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ЛЕЙКЕМОИДНАЯ РЕАКЦИЯ У ПАЦИЕНТА СТАРЧЕСКОГО ВОЗРАСТА С ИНФЕКЦИОННЫМ ЭНДОКАРДИТОМ АОРТАЛЬНОГО КЛАПАНА И АДЕНОКАРЦИНОМОЙ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ

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Leukemoid Reaction in an Elderly Patient with Aortic Valve Infective Endocarditis and Pancreatic Adenocarcinoma

Резюме

Лейкемоидная реакция (ЛР), связанная с солидными опухолями, документируется на протяжении многих десятилетий, и часто ассоциирована с неблагоприятным прогнозом и агрессивным течением заболевания. Вместе с тем, дифференциальная диагностика ЛР представляет значительные трудности при наличии у пациента нескольких потенциальных этиологических факторов, каждый из которых по отдельности может быть причиной ЛР, или, напротив, приводить к системной реакции организма в рамках общего патогенетического сценария.

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Нами представлено клиническое наблюдение пациентки старческого возраста, госпитализированной в отделение реанимации и интенсивной терапии в связи с впервые развившейся слабостью в правых конечностях. При клинико-лабораторно-инструментальном обследовании подтверждено острое нарушение мозгового кровообращения по ишемическому типу на фоне нарастания в течение 5 суток лейкоцитоза до 60 тыс. клеток/мкл со сдвигом лейкоцитарной формулы влево и декомпенсацией состояния пациентки с последующим летальным исходом, несмотря на проводимую терапию.

При аутопсии выявлена низкодифференцированная аденокарцинома хвоста поджелудочной железы с множественным метастатическим поражением региональных лимфатических узлов и печени, а также конкурирующее заболевание — острый инфекционный эндокардит аортального клапана, явившийся причиной развития сепсиса по типу септикопиемии и тромбоэмболии как по большому кругу кровообращения с наличием ишемического инфаркта головного мозга, инфарктов селезенки, так и по малому кругу с развитием тромбоэмболов в правых сегментарных ветвях легочной артерии. Учитывая распространенный характер рака поджелудочной железы и отсутствие прямых данных за активный инфекционный процесс на этапе первичной диагностики, более вероятен паранеопластический характер ЛР, однако инфекционный эндокардит и сопутствующая патология могли также внести свой вклад в развитие ЛР.

Ключевые слова: *лейкемоидная реакция, острый инфекционный эндокардит, аортальный клапан, аденокарцинома поджелудочной железы, паранеопластический синдром*

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Abstract

Leukemoid reaction (LR) associated with solid tumors has been documented for many decades. LR is often associated with an unfavorable prognosis and aggressive course of the disease. However, the differential diagnosis of LR is of significant difficulty when a patient has several potential etiological factors, each of them individually may cause LR or, on the contrary, lead to a systemic reaction of the body within a single pathogenetic chain.

We present a clinical observation of an elderly patient admitted to the intensive care unit due to the first-time encountered weakness in the right extremities. Clinical and instrumental examination revealed an acute cerebral ischemia with leukocytosis increase up to 60.000 cells/μL with leukocyte formula left shift and subsequent patient decompensation with lethal outcome, despite the intensive treatment.

Autopsy revealed a low-differentiated adenocarcinoma of the pancreatic tail with multiple metastatic lesions in regional lymph nodes and liver, as well as a competing disease — acute infective endocarditis of the aortic valve, which was the cause of sepsis development with septicemia type and thromboembolism both in the great circulation circle with the presence of ischemic cerebral infarction, spleen infarcts, and in the small circle with the development of thromboembolism in the right segmental branches of the pulmonary artery. Given the advanced stage of pancreatic cancer and lack of direct evidence of sepsis at primary diagnosis, paraneoplastic nature of LR is more likely, but infective endocarditis and concomitant pathology also may have contributed to the development of LR.

Key words: *leukemoid reaction, acute infective endocarditis, aortic valve, pancreatic adenocarcinoma, paraneoplastic syndrome*

Conflict of interests

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G-CSF — granulocyte colony-stimulating factor, US examination — ultrasound examination, CT — computer tomography, LR — leukemoid response, echoCG — echocardiography

Introduction

Leukemoid response (LR) is characterised by persistent leukocytosis of over 50 k cell/μL in the absence of bone marrow involvement, where acute or chronic myelogenous leukaemia has been ruled out. The relative count of immature forms in LR is negligible or moderate, myelocytes rarely exceed 5–15 %, blasts are practically absent, whereas in leucosis these values are high. LR does not manifest with signs of neoplastic proliferation usually seen in leucosis, therefore, LR is not associated with metaplastic anaemia and thrombocytopenia [1].

There are 4 types of LR. Type 1 — myeloid reactions; most common are neutrophilic reactions with neutrocytosis of over 9×10^9/L and left shift to metamyelocytes and myelocytes; promyelocytic reactions with high promyelocyte counts; eosinophilic reactions, if the absolute

blood eosinophilic leukocyte count is over 0.45×10^9/L, and reactions of two and three myelogenesis lineages, which manifest as neutrocytosis (or leukopenia), hyperthrombocytosis (or thrombocytopenia) and normoblastosis (normocytosis) in peripheral blood. Type 2 — a lymphocytic reaction, which is secondary reactive lymphocytosis with an increase in the absolute lymphocyte count of over 4×10^9/L. Type 3 is represented by monocytic-macrophagal blood reaction, associated with an increase in peripheral blood monocytes over 0.8×10^9/L as a result of infectious, fungal, rickettsial, and protozoan diseases. Type 4 is pseudoblast LR, which is characterised by the presence of numerous cells with a homogeneous nucleus, individual nucleoli, blue thin cytoplasm without granularity, which are mistaken for blast cells, in blood and bone marrow [1, 2].

LR is not an independent pathology; usually, it is secondary to an underlying disease. LR can be caused mostly by severe infections, various intoxications, heavy bleeding or blood clots, more rarely — by solid tumours as part of paraneoplastic syndrome [3, 4]. Despite being quite rare, paraneoplastic LR is a well-described event associated with solid tumours, particularly lung cancer, clear-cell carcinoma and pancreatic cancer [4].

The definitive pathogenesis of paraneoplastic LR is still unclear due to insufficient materials for a detailed investigation; however, data from some publications describe secretion of granulocyte colony-stimulating factor (G-CSF) in the presence of cytokine-producing tumour. G-CSF is a natural glycoprotein which stimulates proliferation and maturation of progenitor cells of bone marrow to become fully differentiated neutrophils. Normally, G-CSF is produced by endotheliocytes, fibroblasts, monocytes, and macrophages. In patients with paraneoplastic LR, G-CSF is secreted directly by tumour cells and results in cytokine-mediated leukocytosis [5].

Outcomes in patients with paraneoplastic LR and solid tumours in various locations show that LR is a predictor of poor outcome. In a retrospective study by Granger et al. (2009), 76 % of patients with paraneoplastic LR died within 12 weeks, which correlates with individual published clinical observations, describing mostly adverse outcomes in these patients [6, 7].

We present a case study of an elderly female patient with metastatic pancreatic cancer, acute infective endocarditis of aortic valve with sepsis in the form of septicopyaemia and thromboembolism, which caused cardioembolic stroke, spleen infarction and marked LR.

Case Study

Female patient E., 83 years old, was admitted to the ICU for patients with acute cerebrovascular accidents; she was complaining of marked weakness in her right-side limbs. Her medical record states that the patient has had high blood pressure and type 2 diabetes mellitus for a long time.

Upon examination, patient's condition is serious; contact with the patient is challenging due to cognitive disorders; skin is pale pink, warm, without swelling. Body temperature — 37.6 °C, body mass index — 24 kg/m^2.

Breathing is regular, rhythmic; chest excursion is symmetric; respiratory rate is 19 per minute. Saturation is 93 % atm. Chest auscultation revealed harsh breathing, bilaterally weakened in lower sections, without secondary respiratory murmurs.

Cardiac tones are muffled, rhythm is regular; heart rate is 87 bpm, blood pressure: 170/85 mm Hg. Main and peripheral artery pulse is adequate. Tongue is dry, with brown plaque. Abdomen is symmetric, soft, painless. Kidney punch is negative on both sides.

Neurological status evaluation: state of consciousness — obtundation, sensorimotor aphasia, meningeal signs are absent. Pupils are symmetric, sensitive to light. Eye bulbs are deflected to the left, right gaze deviation. The right nasolabial fold is smoothened. No nystagmus; swallowing is preserved; the tongue is on the midline. Moderate dysarthria. Quadriparesis: right side — strength reduced to 2 points in the leg, plegia — in the arm; left side: to 3 points in the leg, 1 point in the arm. Overactive tendon and periosteal reflexes on the left side. Babinski's sign is positive on both sides. Sensory and coordination impairment cannot be verified due to the serious condition of the patient. NIHSS (National Institutes of Health Stroke Scale) score is 20 points.

During hospitalisation, leukocytosis got worse with thrombocytopenia up to 70×10^9/L and hypochromatic normocytic anaemia with Hb values as low as 93 g/L (Figure 1). The highest recorded neutrocytosis level was 60.86×10^9/L, with an increase in the relative banded neutrophil value to 94.5 % and left shift to metamyelocytes and appearance of up to 1 % of myeloblasts in peripheral blood (Table 1). Blood procalcitonin was 1.48 ng/mL.

Blood biochemistry results showed hyperglycemia up to 14.9 mmol/L, bilirubinemia up to 24.6 μmol/L, elevated alkaline phosphatase and minor elevation of aspartate aminotransferase (Table 2). Troponin upon admission — 50.7 ng/mL.

Coagulation profile was unremarkable.

Clinical urinalysis: significant proteinuria (protein 6.0 g/L), glucosuria (28.0 mmol/L), erythrocyturia (25–30 per HPF), bacteriuria.

Cerebrospinal fluid examination: light yellow, liquor xanthochromia 1+, completely clear, cytosis 81/3, liquor protein 0.645 g/L, lymphocytes 3, neutrophils 78, liquor glucose 9.6 mmol/L.

ECG upon admission: sinus rhythm, heart rate: 72 bpm, left-sided axis deviation, signs of macrofocal cicatrical changes in the myocardium of the lower left ventricle wall (Figure 2).

Echocardiography (echoCG) showed induration of aorta and cusps of aortic and mitral valves, calcifications on cusps of aortic and mitral valves, minor enlargement of the left atrium to 4.2 cm, left ventricular hypertrophy

(posterior wall thickness of left ventricle: 1.2 cm, interventricular septum thickness: 1.3 cm). Absence of adequate systolic induration of anterior, septal walls at the level of apical segment, apex of left ventricle. Global contractility is slightly lower than normal, Simpson left ventricular ejection fraction: 50 %. Doppler imaging: grade I mitral regurgitation, grade I aortic regurgitation, grade II tricuspid regurgitation. Pericardium is unremarkable. Minor pulmonary hypertension: elevated systolic pressure in pulmonary artery to 40 mm Hg. It is interesting to note that, echoCG upon admission did not reveal any signs of valve vegetation.

Ultrasound examination (US examination) of neck vessels showed signs of atherosclerotic changes in brachiocephalic arteries, signs of haemodynamically insignificant left- and right-side stenosis of carotid bifurcation to 30 %, as well as abnormal tortuosity of internal carotid artery and left subclavian artery without haemodynamic disorders.

Brain computer tomography (CT) upon admission (day 1): intracranial artery atherosclerosis, post-stroke transformation in right hemisphere and right cerebellum. Brain CT two days later demonstrated signs of an ischemic cerebrovascular event in the bed of the left medial cerebral artery and left posterior cerebral artery related to previous changes.

Chest CT upon admission: moderate hypoplastic changes in the posterior basal surface of the lungs. Repeated chest CT showed bilateral multisegmental pneumonia. Microbial examination of blood revealed growth of Enterococcus faecalis, Klebsiella pneumoniae, Acinetobacter baumannii.

