), were more often observed, which was associated with an almost 18-fold increased risk of death (OR, 17,877 (95% CI, 8,677- 36,832) p<0,001) (Table 5). Strong risk factors for lethal outcome were ARDS (OR, 36,667 (95% CI, 27,688-48,556) p<0,001) and sepsis (OR, 33,093 (95% CI, 11,722-93,43)). The development of stroke (OR, 33,093 (95% CI, 11,722-93,43) p<0,001) and AKI (OR, 11,04 (95% CI, 7,846-15,535) p<0,001) significantly increased the risk of death. Cytokine storm (OR, 1,94 (95% CI, 1,355-2,777) p<0,001) and bacterial pneumonia (OR, 1,361 (95% CI, 0,986-1,878)) also increased the death risk in COVID-19 patients. Thus, the most common complications in deceased patients were ARDS (55,59%), AKI (43,50%), cytokine storm (35,97%). Bacterial pneumonia (14,91%), PE (5,59%), sepsis (4,04%) and stroke (3,73%) were somewhat less common. The rare complications were deep vein thrombosis (0,93%) and myocarditis (0,31%).

Conclusion

In terms of sex-related parameters, the AKTIV register patients did not differ significantly from those included in the foreign registries: for comparison, the mean age in the AKTIV register was 63,4 years, which is similar to the registries of China — 64 years [6], USA — 63 years [7], Italy — 63 years [8] and slightly less than in the registers of Spain — 69 years [9] and Great Britain — 73 years [10]. The proportion of women in the AKTIV register was higher (54%) than in the following foreign registers: Italy (18%) [8], Great Britain (40%) [10], USA (40%) [7], Spain (43%) [9] and China (51%) [6]. Mortality in the total cohort was 6,2%, which is higher than in the registries from China (2,3% and 3,2%) [11, 12], in the registry that included patients from the United States and China (4,8%) [13], but slightly lower than in the Italian register (7,2%) [14]. Intrahospital mortality rate in the AKTIV register (7,6%) is lower than in other studies. Thus, according to observational study from the United States, among 2634 inpatients, 21% died [7]. According to the meta-analysis by Abate SM, et al., which included 32 studies and 23082 patients, intrahospital mortality was 15%, while a range of this parameter was 1-52% in different countries [15]. The low intrahospital mortality rate according to the AKTIV register may be due to the fact that patients with a mild COVID-19 were often hospitalized in the Eurasian region, especially in the spring and summer of 2020.

According to the AKTIV register, the most common complication of COVID-19 was a cytokine storm (23,2%), followed by bacterial pneumonia (9,7%), AKI (9,0%), and ARDS (5,9%). According to various studies, cytokine storm was observed in 10-20% of patients with COVID-19 [16, 17], which is consistent with our data. The incidence of AKI according to the AKTIV register corresponds to the meta-analysis by Hansrivijit P, et al. with 26 included studies (n=5497), according to which the average incidence of AKI in COVID-19 patients was 8,4% (95% CI, 6,0-11,7%) with an average renal replacement therapy prevalence of 3,6% (95% CI, 1,8-7,1%) [18].

ARDS in patients from the AKTIV register was observed less frequently than in other studies. For example, one of the first Chinese reports indicated that ARDS occurred in 31% of cases [17]. According

to the meta-analysis by Abate SM, et al., ARDS was diagnosed in 32% of patients [15], which indicates a more severe contingent of hospitalized patients in these studies.

The incidence of in-life diagnosed thrombotic events according to the AKTIV register was less than in other studies: PE — 0,61%, stroke — 0,47%, DVT — 0,44%. According to the Bilaloglu S, et al., the incidence of DVT, PE, and stroke was 3,9%, 3,2%, and 1,6% [19]. According to the study by Mestre-Gómez B, et al., in-life PE was diagnosed in 6,4% of patients [20]. During lower limb deep vein ultrasound, DVT was detected in 46,1% of cases [21]. The low incidence of in-life diagnosed thrombotic events in the AKTIV register is probably due to the fact that in actual clinical practice a targeted search for these conditions was rarely carried out, and lower limb vein ultrasound and multislice computed tomography-angiopulmonography were not performed.

Myocarditis according to the AKTIV register was found in 0,25% of cases, which is much less common than according to Wang D, et al. (7,2%) [22] and according to autopsy studies — 4,5% and 7,2% [23, 24].

Patients in the AKTIV register and a high level of multimorbidity with a predominance of CVD, which coincides with the other studies. The incidence of HTN in hospitalized patients in the AKTIV registry (60,8%) was slightly higher than in the US (45,6%) [7], Italian (48,8%) [8], Chinese registries (30,5%) [6]. According to the large meta-analysis, which included 45 meta-analyzes, the incidence of HTN in all categories of COVID-19 patients was 27% (95% CI, 27-28) [25]. Obesity was observed in a third of the AKTIV register patients (35,5%), which was slightly less than in the register from the USA (41,7%) [7], and more than in the Spanish register (21,2%) [9].