Table 1. *Dynamics of complete blood count with differential during the period of hospitalization*

Parameter	07.01	08.01	09.01	10.01	11.01	Reference	Units
Erythrocytes, RBC	**4,65**	**4,51**	**3,31**	**3,34**	**3,34**	4,2-5,6	10^{12}/L
Hemoglobin, HGB	**130**	**131**	**92**	**94**	**93**	131-172	g/L
Hematocrit, HCT	41,2	41,3	29,1	29,4	29,3	39-50	%
Mean corpuscular volume, MCV	88	91,5	88	88	92,2	80-100	μm^3
Mean corpuscular hemoglobin, MCH	28	29	27,7	28,2	29,2	27-35	pg
Mean corpuscular hemoglobin concentration, MCHC	316	317	315	320	317	320-360	g/L
Red cell distribution, RDW	13	-	15	17	-	11-14,8	%
Platelets, PLT	**151**	**131**	**89**	**78**	**70**	150-400	10^9/L
Mean platelet volume, MPV	10	10,1	11	11	14,2	6-11	μm^3
Plateletcrit, PCT	0,151	-	0,093	0,088	-	0,1-1	%
Platelet distribution width, PDW	13	-	15	17	-	12-18	%
Leucocytes	**18,4**	**15,18**	**22,1**	**53,4**	**60,86**	4-9	10^9/L
Myelocytes	-	-	-	-	17	0	%
Metamyelocytes	-	-	-	-	2	0	%
Myeloblasts	-	-	-	-	1	0	%
Promyelocytes	-	-	-	-	1	0	%
Segmented Neutrophils	-	88	-	-	80 43	47-72	%
Band Neutrophils	-	88,7	-	-	94,5	1-6	%
Lymphocytes	-	6,6	-	-	5	19-37	%
Monocytes	-	4,7	-	-	2	3-11	%
Eosinophils	-	0,1	-	-	0	0,5-5	%
Basophils	-	0,1	-	-	0,6	0-1	%
Neutrophils, ANC	-	**14**	-	-	**57**	2,04-5,8	10^9/L
Lymphocytes, ANC	-	6	-	-	5	1,2-3,0	10^9/L
Monocytes, ANC	-	4	-	-	2	0,09-0,6	10^9/L
Eosinophils, ANC	-	0,02	-	-	0,02	0,02-0,3	10^9/L
Basophils, ANC	-	0,01	-	-	0,38	0,0-0,065	10^9/L

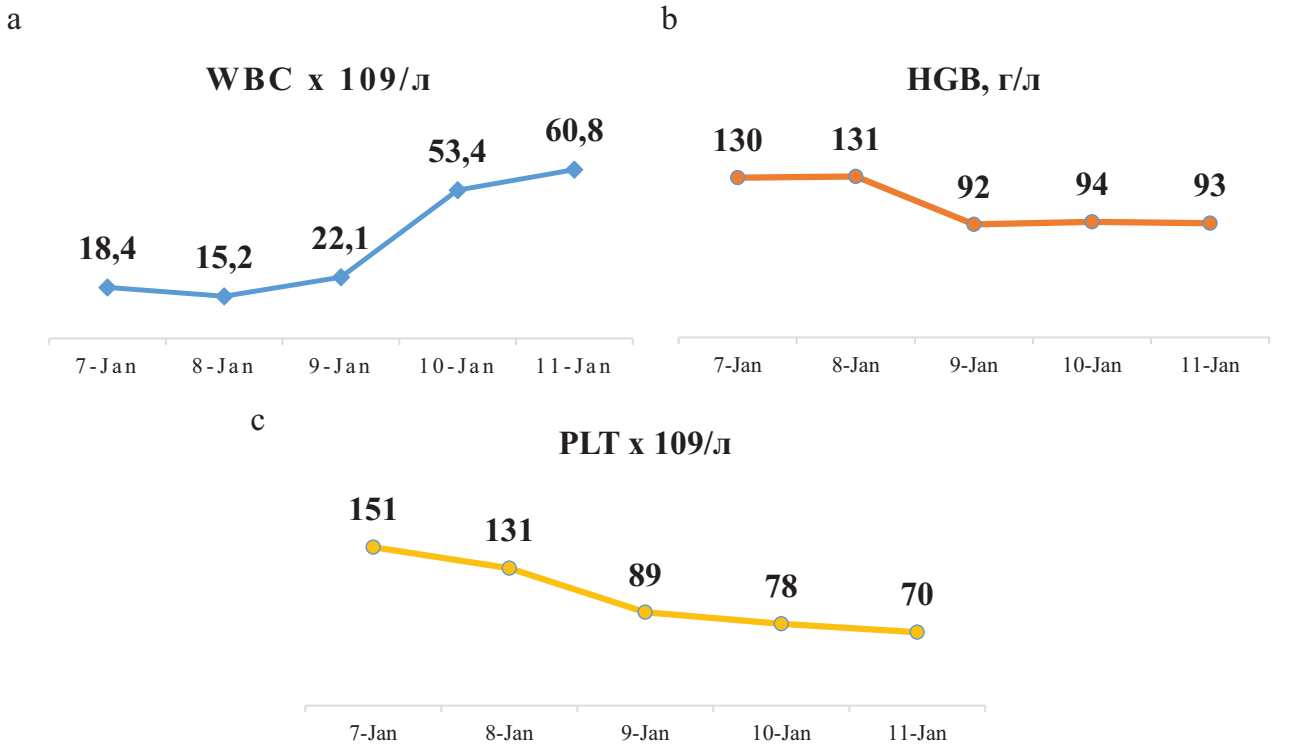

Figure 1. *Complete blood count dynamics: a — leukocytes; b — hemoglobin; c — platelets; WBC — white blood count, HGD — hemoglobin, PLT — platelets.*

Table 2. *Dynamics of the biochemical blood test during the period of hospitalization*

Parameter	07.01	08.01	Reference	Units
Total protein	68	65,5	66-83	g/L
Albumin	-	31,1	35-52	g/L
Total bilirubin	**23,6**	**24,6**	5-21	μmol/L
Direct bilirubin	8,3	8	0-4,4	μmol/L
Bilirubin indirect	15,3	16,6	0-16,6	μmol/L
Cholesterol	6,2	6,46	0-5,20	μmol/L
Urea	**9,7**	**10,8**	2,8-7,2	μmol/L
Creatinine	82,5	77,5	74-110	μmol/L
Blood glucose	**14,9**	**14,1**	4,1-5,9	mmol/L
Potassium	3,82	4,2	3,5-5,1	mmol/L
Sodium	137,6	139	135-145	mmol/L
Chlorine	97,5	98	98-107	mmol/L
Aspartate aminotransferase	**46,8**	**48,8**	11-36	U/L
Alanine aminotransferase	23,9	21,7	10-37	U/L
Creatine phosphokinase	116,5	115,5	26-145	U/L
Alkaline phosphatase	**515**	**453**	30-120	U/L

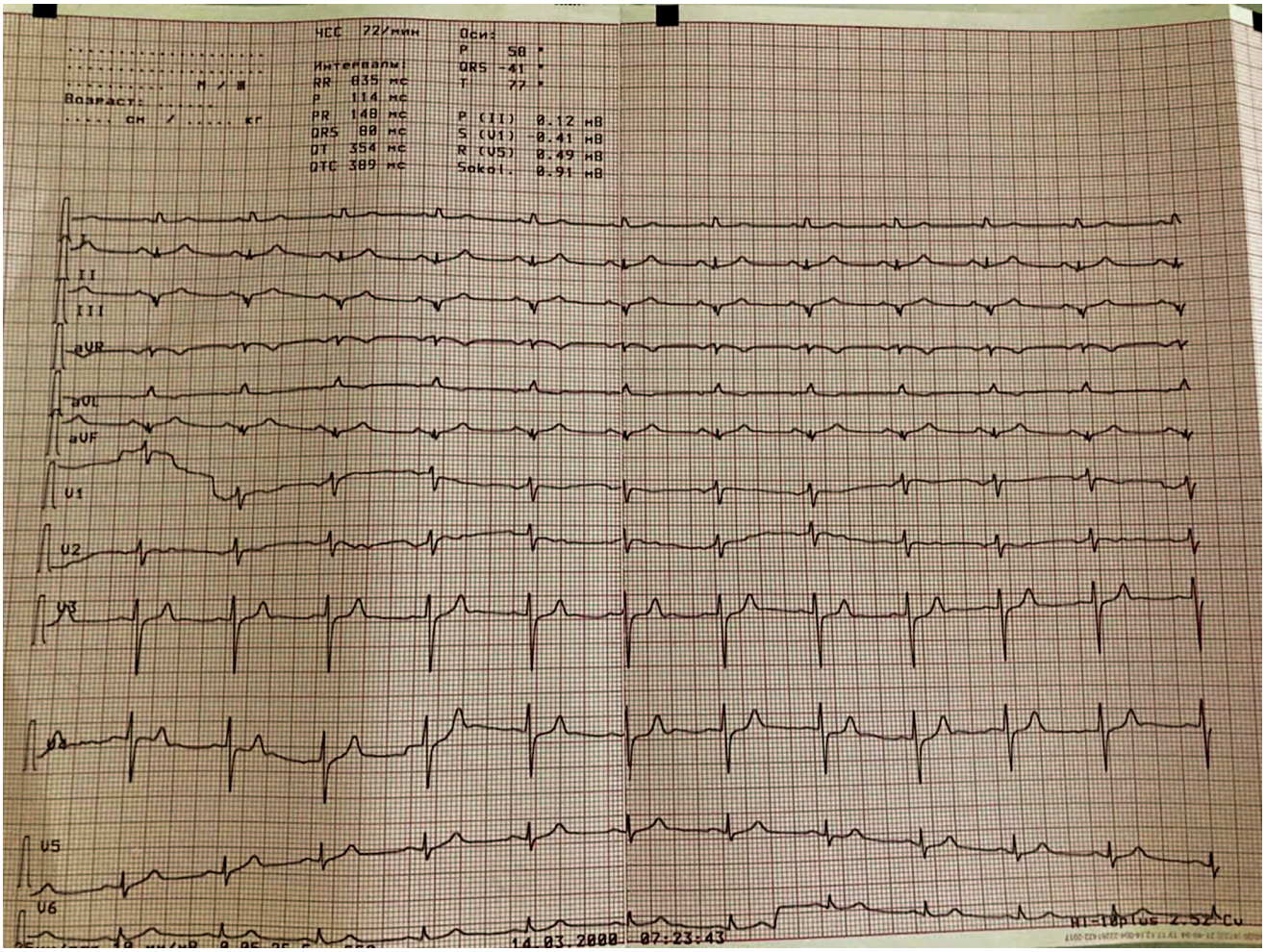

Figure 2. *Electrocardiogram of patient E., 83 years old at admission*

Abdominal ultrasound examination: due to hepatomegaly, both hepatic lobes have numerous mass lesions up to 26 mm with uneven contour, likely to be lot metastatic spread or abscess formation, diffuse changes in pancreas, gall bladder congestion.

US examination of lower extremity veins: signs of vena saphena magna obstruction in the right lower extremity, varicose transformation in branches of the vena saphena magna of lower extremities.

Clinical and instrumental examination results were used to make the *final clinical diagnosis*: *Primary disease*. Ischemic stroke in the bed of the left medial cerebral artery and left posterior cerebral artery, unspecified pathogenetic variant.

Comorbidities: Stage III hypertension, uncontrolled AH. Dyslipidemia. Type 2 diabetes mellitus, target HbA1c level < 7.0 %, very high risk (risk 4).

Primary disease complications: Brain swelling. Dislocation syndrome. Vena saphena magna obstruction in the right lower extremity. Pulmonary embolism. Severe bilateral community-acquired multisegmental pneumonia. Stage III respiratory distress. Sepsis. Hepatic abscesses, cytolytic syndrome, cholestatic syndrome, liver cell failure syndrome. Type 2 myocardial infarction. Killip III pulmonary edema. Multiple organ injury syndrome. Hypochromic anaemia. Thrombocytopenia.