The incidence of coronary artery disease in hospitalized patients in the AKTIV register (23,1%) was close to the data of the Italian register (21,4%) [8], was slightly less than in the US register (27,8%) [7], and significantly more than in the register from China (14,7%) [6]. Attention was drawn to the incidence of HF in patients of the AKTIV register — 16,3%, which was significantly higher than in the registers of the United States (6,9%) [7] and Spain (9,2%) [9].

The incidence of diabetes in the AKTIV register patients (17,5%) was close to that in the register from Italy (17%) [8], Spain (19,4%) [9] and China (14,4%) [6], but was significantly lower than in the US (33,8%) [7] and UK (29,8%) registries [10]. The prevalence of CKD in the AKTIV register patients (7,5%) was close to the register from Spain (6,1%) [9] and significantly more common than in the registers from Italy (3,0%) [8], China (3,4%) [6] and USA (5,0%) [7], and less common more than 2 times than in the UK register (16,0%) [10].

According to the AKTIV register, the death predictors was the age ⩾60 years, which increased the risk for men 3 times, and for women almost 1,5 times, which coincides with the other studies [17, 26-28]. Male sex also had a death risk, increasing the risk by one and a half times, which was noted in many observational studies. Thus, according to the study by Abate SM, et al., men had a 37% higher risk of death compared to women [15].

According to the AKTIV register, among the comorbidities, CVDs had the most unfavorable effect on the prognosis. Thus, HTN and CAD increased the death risk by 3 and almost 4 times, respectively. This is slightly more than in the meta-analysis by Noor FM, et al. with 58 studies (n=122191), which showed that HTN and CAD increases the risk by 2,1 and 3,6 times, respectively [29]. According to the meta-analysis by Parohan M, et al. (14 studies, n=29909), HTN and CAD increases the risk by 2,7 and 3,7 times, respectively [30]. According to the AKTIV register, HF of any functional class is associated with a poor prognosis, increasing the death risk by more than 4 times; severe class III-IV HF increased the death risk by 6 times. Similar findings were reported in the study by Tomasoni D, et al. involving 13 centers and 692 patients: HF was a strong independent predictor of increased intrahospital mortality (OR, 2,25, 95% CI 1,26-4,02, p=0,006) [31]. According to the study by Rey JR, et al., patients with HF were more likely to develop acute heart failure (11,2% vs 2,1%, p<0,001) and had a higher level of NT-proBNP. In addition, in the HF group, the mortality rate was higher (48,7% vs 19,0%, p<0,001) [32].

According to the AKTIV register, prior stroke was of great importance for the outcome, which increased the death risk by 5 times. According to the review by Trejo-Gabriel-Galán JM, prior stroke increases the death risk from COVID-19 by 3 times [33].

According to the AKTIV register, type 1 and 2 diabetes was associated with an increased risk of death by 3,8 and 2,7 times, respectively. Other researchers have also reported adverse effects of diabetes on prognosis. For example, according to the meta-analysis by Noor FM, et al. [29], diabetes increased the death risk by 1,9 times, and according to the meta-analysis by Parohan M, et al. [30] — 2,4 times. According to the AKTIV register, CKD was also associated with a poor prognosis, increasing the risk by more than 3 times, and the risk was maximally increased at a GFR <45 ml/min/1,73 m^2.

The meta-analysis by Noor FM, et al. [29] also indicated a 2,1-fold increase in the death risk in patients with CKD.

According to the AKTIV register, obesity in patients aged ⩾60 years was an unfavorable factor that increased the death risk by 2 times, but a significantly reduced body weight (BMI <18,5 kg/m^2) was also associated with a poor prognosis. Thus, U-shaped dependence of risk on the patient's body weight. The negative impact of obesity on prognosis has been reported by many researchers [29, 34]. Previously, it was also indicated that there is a U-shaped relationship between BMI and influenza pneumonia risk [35]. According to Zheng KI, et al., the association between obesity and the COVID-19 severity remained significant even after statistical adjustments for age, sex, smoking, diabetes, HTN, and dyslipidemia [36]. According to the AKTIV register, obesity posed the greatest danger for patients aged ⩾60 years. In contrast, Lighter J, et al. showed that obesity was more dangerous for patients younger than 60 years old [37].

According to the AKTIV register, any type of AF increased the death risk by more than 4 times. This factor represented the greatest risk for patients over 60 years of age. The incidence of AF in this registry was less (6,78%) than on other studies, according to which, among patients with COVID-19, AF was detected from 19% to 21% of all cases and was more common in patients with a severe COVID-19 course, and in the death cohort was observed in 44% of cases [38].

According to the current register, COPD had a negative impact on the prognosis, increasing the death risk by 2 times. According to the meta-analysis by Lippi G, et al., which included 7 studies involving 1592 COVID-19 patients, COPD was found to be significantly associated with severe COVID-19 (hazard ratio (HR), 5,69 (95% CI, 2,49-13,00) [39].

As for the effect of cancer on the COVID-19 severity, the literature data are contradictory. According to the AKTIV register, active cancer is a predictor of an unfavorable outcome and increases the death risk by 2,5 times, which was most significant for patients aged ⩾60 years. These data are consistent with the South Korean registry (n=7590), which showed that cancer is a predictor of a poor prognosis: among deceased patients, it was found significantly more often compared with survivors (11,9 vs 3,2%, p<0,001) [40].

According to the AKTIV register, anemia was a death predictor, increasing its risk by more than 2,5 times. The deceased patients had a lower hemoglobin level in comparison with the survivors: 127,05 (111-144) vs 134,51 (125-146) g/L (p<0,001). Similar data were found in the meta-analysis by Taneri PE, et al., which showed that, compared with moderate course, patients with severe COVID-19 had lower hemoglobin (weighted mean difference (WMD), -4,08 g/L (95% CI, -5, 12; -3,05) and red blood cell levels (WMD, -0,16×10^{12}/L (95% CI, -0,31; -0,014), as well as higher ferritin (WMD, -473,25 ng/ml (95% CI, 382,52; 563,98)); but unlike our study, this meta-analysis found a significant difference only in mean ferritin levels of 606,37 ng/ml (95% CI, 461,86; 750,88) between surviving and deceased patients but not in hemoglobin ones [41].

According to the AKTIV register, the most important risk factor of lethal outcome is multimorbidity, while a pattern is observed: the more comorbidities, the more unfavorable the prognosis in COVID-19. For patients aged ⩾60 years, the presence of 2 or more comorbidities was associated with an increased death risk by more than 4,5 times. According to other studies, multimorbidity was also a predictor of an unfavorable disease course. According to the meta-analysis by Abate SM, et al., mortality among COVID-19 inpatients was 2 times higher in those with any comorbidities compared with those without comorbidities (HR, 2,20 (95% CI, 1,75-2,77) [15]. According to the Cho SI registry, et al., age-adjusted Charlson comorbidity index (CCI) correlated with patient mortality, and an ICI threshold >3,5 provided the best cut-off point for predicting mortality [40]. Analysis of the AKTIV register revealed the most common clusters of comorbidities and their influence on the patient prognosis. The clusters were dominated by CVDs in various combinations and diabetes. Four-disease cluster (HTN, CAD, HF, diabetes) had the most unfavorable effect on the prognosis. No similar data were found in the available literature.

According to the AKTIV register, patients with a poor prognosis were characterized by a complete blood count abnormalities: a decrease in hemoglobin and lymphocyte (%) levels, platelet count, as well as an increase in white blood cell count. In addition, the deceased patients had higher levels of CRP, D-dimer, AST and troponin, which is consistent with the other studies [17]. According to the AKTIV register, a troponin increase was observed in 16,33% of deceased patients, which increased the death risk by more than 3,5 times. According to the meta-analysis by Bavishi C, et al. an increase in Tn level occurs in 20% of inpatients with COVID-19 [42]. Qin JJ, et al showed that increased Tn level is a strong predictor of 28-day mortality (HR, 7,12 (95% CI, 4,60-11,03, p<0,001) [43].

Conclusion

The international AKTIV register presents a detailed description of out- and inpatients with COVID-19

in the Eurasian region. Hospitalized patients had more comorbidities and were older, as well as there were more men than among outpatients. Among the traditional risk factors, obesity and HTN had a significant negative effect on prognosis, which was more significant for patients 60 years of age and older. Among comorbidities, CVDs had the maximum negative effect on prognosis, and this effect was more significant for patients 60 years of age and older. Among other comorbidities, type 2 and 1 diabetes, CKD, COPD, cancer and anemia had a negative impact on the prognosis. This effect was also more significant (with the exception of T1D) for patients 60 years and older. The death risk in patients with COVID-19 depended on the severity and type of multimorbidity. Clusters of diseases typical for deceased patients and their impact on prognosis were identified. The most unfavorable was a cluster of 4 diseases, including hypertension, coronary artery disease, heart failure, and diabetes mellitus. The data obtained should be taken into account when planning measures for prevention (vaccination priority groups), treatment and rehabilitation of COVID-19 survivors.

Relationships and Activities: none.

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