In in-patient settings, the patient was undergoing antibacterial (Cefoperazone + Sulbactam), anticoagulation (nadroparin calcium) and detoxication therapy, corrections of fluid and electrolyte disorders and other symptomatic therapy (Sterofundin, meglumine sodium succinate). The patient was consulted by a haematologist because of a marked increase in leukocytosis and blasts in peripheral blood; it was recommended to consider sternal puncture in order to clarify the nature of LR. However, despite the therapy before the examination, on day 5 of hospitalisation, cardiac arrest was observed; resuscitation was inefficient; and natural death was recorded.

Postmortem examination of the brain showed an area of softening in parietal-temporal-occipital region of the left brain. Near basal ganglia, there were cysts with dark reddish walls 0.1–0.2 cm in diameter; near the right cerebellar hemisphere cortex, there is a cyst with yellowish-brown walls 1.5 cm in diameter. The tissue specimen contains cerebellum tissue with marked perivascular and pericellular swelling, an area of cortex necrosis with a significant plasmocytic macrophagal reaction.

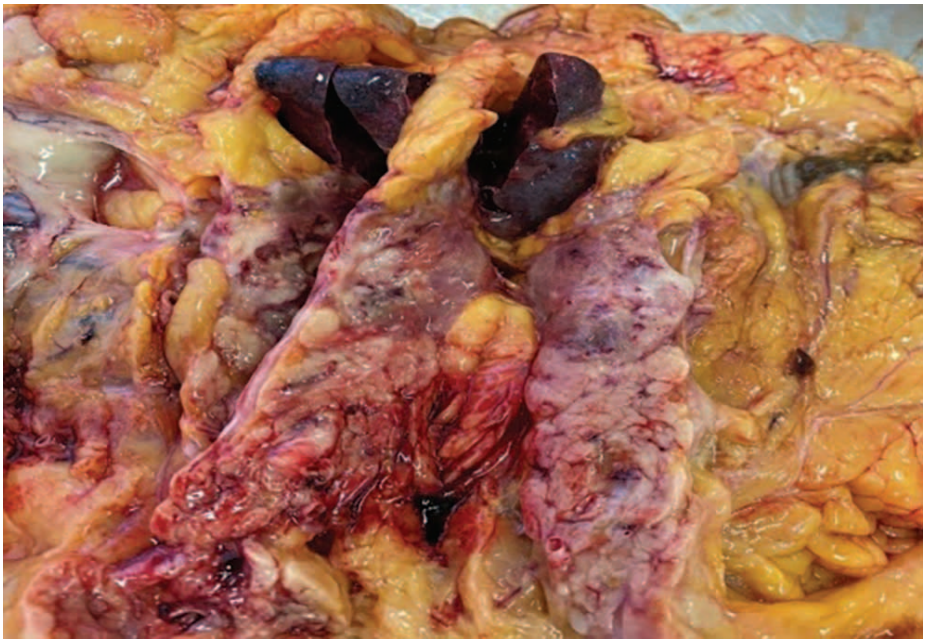

Figure 3. *Pancreatic tumor of the tail with parapancreatic soft tissue and spleen involvement*

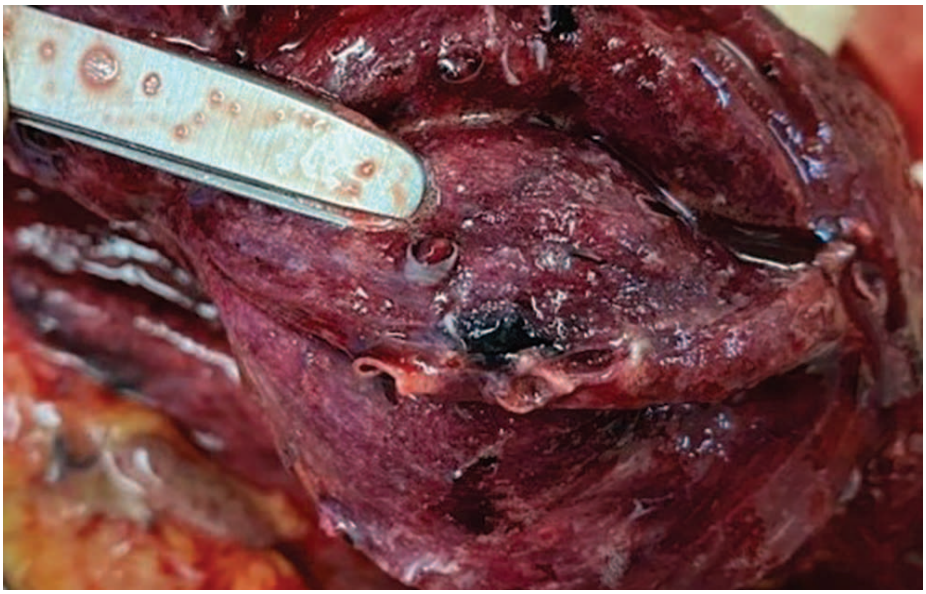

Figure 4. *Thrombus of segmental branches of the right pulmonary artery*

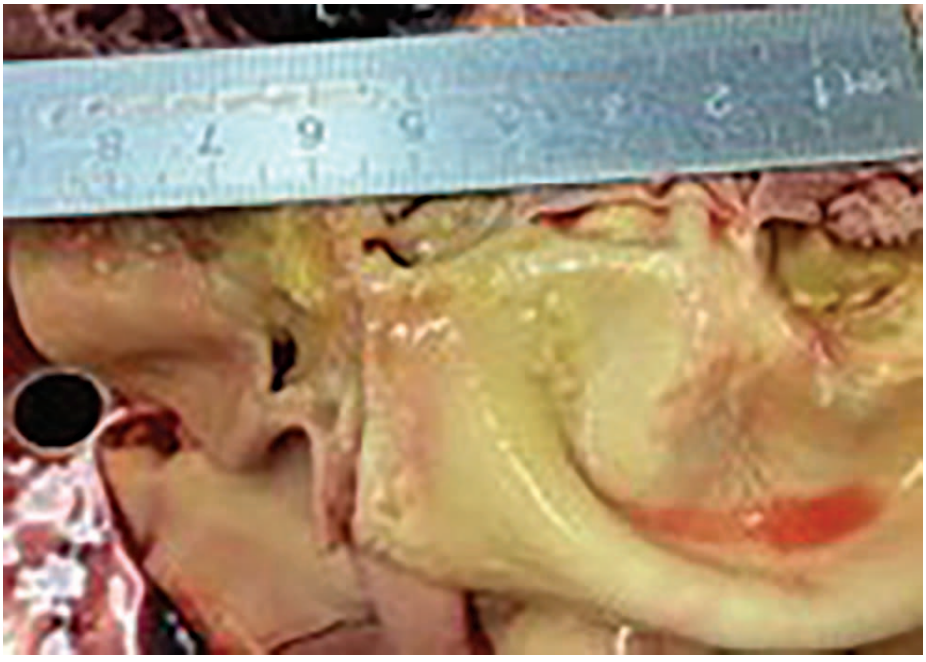

Figure 5. *Vegetations on the aortic valve leaflet*

Pancreas examination: the tissue is dense and elastic, 14.0 × 3.0 × 2.0 cm. Near the pancreatic head, there is grey-pink lobular proliferation with haemorrhaging; near the pancreatic tail, there is an area of dense whitish-grey tissue, 4 × 3 × 4.5 cm, invading adjacent parapancreatic cellular tissue and splenic hilum area, with haemorrhaging; and also whitish areas of 3.0 × 4.0 × 0.7 cm with clear contours and haemorrhaging in 200.0 g splenic pulp. The splenic valve has a dark-cherry blood clot (Figure 3).

Spleen segment histology: marked hyaline degeneration of artery and vein walls, extensive haemorrhaging and necrosis — infarction.

The liver is brown-yellowish with nutmeg pattern and roundish whitish-pink masses in its parenchyma up to 0.5–5 cm in diameter with haemorrhaging and degradation. Para-aortic lymph nodes are dense, enlarged up to 1.0 × 1.0 × 0.5 cm.

The histological examination confirmed high-grade ductal pancreatic adenocarcinoma with metastases to para-pancreatic and para-aortic lymph nodes, lymph nodes in hepatic hilum and parenchyma: adenocarcinoma metastasis with degradation and inflammatory infiltration. Adjacent hepatic tissue has preserved frame and lobular pattern, marked oedema; necrobiosis of hepatic cells; between hepatic cells, there is focal inflammatory infiltration with neutrophils and lymphocytes; portal ducts have marked lymphatic histiocytic infiltration with some segmented neutrophils, sinusoidal repletion and uneven repletion around central veins.

Dark-red and dark-cherry blood clot parts can be seen in the lumen of segmental branches of the right pulmonary artery (Figure 4).

Heart examination: the endocardium of the aortic valve has a greyish wrinkled polypoid mass, tightly fused with the valve cusp, 1.2 × 0.7 × 0.6 cm.

The histological examination shows that the flap of the aortic valve is swollen and has extensive areas of necrosis, parietal blood clots with segmented infiltration (Figure 5).

A microbiological examination of the aortic valve tissue shows Enterococcus faecalis, Klebsiella pneumoniae, Acinetobacter baumannii. A microbiological examination of sputum revealed Acinetobacter baumannii.

Morphological examination: a sample of red bone marrow is represented by three hemopoiesis lineages with haemorrhaging.

According to the postmortem examination results, the cause of death (primary disease) was adenocarcinoma of the tail of the pancreas T3bN1M1 with degradation, invasion of parapancreatic cellular tissue and splenic hilum, with numerous metastases to regional lymph nodes, liver; concurrent diseases — acute infective endocarditis of the aortic valve. Immediate cause of death: sepsis caused by cancer intoxication.

Discussion

This case study describes myeloid LR associated with verified advanced adenocarcinoma of the tail of the pancreas and a concurrent disease — acute infective endocarditis. The patient who was admitted to the hospital with neurological symptoms was diagnosed with signs of severe multiple organ failure, systemic inflammation reaction, septicopyaemia in the form of severe bilateral multisegmental pneumonia, hepatic abscesses, signs of type 2 myocardial infarction and marked leukocytosis 60×10^9/L with left shift to myeloblasts.

The postmortem examination showed high-grade ductal adenocarcinoma of the tail of the pancreas with degradation and metastases to lymph nodes and liver, related to acute infective endocarditis, involving the aortic valve, with sepsis in the form of septicopyaemia and thromboembolism in the systemic and lesser circulation. The resulting severe combined pathology with a potential paraneoplastic component caused the development of a neutrophilic myeloid reaction with a marked left shift and an increase in the relative banded neutrophil count to 94.5 %.

In this case study, it is not possible to make a firm conclusion about the onset of infective endocarditis (IE) and its variant. At the same time, given the extent of the tumour, presence and aggravation of leucocytosis from day 1 of hospitalisation, acute IE is possible, taking into account LR development with patient's condition worsening.

In the absence of life-time signs of vegetation on aortic valve cusps, incomplete correlation of the clinical pattern with the modified Duke criteria, a differential diagnosis of IE includes non-bacterial thrombotic endocarditis (NBTE). Life-time diagnosis of NBTE is challenging, postmortem examinations reveal NBTE only in 1.2–3.4 % of cases [7]. According to retrospective studies, NBTE is diagnosed in 4 % of all patients with advanced solid malignancies; however, its exact incidence is unknown [8]. In a majority of cases, NBTE is associated with adenocarcinoma of lungs, pancreas, stomach and ovaries [9].

The differential diagnosis of NBTE and IE is crucial for optimal management; however, there are no pathognomonic signs which can reliably differentiate between these two conditions. It is essential to take into account a comorbidity or concurrent disease, which can increase the risk of NBTE, especially malignancies. Nevertheless, very often cancer patients have poor immunity as a result of drug therapy or progressing tumour and are at high risk of IE due to frequent vein catherisation. Therefore, the diagnosis of NBTE should include assessment of individual risk factors, clinical, laboratory and instrumental data in order to rule out other pathologies, particularly infective endocarditis and endocarditis with negative blood culture.

Despite the fact that a majority of LR are associated with solid tumours, LR in pancreatic cancer has been

described in a few case studies [10–12]. Patients with paraneoplastic syndrome can have fever, which makes differential diagnosis of LR more difficult and impels to search for an infectious pathology as the most common cause of LR. Various infections should be ruled out in the first place, not only because they are more common than paraneoplastic LR, but because they can limit further therapy of cancer [13].

If a malignancy has no clinical manifestations, tumour-associated leucocytosis can be interpreted as an infection or myeloproliferative disorder, thus resulting in unnecessary diagnostic procedures, including bone marrow biopsy and molecular genetic testing. Reduction in leucocytosis with antitumour therapy can be an indirect sign of therapy efficacy, or can be used as a marker of disease progression in these patients if LR aggravates [14].

Infective endocarditis is very rarely a separate cause of LR. Such LR cases are described in patients with infective marantic (initially non-infective thrombotic) endocarditis related to an oncological disease [11]. At the same time, in the absence of a progressing malignancy, the most common cause of LR is a systemic infectious process. In a retrospective cohort study conducted in a hospital in Porto Alegre (Brazil), among 105 patients, LR was associated with infection in 55 % of cases (mostly infections of lower respiratory tract and urinary tract) [15]. Israeli researchers presented similar results of an assessment of outcomes in 173 hospitalised patients: an infectious process was a cause of LR in 48 % of cases, including sepsis in 9 % of patients [16]. Independent predictors of death were age (odds ratio 2.5, $p = 0.014$) and diagnosed sepsis (odds ratio 3.8, $p < 0.001$) [16].

In microbiological examination of blood samples taken from patients with LR, the most common finding is gram-negative microorganisms; however, a potential pathogen can be Micobacterium tuberculosis in disseminated tuberculosis [17]. In a number of clinical observations, a clostridial infection, including pseudomembranous colitis, was also described as one of the causes of LR [18, 19]. Large retrospective analyses of patients with LR were conducted before COVID-19; however, the novel coronavirus infection can also cause LR, particularly in patients with severe COVID-19 [20].

Conclusion

Therefore, the diagnostic search in LR patients, including elderly and old patients, with initially unclear origin should include cancer alertness; however, it should not neglect assessments for other possible causes, including IE and NBTE, requiring a multidisciplinary approach in intricate diagnostic situations. Prognosis in patients with LR is greatly dependent on the course of the primary disease, and is very poor in cancer-associated LR.

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ЭФФЕКТИВНОСТЬ МЕПОЛИЗУМАБА В ЛЕЧЕНИИ ТЯЖЕЛОЙ АСТМЫ СО СМЕШАННЫМ ГРАНУЛОЦИТАРНЫМ ПАТТЕРНОМ ВОСПАЛЕНИЯ ДЫХАТЕЛЬНЫХ ПУТЕЙ (ОПИСАНИЕ КЛИНИЧЕСКИХ СЛУЧАЕВ)

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Efficacy of Mepolizumab in the Treatment of Severe Asthma with a Mixed Granulocytic Pattern of Airway Inflammation (Case Report)

Резюме

В данной статье представлено описание двух клинических наблюдений применения меполизумаба у пациентов с тяжелой неконтролируемой астмой со смешанным гранулоцитарным паттерном воспаления в бронхах на фоне коморбидной патологии.

Смешанная гранулоцитарная форма тяжелой бронхиальной астмы характеризуется сочетанием в себе признаков как Т2-эндотипа, так и не-Т2-эндотипа. Наиболее часто смешанный гранулоцитарный паттерн тяжелой астмы встречается при коморбидной патологии, в частности, при ее сочетании с хронической обструктивной болезнью легких или бронхоэктазами.

В представленных наблюдениях оба пациента отличались наличием стажа курения, поздней манифестацией астмы с развитием центрилобулярной эмфиземы, необратимым снижением отношения $ОФВ_1$/ФЖЕЛ в рамках формирования хронической обструктивной болезни легких. Особенностью одного из случаев стало наличие у пациента цилиндрических бронхоэктазов обоих легких. Выбор меполизумаба в качестве дополнительного агента поддерживающей терапии на ступени 5 GINA в обоих случаях был обоснован неконтролируемым течением астмы, несмотря на применение высокой дозы ингаляционных глюкокортикостероидов в сочетании с другими базисными препаратами и потребность в применении системных глюкокортикостероидах >50 % времени в году, историей повторяющихся обострений в предшествующие 12 месяцев, наличием персистирующей эозинофилии крови (>150 клеток/мкл), а также сочетанием бронхиальной астмы с полипозным риносинуситом у одного из пациентов.

В целом применение меполизумаба в дозе 100 мг каждые четыре недели подкожно в дополнение к регулярной максимальной оптимизированной поддерживающей терапии характеризовалось быстрой, значимой и устойчивой эффективностью, которая выражалась в раннем достижении контроля астмы в течение первых 16 недель от начала терапии.

Ключевые слова: *тяжелая бронхиальная астма, меполизумаб, таргетная терапия, ХОБЛ, бронхоэктазы, смешанный гранулоцитарный паттерн воспаления*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
This article describes two clinical observations of the use of mepolizumab in patients with severe uncontrolled asthma with a mixed granulocytic pattern of inflammation in the bronchi and comorbid pathology.
The mixed granulocytic form of severe asthma is characterized by a combination of T2 endotype and non-T2 endotype. The most common mixed granulocytic pattern of severe asthma occurs in comorbid pathology, in particular, when it is combined with chronic obstructive pulmonary disease (COPD) or bronchiectasis.
In the presented observations, both patients had an experience of smoking, a late manifestation of bronchial asthma with the development of centrilobular emphysema and an irreversible decrease in the FEV/FVC ratio as part of the development of COPD. A feature of one of the cases was the presence of cylindrical bronchiectasis in both lungs. The choice of mepolizumab as an additional maintenance agent at GINA stage 5 in both cases was justified by the uncontrolled course of asthma despite the use of a high dose of glucocorticosteroids in combination with other basic drugs and the need for the use of systemic corticosteroids > 50 % of the time per year, a history of recurrent exacerbations in previous 12 months, the presence of persistent blood eosinophilia (>150 cells/μl), as well as a combination of asthma with polypous rhinosinusitis in one of the patients.
Overall, the use of mepolizumab 100 mg subcutaneously every four weeks in addition to regular maximum optimized maintenance therapy was characterized by rapid, significant and sustained efficacy, which was expressed in early achievement of asthma control within the first 16 weeks of therapy.

Key words: *severe asthma, mepolizumab, targeted therapy, COPD, bronchiectasis, mixed granulocytic type of inflammation*

Conflict of interests
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BA — bronchial asthma, GCS — glucocorticosteroids, GEBD — genetically engineered biologic drugs, LABA — long-lasting beta-2 agonists, iGCS — inhaled glucocorticosteroids, thoracic CT — computer tomography of thoracic organs, FEV_1 — forced expiratory volume over the first second, PFT — pulmonary function test, FLC — functional lung capacity, COPD — chronic obstructive pulmonary disease, тACQ-5 — Asthma Control Questionnaire–5, ACT — Asthma Control Test, GINA — Global Initiative for Asthma, IgE — immunoglobulin E, mMRC — Modified Medical Research Council

Introduction

Severe bronchial asthma with a mixed granulocytic inflammation pattern combines signs both of T2 endotypes and non-T2-endotypes, with a concurrent high neutrophil and eosinophil count in induced sputum or bronchoalveolar lavage samples [1]. According to various sources, the incidence of this variant of inflammation in asthmatic patients is 3 % (with eosinophils of ≥ 3 % and neutrophils of ≥ 76 % in induced sputum) to 22 % (with eosinophils of ≥ 2 % and neutrophils of ≥ 50 % in induced sputum) [2]. The mixed granulocytic inflammation pattern is most common in smokers, in comorbidities, in particular in bronchial asthma with chronic obstructive pulmonary disease (COPD) or bronchiectasis [1].

Bronchial asthma, COPD and bronchiectasis are common conditions; their combination makes patient curation very challenging and a risk of an uncontrolled disease significantly higher; response to conventional maintenance therapy deteriorates, necessitating an increase in the dose of inhaled glucocorticosteroids (iGCS), administration of additional long-lasting beta-2 agonists (LABA) and long-lasting M3-cholinoblockers; often, systemic glucocorticosteroids (GCS) are required; infection-dependent exacerbations and associated antibiotic therapy and hospitalisation become more common [3].

In accordance with the staggered approach, patients with severe bronchial asthma may have genetically engineered biologic drugs (GEBD) prescribed, including mepolizumab, a humanised monoclonal antibody with high affinity to interleukin-5. In clinical trials, COPD and bronchiectatic disease are often non-inclusion criteria; therefore, limited data are available on the efficacy of target therapy in patients with this comorbidity.

In 2017, the results of two randomised double-blind trials (METPEX and METREO) were published; they compared the 52-week efficacy of mepolizumab and placebo in COPD patients who had moderate and severe exacerbations during the previous year while taking triple maintenance therapy. The use of mepolizumab at a dose of 100 mg as an adjuvant therapy to the conventional

baseline therapy was associated with a lower rate of exacerbations during the year [4].

In 2021, Crimi C. et al. presented the results of a single-center retrospective study in patients with severe bronchial asthma (BA) and bronchiectasis. The authors concluded that the use of mepolizumab as an adjuvant to the maintenance therapy improved asthma control, reduced the number of exacerbations during the year, and reduced the need for systemic glucocorticosteroids [5].

This article describes clinical cases illustrating management of patients with a mixed granulocytic inflammation at the Intermediate Therapeutic Clinic of the Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of the Ministry of Health of Russia (Tomsk), with long-lasting continuous therapy with mepolizumab at a dose of 100 mg every four weeks (q4w).

Patients in both clinical cases provided their written consent, with their personal data being presented anonymized.

Case Study No. 1

Severe bronchial asthma, recurrent rhinosinusitis polyposa and COPD in a patient with a long-lasting history of smoking and a mixed granulocytic inflammation of upper respiratory tract

Male patient M., 70 years old; in June 2021, he was referred by a pulmonologist, complaining of attack-like cough with viscous white-yellowish sputum; mixed-pattern shortness of breath while walking (mMRC score: two points), worsening when the patient walks uphill or climbs 1–2 flights of stairs; episodes of expiratory suffocation, mostly spontaneous in the evening and predawn time, as well as outside in cold weather. To relieve the symptoms, the patient used medications containing short-lasting beta-2-agonists (salbutamol, fenoterol/ipratropium bromide) up to 3–4 times during the day and at night.

Past medical history and current therapy

The patient is followed up by a pulmonologist for the underlying comorbidity, comprising two conflicting conditions.

In 2014, the patient was diagnosed with bronchial asthma; however, typical respiratory symptoms (respiratory discomfort, expiratory dyspnoea with intense exercises) were noted in 2008. When the condition was diagnosed, the patient was 57 years old (late-onset asthma). Also, in 2014 an entry was made in the medical record about chronic obstructive pulmonary disease with predominant emphysematous phenotype, diagnosed with due account of a long history of smoking and typical changes seen on CT scans (bilateral centrilobular, mostly supralobar emphysema, trapped air and hyperinflation) and respirometry results (persistent obstructive changes in pulmonary function tests (PFT) with a stable reduction in the post-bronchodilatatory ratio of forced expiratory volume over first second (FEV_1) and functional lung capacity (FLC) to < 0.7, despite a multi-component inhalation therapy).

Immediately after diagnosis confirmation, BA severity was assessed as moderate in accordance with the current recommendations of the Global Initiative for Asthma (GINA); thus, in 2014–2017, the patient was constantly using a fixed combination of a low-dose iGCS (fluticasone propionate 500 μg/day) and LABA (salmeterol 100 μg/day). In 2018, when asthma was no longer controlled, the dose of fluticasone propionate was increased to 1,000 μg/day, the condition was still uncontrolled and pulmonary function tests were below normal values. As a result, from January 2019 and up to the target therapy initiation, the patient had been constantly using a fixed dose of budesonide/formoterol at a dose of 640/18 μg/day (metered-dose powder inhaler), as well 5 μg of tiotropium bromide for inhalation (Respimat delivery system) and 10 mg of oral monteleukast before bed. Transition to the three-component inhalation therapy with medium doses of iCGS, LABA and long-lasting anticholinergic product combined with an oral leukotriene receptor antagonist initially improved the clinical condition of the patient; however, starting from September 2019, the patient was unable to control the disease. Over the past two years, asthma relapses were recorded (up to 6–8 episodes a year) and the patient needed broncholytic nebulizer therapy and an increase in the daily GCS doses: addition of a nebulized budesonide suspension and/or a short (5–7 days) course of prednisolone at a dose of 90 mg/day with aminophylline solution 4 times over 12 months, which preceded the GEBD therapy initiation. The last course of infusion therapy with systemic GCSs because of asthma and COPD relapse caused by an acute viral infection was recorded in May 2021.

The nature of upper respiratory tract involvement

The patient has had rhinosinusitis polyposa since 1996. Surgery to remove sinonasal polypous vegetation from the nasal cavity and paranasal sinuses was performed in 1996, 1999, 2013, 2017, and March 2021. Upon admission for GEBD therapy initiation, the patient was taking mometasone furoate, an intranasal GCS, at a dose of 200 μg/day; however, the patient complained of nasal airflow obstruction and small amount of pale nasal discharges.

History of allergies is unremarkable: there is no solid evidence of bronchial asthma or allergies in close relatives. During a detailed interview, review of the patient's medical record and taking into account an Immunocap test of allergen-specific immunoglobulin E (IgE) concentrations (June 2021), no data were found to confirm allergic hypersensitivity to the main (domestic,

fungal, pollen, epidermal) airborne allergens, pharmaceutical anaphylaxis or individual hypersensitivity reactions to any medicines, including non-steroidal anti-inflammatory drugs.

History of smoking

The patient is a former smoker who used to smoke 10–20 cigarettes a day for 45 years. The minimum and the maximum smoking rates were 22.5 pack/years and 45 pack/years, respectively. The patient quit smoking in 2014.

Physical examination

Height: 165 cm, weight: 60 kg, body mass index: 22.33 kg/m^2, normosthenic composition. Condition is rather satisfactory.

Chest is normal, painless on palpation. Percussion sound is slightly hyperresonant, similar above symmetric lung sections. Auscultatory breathing is harsh, with individual dry rales above the middle section of the lungs. Respiratory rate is 16 per minute. Peripheral oxygenation is 98 %.

Cardiac sounds are clear, rhythmic, with loud second heart sound above aorta. No pathologic heart murmurs. Heart rate is 70 bpm. Blood pressure is 124/76 mm Hg.

Other organs and systems are unremarkable.

Laboratory and instrumental examination results supporting the diagnosis and selected therapy strategy

A mixed nature of granulocytic inflammation in the respiratory tract in this patient is confirmed by cytological examination of bronchoalveolar lavage fluid in February 2019 (eosinophils 40 % and neutrophils 50 % of the cellular composition), induced sputum in July 2020 (eosinophils 18 % and neutrophils 60 % of the cellular composition) and in March 2021 (eosinophils 22 % and neutrophils 68 % of the cellular composition).

When the patient was hospitalised in July 2021, the anti-T2-cytokine therapy was favoured due to the blood eosinophil level (4.5 % of WBC count and 390 cell/μL) and the total immunoglobulin E level (177 IU/mL).

Of note, when the target therapy was initiated, the patient demonstrated significantly reduced FLC values. In July 2021, baseline FEV1 was 1.51 L (59.5 % of the normal value) and 1.64 L (64.5 % of the normal value) before and after salbutamol test, respectively; post-bronchodilatatory lung capacity was 94 % and FLC was 104 % of the normal values, with FEV1/FLC being 0.52. A β2-adrenoceptor agonist test gave positive results: FEV1 increased by 34 % and 470 mL.

Examinations of other systems of organs, including ECG and EchoCG, thoracic CT and referral to rule out systemic eosinophilia (for instance, eosinophilic granulomatosis with polyangitis), did not reveal any other significant pathologies which could affect the management of the patient.

Therefore, based on the complaints, medical record, examination and test results, the underlying comorbidity has been updated: bronchial asthma, T2-endotype, non-allergic, eosinophilic phenotype, severe (GINA stage 5) uncontrolled disease with a high risk of relapses; chronic obstructive pulmonary disease, mostly emphysematous phenotype, GOLD 2 obstruction, with marked symptoms (mMRC: 2 points) and frequent relapses, group D (clinical guidelines of the Ministry of Health of Russia, 2021); other diseases: recurrent rhinosinusitis polyposa (surgery in 2012, 2013, 2017, and March 2021).

Since the optimised multicomponent baseline therapy, including iGCS with the need for frequent courses of prednisolone due to asthma relapses, was inefficient, taking into account persistent blood and respiratory eosinophilia, as well as lack of clinically significant allergic hypersensitivity, regular target therapy with mepolizumab 100 mg q4w SC was initiated in July 2021.

Further follow-up during mepolizumab therapy demonstrated significant improvements. Early efficiency of the target therapy noted just four weeks after the first injection was seen as the absence of shortness of breath during physical exercises, absence of episodes of suffocation, and no need for rescue medications. The patient, however, still had a cough with a small amount of clear sputum. By the time of the initial GINA-recommended assessment (16 weeks), the patient noted improvement: fewer episodes of cough (a cough with a small amount of white sputum, characterised by the patient as "minor", was uncommon), relief of shortness of breath: shortness of breath appeared only with moderate activities (normal walking) — two points on the mMRC (Modified Medical Research Council) scale. Also, the patient noted absence of episodes of suffocation and need for rescue medications. Objective improvement in asthma control was recorded (Asthma Control Questionnaire–5 (ACQ-5) reduction from 1.5 to 0.8 points).

One year after therapy initiation, the patient does not have any major complaints; Asthma Control Test (ACT) was 23 points (well-controlled), ACQ-5 – 0.2 points (well-controlled).

Respirometry results obtained with the use of the target therapy demonstrated an increase in pre-FEV1 from 1.51 L (59.5 % of the normal value) at baseline to 1.92 L (77.7 % of the normal value) 12 month after GEBD therapy initiation. An absolute increase in FEV1 was 300 mL after a year of therapy, meaning significant response to the therapy.

Over two years of continuous mepolizumab therapy, there were no asthma and COPD relapses and no need for systemic GCS.

Also, rhinosinusitis polyposa improvement was noted with GEBD therapy. The patient noted better nasal airflow; nasal discharges disappeared after 16 weeks of therapy. No rhinosinusitis relapses were recorded over 24 weeks of therapy.

Table 1. Control of asthma, severity of shortness of breath and respiratory function (clinical observation No. 1)

Parameter	Initial results	16 weeks of mepolizumab therapy	12 months mepolizumab therapy	24 months mepolizumab therapy
Pre-FEV1, l	1,51	1,81	1,92	1,81
Pre-FEV1 % predicted value	59,5	71	77,7	71,6
Post-FEV1, l	1,64	1,82	2,06	1,82
Post-FEV1 % predicted value	64,5	71,5	80,8	79,4
Post-FEV1/FVC	0,51	0,57	0,56	0,54
mMRC, points	3	2	0	0
ACT, points	17	17	23	25
ACQ-5, points	1,5	0,8	0,2	0,2
Blood eosinophils, cells/μl	390	50	52	50

Note: FEV1 — forced expiratory volume in the first second; FVC — forced vital capacity; pre-FEV1 — forced expiratory volume in the first second pre-bronchodilator; post-FEV1 — forced expiratory volume in the first second post-bronchodilator; ACT — asthma control test; ACQ-5 — Asthma Control Questionnaire–5; mMRC — Modified Medical Research Council

Changes in scores of the asthma control and dyspnoea severity questionnaire, as well as changes in peripheral blood eosinophils and PFT values, are presented in Table 1.

Case Study No. 2

Severe bronchial asthma with bronchiectasis in a patient with a mid-lasting history of smoking and a mixed granulocytic inflammation of upper respiratory tract

Male patient P., 48 years old; in September 2021, he was referred by a pulmonologist, complaining of spontaneous day-time episodes of suffocation and suffocation after moderate physical activity (up to four times a week) and night suffocation 1–2 times a week; need in salbutamol to relieve shortness of breath (up to 2–4 times a week); expiratory suffocation when the patient walks uphill or climbs 1–2 flights of stairs (mMRC score: 3 points); wheezing; attack-like cough with a small amount of viscous yellow-greenish sputum.

Past medical history and current therapy

BA was diagnosed in 2001 (the patient was 28 years old). Once the diagnosis was made, a therapy was initiated: a fixed combination of mid-dose iGCS (budesonid 640 μg/day) and LABA (formoterol 18 μg/day) as a metered-dose powder inhaler. The patient was undergoing this therapy in 2001–2021. Also, during the past two years, the patient had occasional short-term (1–2 months) courses of tiotropium bromide (Respimat delivery system) at a dose of 5 μg/day and monteleukast 10 μg/day.

In 2020–2021, the patient noted stable worsening in his asthma: worse shortness of breath, more episodes of suffocation and the need to use rescue medications up to 4–6 times daily, more severe cough with more sputum, very often it was very viscous and yellow-greenish. Exacerbations occurred up to 6 times a year, and GCSs were required.

In July 2021, a pulmonologist corrected the therapy and recommended daily use of vilanterol/fluticasone furoate at a dose of 22/184 μg in the evening, tiotropium bromide for inhalation (Respimat delivery system) at a dose of 5 μg in the morning and monteleukast 10 μg before bed. With the corrected therapy, in August 2021 the patient experienced another (a third within 12 months) BA relapse, which required a course of nebulizer therapy (budesonide 2,000 μg/day, fenoterol/ipratropium bromide solution for inhalation) and oral prednisolone (30 mg for 7 days, then the dose was reduced to 5 mg and daily systemic GCS at a mentioned dose). Also, since the patient had large amounts of green sputum, clarithromycin 1,000 mg daily was added for 7 days.

History of allergies

According to the patient, his grandmother and father have asthma. In 2015, a skin allergen test revealed hypersensitivity to domestic dust, and allergen-specific therapy was initiated, which was later interrupted because of uncontrolled asthma. Since childhood, the patient has been suffering from all-year-round nasal allergy; in addition to domestic dust, he is sensitive to cats, library dust (itchy eyes, eye tearing), episodes of suffocation during finishing works. He has a history of itchy skin when taking bicillin.

History of smoking

The patient confirmed short periods of episodic smoking for 20 years. An approximate smoking rate is no more than 10 packs/year. When the target therapy was started, the patient was a non-smoker.

Physical examination

Height: 182 cm, weight: 79 kg, body mass index: 23.9 kg/m^2, normosthenic composition. Condition is rather satisfactory. Chest is normal, painless on palpation. Percussion sound comes from lungs, similar above symmetric lung sections. Auscultatory breathing is harsh, with multiple dry rales above the middle and lower section of the lungs. Respiratory rate is 19 per minute. Peripheral oxygenation is 96 %. Cardiac sounds are clear, rhythmic. No pathologic heart murmurs. Heart rate is 76 bpm. Blood pressure is 138/88 mm Hg. Other organs and systems are unremarkable.

Key laboratory and instrumental examination results supporting the diagnosis and selected therapy strategy

For a considerable period of time before GEBD therapy initiation, patient's peripheral blood tests revealed persistent high eosinophil count ≥ 150 cell/μL. When GEBD therapy was initiated, blood eosinophils were 2.8 % and 242 cell/μL. Of note, this patient was taking prednisolone 5 mg daily. Total IgE on August 3, 2021 was 227 IU/mL. However, allergen-specific EIA IgE test (main allergens — domestic, fungal, pollen, epidermal) dated August 3, 2021 demonstrated a negative result, thus ruling out *Alternaria tenuis*; also, allergen-specific IgE to it was clinically normal (0.111 kU/L).

In 2018, during one of the asthma relapses caused by a respiratory infection with long-lasting cough and purulent sputum, chest CT demonstrated cylindrical bronchiectasis in individual segmental and subsegmental bronchi in both lungs. Cytological examination of sputum revealed a combination of high eosinophil (8 % of the cellular composition) and neutrophil counts (82 % of cells). When the target therapy was initiated (August 2021), thoracic CT demonstrated bronchial wall induration, cylindrical dilation of individual segmental and subsegmental bronchi (cylindrical bronchiectasis), with small bands and adhesions in subpleural sections of the apex of lung, as well small apical overlaps on both sides.

In addition to clear clinical signs of uncontrolled asthma with frequent relapses, probably associated with an infectious trigger (bacterial contamination of the respiratory tract), this patient had impaired PFTs. Spirography results dated August 2021 demonstrated pre-FEV1 of 67 % and 78 % of the normal value before and after salbutamol 400 μg, respectively (an increase in FEV_1 was 16.35 % and 610 mL); the post-FLC value was 100 % of the normal value, while the post-FEV_1/FLC ratio was 0.63.

Based on the patient's complaints, past medical records and examination results, the following condition was diagnosed: a mixed-type bronchial asthma, eosinophilic phenotype, severe (GINA stage 5) uncontrolled disease with a high risk of infection-dependent relapses. Comorbidities: cylindrical bronchiectasis in individual segmental and subsegmental bronchi in both lungs. Moderate persistent nasal allergy caused by domestic and epidermal allergens.

Since despite the optimal baseline therapy including a fixed combination of high doses of iGCS/LABA, long-lasting M-cholinoblocker, leukotriene receptor antagonis and systemic GCSs at a dose of 5 mg (prednisolone), the patient could not achieve stable asthma control (ACT: 9 points, ACQ-5: 3.6 points), the medical panel decided to initiate the target therapy with mepolizumab, an anti-interleukin-5 GEBD, at a dose of 100 mg q4w SC from September 2021.

Further follow-up during mepolizumab therapy demonstrated significant improvements. Early efficiency of the target therapy noted just four weeks after the initiation of the therapy was seen as withdrawal from prednisolone, absence of episodes of suffocation at night, improvement in shortness of breath, absence of wheezing, and smaller amounts of discharges with cough.

Table 2. *Control of asthma, severity of shortness of breath and respiratory function (clinical observation No. 2)*

Parameter	Initial results	16 weeks of mepolizumab therapy	12 months mepolizumab therapy	24 months mepolizumab therapy
Pre-FEV_1, l	2,57	3,27	3,11	3,17
Pre-FEV_1 % predicted value	67	83,5	79	81,7
Post-FEV_1, l	2,73	3,3	3,04	3,2
Post-FEV_1 % predicted value	78	84,4	78	82,3
Post-FEV_1/FVC	0,63	0,64	0,57	0,6
mMRC, points	3	2	0	0
ACT, points	9	25	25	25
ACQ-5, points	3,6	0,4	0,4	0,4
Blood eosinophils, cells/μl	241	47	70	32

Note: FEV1 — forced expiratory volume in the first second; FVC — forced vital capacity; pre-FEV1 — forced expiratory volume in the first second pre-bronchodilator; post-FEV1 — forced expiratory volume in the first second post-bronchodilator; ACT — asthma control test; ACQ-5 — Asthma Control Questionnaire–5; mMRC — Modified Medical Research Council

By the time of the initial GINA-recommended assessment (16 weeks), the patient noted improvement: no episodes of suffocation and no need in rescue medications, significantly reduced number of episodes of cough (cough was uncommon, without sputum), improvements in shortness of breath (only with moderate physical activity). Objective evidence of asthma control (ACT = 25 points, ACQ-5 = 0.4 points). During the year after therapy initiation, the patient does not have any major complaints; his asthma is well-controlled without new relapses.

Respirometry results obtained with the use of the target therapy with mepolizumab demonstrated an increase in pre-FEV_1 value from 67 % of the normal value (at the moment of therapy initiation) to 81.7 % of the normal value (24 months of therapy). An absolute increase in FEV_1 over the first 12 months of therapy was 540 mL and over 24 months of therapy — 600 mL, meaning significant response to the therapy. Normalised FEV_1/FLC ratio with the use of the target therapy with mepolizumab (post-FEV_1/FLC > 0.7) is also worth mentioning.

Changes in scores of the asthma control and dyspnoea severity questionnaire, as well as changes in peripheral blood eosinophils and PFT values, are presented in Table 2.

Discussion

Severe bronchial asthma with a mixed granulocytic inflammation pattern and a history of smoking in a combination with such comorbidity as chronic obstructive pulmonary disease and bronchiectasis, is associated with bacterial contamination. In turn, it increases the risk of an uncontrolled disease with a worse response to conventional maintenance therapy, necessitating an increase in the dose of inhaled GCSs, additional long-lasting beta-2 agonists and long-lasting M3-cholinoblockers; often, systemic GCSs are required; infection-dependent exacerbations and associated antibiotic therapy and hospitalisation become more common [3].

Currently, in accordance with the staggered approach, patients with severe bronchial asthma have GEBDs prescribed, including those binding to the key driver of interleukin-5. Given the pathogenetic interconnection of neutrophil and eosinophil inflammation patterns in this group of comorbid patients, reduction of the number of recruited eosinophils in the area of inflammation can have positive effect on the activity of associated neutrophil inflammation.

Currently available trials to study the use of mepolizumab in patients with a mixed granulocytic pattern in severe uncontrolled bronchial asthma with COPD and bronchiectasis demonstrate high efficacy of the target genetically engineered therapy, namely: improved asthma control and patients' quality of life, reduced number of relapses per year, and reduced need in systemic glucocorticosteroids [4, 5].

These clinical cases demonstrate the efficacy of mepolizumab in patients with a mixed granulocytic phenotype of BA in combination with a comorbidity (COPD, bronchiectasis).

Conclusion

The use of mepolizumab at a dose of 100 mg every four weeks subcutaneously as adjuvant therapy to the optimised maintenance therapy (GINA stage 5) demonstrated high efficiency in the management of severe BA with a mixed granulocytic bronchial inflammation with a history of smoking and comorbidities (COPD, bronchiectasis). Therapy efficacy was seen as early (within 16 weeks after therapy initiation) and steady asthma control, no need to take systemic GCSs, absence of BA exacerbations during at least 24 months of follow-up, and marked improvement in PFT values.

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КЛИНИКО-ЭКОНОМИЧЕСКАЯ ЭФФЕКТИВНОСТЬ ПРЕПАРАТА РЕМАКСОЛ В ЛЕЧЕНИИ АЛКОГОЛЬНОГО ГЕПАТИТА В РЕАЛЬНОЙ ПРАКТИКЕ

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Real-World Clinical and Economic Efficacy of Succinate-Based Therapy with Remaxol of Alcohol Hepatitis

Резюме

Проведено проспективное исследование в условиях реальной клинической практики с целью клинико-экономической оценки применения сукцинатсодержащих препаратов у пациентов с алкогольной болезнью печени. Основной анализируемый фактор — длительность госпитализации в днях. Были включены 60 пациентов с алкогольной болезнью печени и превышением трансаминаз более двух норм и аммиака в крови более полутора норм, из которых у 36 в составе комплексной терапии использовались сукцинат-содержащие препараты (основная группа), а 24 — не получали их (группа контроля) на базе двух медицинских центров «Городская клиническая больница им. В.М. Буянова», г. Москва» и «Клиническая больница им. С.Р. Миротворцева СГМУ» Саратов в период с 2019 по 2022 гг.

Динамика показателей клинико-инструментального статуса в группах не отличалась (V=0,35; F=0,87; p=0,614). По результатам клинико-экономической оценки, применение препаратов, содержащих сукцинаты в комплексной терапии алкогольной болезнью печени, позволяет медицинскому учреждению экономить до 8,3 % затрат за счет сокращения в среднем на 2,42 койко-дня сроков госпитализации пациентов.

Ключевые слова: *Алкогольная болезнь печени, алкогольный гепатит, ремаксол*

Конфликт интересов

Исследование проведено при поддержке ООО «НТФФ «ПОЛИСАН»

Источники финансирования

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Abstract

A real-world study with clinical and economic assessment of the use of succinate-containing drugs in patients with alcoholic liver disease was conducted. The study was based on data from Buyanov City Clinical Hospital in Moscow and Mirotvortsev Clinical Hospital in Saratov. The period of the study was from 2019 to 2022. The main analyzed factor was the duration of hospitalization and 60 patients with alcoholic liver disease and blood transaminases exceeding two norms and blood ammonia more than one and a half norms were included in the study. Of 60 patients 36 used succinate-containing drugs as part of complex therapy (main group) and 24 did not receive them (control group).

The dynamics of indicators of clinical and instrumental status of patients did not differ in both groups (V=0.35; F=0.87; p=0.614). The modelling by Markov chains was performed. The use of succinate-containing drugs demonstrated 8.3 % reducing of costs per case of alcoholic liver disease cure due to the average reduction of hospitalization by 2.42 days.

Key words: *Alcoholic liver disease, alcoholic hepatitis, remaxol*

Conflict of interests

The study was conducted with the support of NTFF POLYSAN LLC.

Sources of funding

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ALD — alcoholic liver disease, ALT — alanine aminotransferase, AST — aspartate aminotransferase, GGTP — gamma glutamine transpeptidase, DF — Maddrey's discriminant function, EE — economic evaluation, RCP — real-life clinical practice, SCPs — succinate-containing products, NCT — Number Connecting Test, AP — alkaline phosphatase

Relevance

The problem of chronic alcoholism is still relevant, despite the fact the population is highly socialized and intellectually developed. According to a systematic review by G. Max et al. [1], deaths from alcohol consumption account for approximately 10 % of the employable world population. According to an analysis by the Federal State Statistics Service (Rosstat), in 2017 the incidence of alcoholism in Russia was 1,304,600 people [2]. Chronic alcohol consumption is one of the most common external causes of hepatic disorders. Ethanol intoxication over a number of years can result in one of the three key forms of alcoholic liver disease (ALD): alcoholic steatosis (60–90 % of all cases), alcoholic hepatitis (10–30 % of all cases) and alcoholic cirrhosis (8–20 % of all cases) [3].

Modern medical care for patients with ALD includes a wide range of measures to reduce the intoxication load for the body, prevention of further damage to hepatic tissue and progression to a life-threatening disease — cirrhosis. The professional medical community constantly improves the quality of care and timely updates clinical guidelines, taking into account both Russian and foreign experience [2].

Active introduction of new treatment methods and regimens, as well as new medicinal products to the comprehensive management of ALD requires evaluation not only of clinical efficacy of medication, but also economic feasibility, which ensures quality care to many patients. Usually, economic evaluation (EE) starts from the commencement of commercial distribution of the product and/or its inclusion in a certain system of reimbursement and ends with product withdrawal from the pharmaceutical market.

One of the tools used to gather information for EE is the data from the real-life clinical practice (RCP) [4, 5]. A distinctive feature of EE is its non-interventional nature, associated with some limitations, e.g. no placebo groups or passive control. Specifically, with personified therapy, the use of high-potency products and development of patient discharge criteria, as in ALD patients [2], by the end of in-patient care, patients do not demonstrate any differences in clinical parameters; and even statistically confirmed differences cannot be treated as markers of high efficacy (higher efficiency) of a certain product. At the same time, the rate of action onset also differs and impacts the overall performance — duration of hospitalisation. In-patient bed-days is a key criterion to evaluate not only the clinical, but also economic efficiency of a medicinal product, since reduction in the duration of therapy allows increasing the bed turnover, and the number of paid cases of treatment increases, while costs reduce, thus ensuring significant savings for the medical institution.

Succinate-containing products (SCPs) are among reputable products for the therapy of adult patients with ALD and are included in the current clinical guidelines [2]. By boosting cell resistance to hypoxia, which is a common sign of any chronic inflammation, SCPs improve membrane resistance to peroxidation and activate reparative processes [6]. Overall, products from similar groups are actively used not only in ALD, but also in other chronic [7, 8] and acute conditions [9-11].

At the same time, economic evaluation of SCPs in the real-life practice has not been performed yet, defining the relevance and the objective of this study.

Materials and Methods

Given the objective of an economic evaluation of the use of SCPs in patients with ALD, we have conducted a prospective real-life clinical study at two study sites: V. M. Buyanov City Clinical Hospital (Moscow) and S. R. Mirotvortsev Clinical Hospital of the Samara State Medical University (Saratov) in 2019–2022.

Patients were diagnosed with ALD if they had a history of alcoholism, relevant CAGE and AUDIT scores, identified markers of hepatic pathology (steatosis or steatohepatitis, enhanced echogenicity, increased transaminases or GGTP, etc.).

ALD therapy included fluid maintenance, hepatoprotectors, glucocorticoids where necessary, and ursodeoxycholic acid. Some patients received infusions Remaxol 400 ml per day.

Inclusion criteria:

1. Patients with ALD (ICD code: K70)
2. Age: 25–70 years old, both males and females
3. 1.5-fold increase in reference values of blood ammonia (PoketChem) (80–300 μmol/L), at least 2-fold increase in ALT or AST vs. ULN (NLT 80 U/L)
4. Signed informed consent from.

Not included were the patients with the following clinical conditions: HIV infection, syphilis, TB, acute infectious disease, Child-Pugh class C hepatic cirrhosis, viral cirrhosis, obstructive jaundice, autoimmune hemolytic anaemia (positive Coombs' test), insulin-dependent diabetes mellitus, malignancy, acute cerebrovascular accident or acute coronary syndrome, hemodialysis-dependent patients, any decompressed condition, mental disorders, pregnancy, breastfeeding, surgical pathologies.

Key analysed factor: duration of hospitalisation (days). Numerous exclusion criteria were due to the need to eliminate the impact of other medical conditions on this clinical and economic efficacy endpoint.

Recorded clinical parameters, used by the medical professional to decide whether the patient was fit for discharge from the in-patient clinic, included: transaminase activity (AST and ALT), gamma glutamine transpeptidase (GGTP), alkaline phosphatase (AP), conjugated and free bilirubin, Maddrey's discriminant function (DF) results, and Number Connecting Test (NCT) results. These parameters were recorded on day 1, day 5 and day 9 and were entered to the database.

During the study, data from 60 ALD patients were collected, of which 36 patients were treated with SCPs as part of their combined therapy (main group) and 24 patients did not receive SCPs — Remaxol (controls).

A distinguishing feature of RCP data is non-randomisation, which can be a reason for the absence of the balance in interfering variables between treatment groups. The non-handling of such variables inevitably leads to bias of an estimate and incorrect conclusions, while the non-interventional nature of an RCP study can cause missing data, since referral to an assessment depends not on the protocol, but on the doctor's opinion.

Statistical data processing was performed using Python 3.9 and IBM SPSS v 23. Given the features of RCP data, it was supplemented by multiple imputation and propensity score matching 1 : 1 on a smaller sample size. Patients were selected using the method to calculate the odds of randomisation to any of the groups using logistic regression with the inclusion of recorded values of transaminases, GGTP, AP, bilirubin, Maddrey's DF, and NCT. Changes in the clinical and instrumental status were evaluated using MANOVA (Pillai's V-trace) with the inclusion of the change factor (visit: days 1, 5 and 10) and its correlation with the grouping factor (group * visit). Duration of hospitalisation was compared using Student–Welch t-test. Since the time to discharge is time-to-event data, survival rates were compared using Gehan generalised Wilcoxon Z-test.

In order to evaluate the economic feasibility, a Markovian chain was used to model the transition between "in-patient patient" and "discharged", with the generation size of 10,000 patients. For each group, the odds of discharge on each day were calculated using Kaplan–Mayer survival analysis. During modelling, the cost of therapy of the "in-patient patients" was calculated. After modelling, costs per group were compared, and savings (overpaid amount) were evaluated in the main group vs. controls.

The significance threshold to discard zero hypotheses of the lack of difference was $p = 0.05$.

The study was approved by the Ethics Committee of the Autonomous Non-Profit Organisation Central Bureau of Forensic Examination No. 1, Order No. 65 dated 10 December 2018.

Results

Following the interim analysis, missing data were found to be accidental (Little criterion: $\chi^2 = 1565.9$, $p \approx 1.0$), making it possible to perform MICE (Multiple Imputation by Chained Equations) imputation. Then, propensity score matching 1 : 1 was performed. The smaller group (controls) included 24 subjects; 24 subjects were selected from the main group as well. Baseline characteristics of subjects in the study groups are presented in Table 1.

Changes in clinical and instrumental status in the groups did not differ ($V = 0.35$; $F = 0.87$; $p = 0.614$), while overall it was statistically significant ($V = 0.80$; $F = 6.40$; $p < 0.001$). MANOVA results demonstrate that the change factor accounted for approx. 80 % of the dispersion (partial $\eta^2 = 0.799$), while its interference with the grouping factor did not have any statistically significant impact.

Analysis of duration of hospitalisation is presented in Table 2.

Table 1. Population baseline characteristics

Parameter	Succinate-based therapy (n=24)	Control (n=24)
Age	50,71 (11,92)	51,67 (11,12)
Male	9 (37,50 %)	6 (25,00 %)
Capillary blood Ammonia	99,23 (34,84)	90,95 (30,38)
Maddrey's index	23,35 (14,2)	30,96 (27,44)
Number connection test	79,63 (25,5)	86,46 (27,06)
Alanine aminotransferase	138,42 (152,09)	130,44 (169,25)
Aspartate aminotransferase	168,27 (99,98)	151,02 (119,74)
Alkaline phosphatase	398,54 (367,73)	402,08 (281,99)
Gamma-glutamyl transpeptidase	562,8 (599,91)	421,63 (416,55)
Direct bilirubin	36,55 (36,14)	47,99 (70,5)
Indirect bilirubin	39,48 (31,05)	81,25 (133,9)

Note: data presented as mean (standard deviation) or count (%), there is no statistically significant difference between groups on baseline

Table 2. Mean hospital time comparison results comparison

Parameter	Overall (n=48)	Succinate-based therapy (n=24)	Control (n=24)
Days in Hospital	14,00 (3,60)	12,79 (3,06)†	15,21 (3,74)†
Survival median	–	12,75	16,00

Note: data presented as mean (standard deviation); † — differences between groups are statistically significant (t=-2,45; df=46; p=0,018).

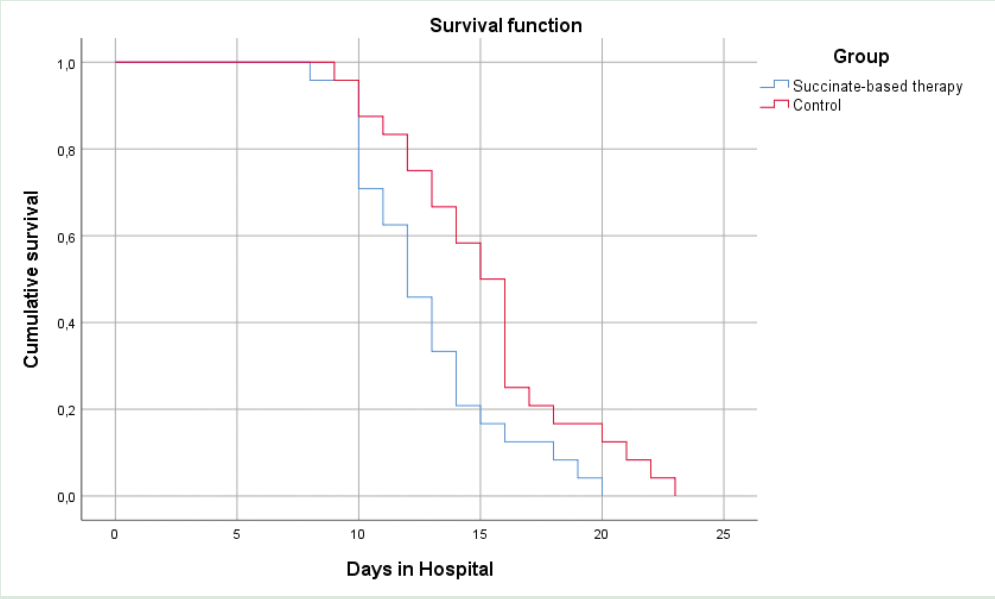

Figure 1. *Survival comparison of group of therapies of Alcohol Hepatitis*

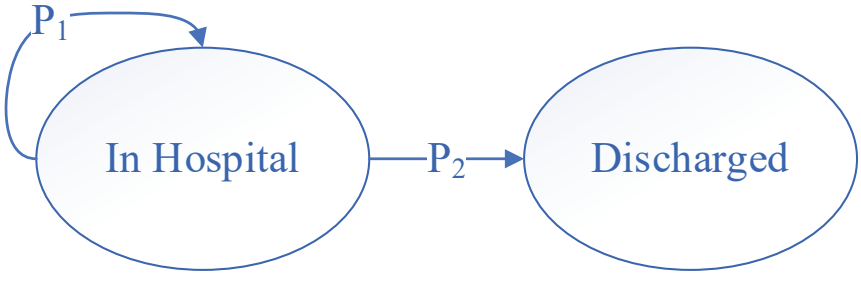

Figure 2. *Marcov's chain scheme*

Таблица 3. *Расчетные вероятности выписки пациентов с АБП в анализируемых группах*
Table 3. *Discharge probabilities in experimental and control group*

Day	Succinate-based therapy	Control
0	0,000	0,000
1	0,000	0,000
2	0,000	0,000
3	0,000	0,000
4	0,000	0,000
5	0,000	0,000
6	0,000	0,000
7	0,000	0,000
8	0,042	0,000
9	0,000	0,042
10	0,250	0,083
11	0,083	0,042
12	0,167	0,083
13	0,125	0,083
14	0,125	0,083
15	0,042	0,083
16	0,042	0,250
17	0,000	0,042
18	0,042	0,042
19	0,042	0,000
20	0,042	0,042
21	-	0,042
22	-	0,042
23	-	0,042

The next step was to analyse survival (Fig. 1). The survival functions demonstrated statistically significant difference ($Z = 5.69$; $df = 1$; $p = 0.017$), making it possible to use the calculated probability (Table 3) in modelling.

The Markovian chain, used to describe the transition between "in-patient patient" and "discharged", is given in Figure 2. For it to be functional, it was assumed that at a given time unit (day) a patient has "P_1" probability to stay in the in-patient clinic or "P_2" probability to be discharged; no provisions were made for other outcomes (death, complication, adverse events, etc.). No reverse transition is possible. Taking into account the two mutually exclusive conditions ($P_1+P_2= 1.0$), Table 3 contains only the odds of discharging the patient from the in-patient clinic (P_2).

Given that the average duration of hospitalisation in the total population was 14 days, modelling covered this period. Costs were calculated on the basis of the clinically statistical group. st04.003 "Non-viral hepatic diseases (level 1)"; rate of RUB 35,997.97 (taking into account the coefficient and relative cost intensity, excluding the rest coefficients), according to the State Program guarantees of free provision of medical services to citizens Qing aid for 2023 and for the planning period 2024 and 2025. Therefore, the cost of a bed-day during a 14-day in-patient hospitalisation is RUB 2,571.28 net of input intensity coefficient, etc.

The modelling result is presented in Figure 3.

The modelling demonstrates that the cost savings of a medical institution resulting from a shorter period of hospitalisation when using SCPs (Remaxol 400 ml per day for 10 days) in the combined therapy of ALD was 8.3 %.

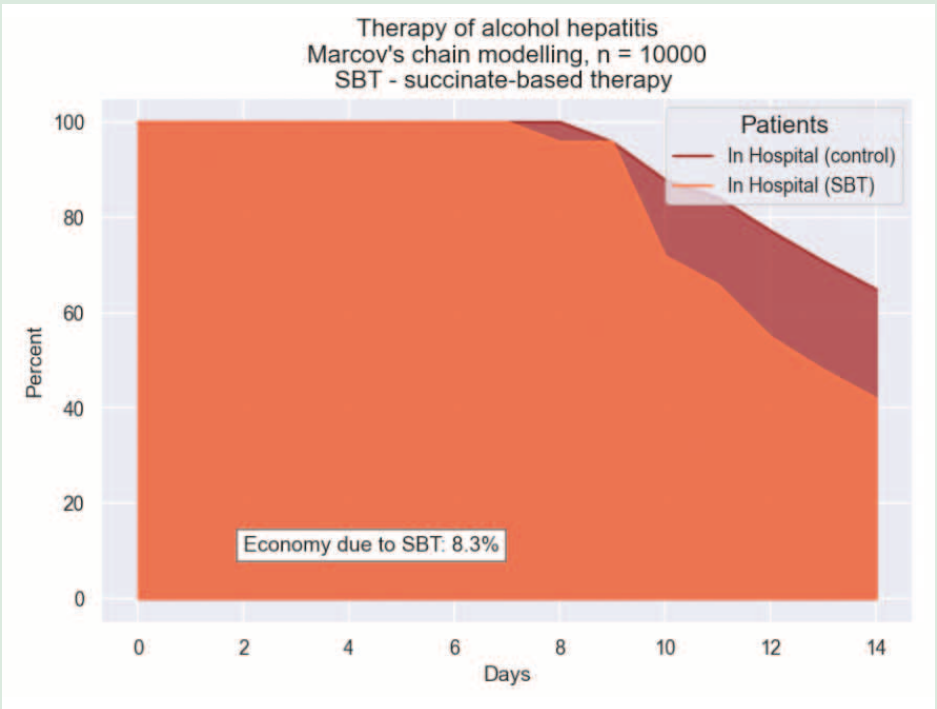

Figure 3. *Marcov's chain modelling of alcohol hepatitis treatment with and without succinate-based therapy*

Discussion

Succinate-containing products offer metabolic support in a chronic inflammation or in an acute condition. Their clinical efficacy has been demonstrated in a number of medical conditions, where these products are used in a combined therapy.

The key point of SCPs application is the oxidative process, inevitably associated with ALD [12, 13]. Less active free-radical oxidation, tissue hypoxia compensation and antioxidant defence reconstruction facilitate faster recovery and reduce duration of hospitalisation. A similar study [14] demonstrated that the use of antihypoxic and antioxidative products helped to mitigate consequences of liver impairment.

Of note, no adverse drug reactions were recorded in this study.

This study provided an economic evaluation of SCPs in the management of patients with alcohol liver damage. Earlier discharge (2.42 days earlier on the average) reduces costs of a medical institution by 8.3 %. Similar studies demonstrate their economic efficiency as a result of complication prevention by using SCPs in the primary treatment regimens [15], or by reducing duration of hospitalisation [16]. At the same time, no economic evaluations of SCPs have ever been performed in Russia on the basis of the real-life practice.

This study has some limitations.

First, it took into account only the clinical statistical costs. However, this indicator is integral and allows evaluating a wide range of costs incurred by a medical institution, from procurement of medications to salaries to healthcare professionals.

Second, the modelling did not take into account possible deaths, complications and adverse events from SCP therapy. This is due to the small size of the study groups and the absence of such outcomes in the groups. No doubt, PCP studies can assess rare outcomes as well, and as soon as SCP therapy is more common, the process modelling can be updated for in-patient therapy of patients with ALD.

Conclusions

The economic evaluation demonstrated that when a medical institution uses succinate-containing products in the combined therapy of ALD, its savings are up to 8.3 % as a result of the reduction of hospitalisation duration on the average by 2.42 bed-days.

This study can be used in the real-life clinical practice as a starting point for the selection of optimal treatment regimens for patients with alcohol liver damage. As long as there are enough data on the real-life clinical practice, modelling can be repeated in order to obtain a more accurate result.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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ФАКТОРЫ РИСКА СТРУКТУРНОЙ ПЕРЕСТРОЙКИ МИКРОЦИРКУЛЯТОРНОГО РУСЛА ПОЧЕК У ПАЦИЕНТОВ С ГЛОМЕРУЛОНЕФРИТОМ И АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ

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Factor Analysis for Predicting the Structural Reorganization of the Microvasculature of the Kidneys in Patients with Glomerulonephritis and Arterial Hypertension

Резюме

Цель. Оценка взаимосвязи клинико-лабораторных и морфологических факторов с ремоделированием артерий почек малого диаметра у пациентов с гломерулонефритом (ГН) и артериальной гипертензией (АГ). **Материалы и методы.** В исследование включено 105 пациентов (средний возраст 37,1±1,2 лет) с первичным ГН и АГ, показаниями к выполнению нефробиопсии. Всем пациентам проведено стандартное нефрологическому профилю обследование, морфологическое исследование нефробиоптата с оценкой изменений почечной ткани с описанием изменений, происходящих при наличии гломерулонефрита, соответствующее индивидуальной выраженности патологического процесса. Оценивалось наличие признаков тубулоинтерстициального компонента повреждения (или тубулоинтерстициальный компонент — ТИК) в виде тубулоинтерстициального воспаления (ТИВ), фиброза (ТИФ). Выполнена вазометрия междольковой артерии (МА). Признаком ремоделирования МА было принято считать величину комплекса интима-медиа (КИМ) более 30,43 мкм. **Результаты.** Среди клинико-лабораторных факторов риска статистически значимое влияние на вероятность увеличения КИМ имеют повышение уровня систолического артериального давления

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(χ^2-критерий = 5,76, p = 0,016), стадии АГ (χ^2-критерий = 9,45, p = 0,002), уровня мочевины крови (χ^2-критерий = 8,11, p = 0,004), уменьшение скорости клубочковой фильтрации (χ^2-критерий = 5,0, p = 0,025), увеличение стадии хронической болезни почек (χ^2-критерий = 10,32, p = 0,001). Наличие признаков прогрессирования ГН, таких как повышение скорости оседания эритроцитов (СОЭ) или белка в моче, статистически значимого влияния на риск ремоделирования МА не установило (p>0,05). На вероятность увеличения КИМ МА влияют наличие гиалиноза капиллярных петель клубочка (χ^2-критерий = 7,56, p = 0,006), перигломерулярного гиалиноза (χ^2-критерий = 6,96, p = 0,008), склероза клубочка (χ^2-критерий = 3,9, p = 0,048), увеличение фиброза тубулоинтерстиция (χ^2-критерий = 12,16, p = 0,0005). **Заключение.** При ГН и АГ ремоделирование сосудов почек малого диаметра происходит из-за влияния АГ и ее выраженности, тубулоинтерстициальных изменений почечной ткани. Получены новые факторы риска сосудистого ремоделирования –гломерулопатии, которые проявляются в склерозе клубочка, перигломерулярном гиалинозе и гиалинозе капиллярных петель клубочка. В то же время, воспалительные и аутоиммунные механизмы ГН не влияют на изменение сосудистой стенки. Роль АГ является определяющей в изменении структуры почек малого диаметра.

Ключевые слова: *гломерулонефрит, артериальная гипертензия, ремоделирование артерий малого диаметра, междольковая артерия*

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Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Objectives. Evaluation of the relationship of clinical, laboratory and morphological factors with remodeling of small-diameter renal arteries in patients with glomerulonephritis (GN) and arterial hypertension (AH). **Materials and methods.** The study included 105 patients (average age 37.1±1.2 years) with primary GN and hypertension who had indications for morphological investigation of kidney tissue. All patients underwent a standard examination for kidney disease, a morphological study of kidney tissue with a description of the changes that occur in the presence of glomerulonephritis, corresponding to the individual severity of the pathological process. The presence of signs of a tubulointerstitial component of damage (or tubulointerstitial component — TIC) in the form of tubulointerstitial inflammation (TIV), fibrosis (TIF) was assessed. Vasometry of the interlobular artery (IA) was performed. The value of the intima-media complex (IMC) was considered to be a sign of IA remodeling. A sign of MA remodeling was considered to be an intima-media complex (IMC) value of more than 30.43 μm. **Results.** Among clinical and laboratory risk factors, an increase in systolic blood pressure has a statistically significant effect on the likelihood of increasing IMC (χ2-criterion = 5.76, p = 0.016), arterial hypertension stage (χ2-criterion = 9.45, p = 0.002), blood urea level (χ2-criterion = 8.11, p = 0.004), decrease in glomerular filtration rate (χ2-criterion = 5.0, p = 0.025), increase in the stage of chronic kidney disease (χ2-criterion = 10.32, p = 0.001). The presence of signs of GN progression, such as an increase in erythrocyte sedimentation rate (ESR) or proteinuria, did not have a statistically significant effect on the risk of IA remodeling (p>0.05). The increase in IA IMC is affected by the presence of hyalinosis of glomerular capillary loops (χ2-criterion = 7.56, p = 0.006), periglomerular hyalinosis (χ2-criterion = 6.96, p = 0.008), sclerosis of the glomerulus (χ2-criterion = 3.9, p = 0.048), increased fibrosis of tubulointerstitium (χ2-criterion = 12.16, p = 0.0005). **Conclusion.** In GN and AH, remodeling of small-diameter renal vessels occurs due to the influence of AH and its severity, tubulointerstitial changes in the renal tissue. New risk factors for vascular remodeling have been obtained — changes in the glomerulus. At the same time, the inflammatory and autoimmune mechanisms of GN were not associated with changes in the vascular wall. The role of hypertension is decisive in changing the structure of small-diameter kidneys.

Key words: *glomerulonephritis, arterial hypertension, remodeling of small diameter arteries, interlobular artery*

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AH — arterial hypertension, BP — blood pressure, GN — glomerular nephritis, DBP — diastolic blood pressure, IMC — intima-media complex, IA — interlobular artery, SUP — spot urine protein, SBP — systolic blood pressure, eGFR — estimated glomerular filtration rate, DUP — daily urine protein, TII — tubulointerstitial inflammation, TIC — tubulointerstitial component, TIF — tubulointerstitial fibrosis, CKD — chronic kidney disease

Introduction

Kidney vascular supply has a unique anatomical and functional organisation [1], which determines the vital physiological functions of the organ with adequate blood supply, formation and regulation of the perfusion pressure. Vascular structural or functional remodelling is associated with impaired organ trophism and organ failure development. It is worth noting that the condition of the arterial bed should be monitored not only at the main artery level, but also in the microcirculation. General damage to small arteries and arterioles can result in irreversible remodelling of main arteries and kidney dysfunction.

Glomerular nephritis (GN) is a socially significant disease [2, 3]. The natural course of GN results in chronic kidney disease, associated diseases and conditions (arterial hypertension, anaemia, thrombosis, etc.), high risk of death and permanent disability. It is well known that the pathogenic mechanism behind GN is intraglomerular immune inflammation, that leads to glomerular and tubulointerstitial damage [4]. However, morphological examination shows not only damage to glomerulus cells, but also structural changes in small arteries in the kidney. The nature of vascular remodelling in arteries and arterioles in GN is still not completely clear [5]. There are key conditions that cause structural remodelling in the microcirculation in patients with GN. "Vascular exhaustion" is a phenomenon that underlies the basic theory of changes in small arteries in response to tissue rearrangements in the dependent organ. This process can be seen in the pathophysiological mechanism "function, then form", i.e. the vascular bed changes in response to a larger demand by structurally modified renal tissue. Another condition for remodelling of small arteries is high blood pressure (BP) which is a common clinical manifestation of GN. Also, there can be the effect of endotheliotropic factors, a higher level of which is observed in cytokine inflammation in response to an autoimmune process, oxidative stress, effect of toxic metabolites in GN.

The objective of our study was to assess the association between clinical, laboratory and morphological factors and remodelling of small renal arteries in patients with GN and AH.

Materials and Methods

The study enrolled 105 patients with GN and AH, of which 62 were men and 43 were women. The mean GN duration was 4.13 [0.04; 20.0] years. The age of patients was 37.1 ± 1.2 years. Clinical study design is presented in Figure 1.

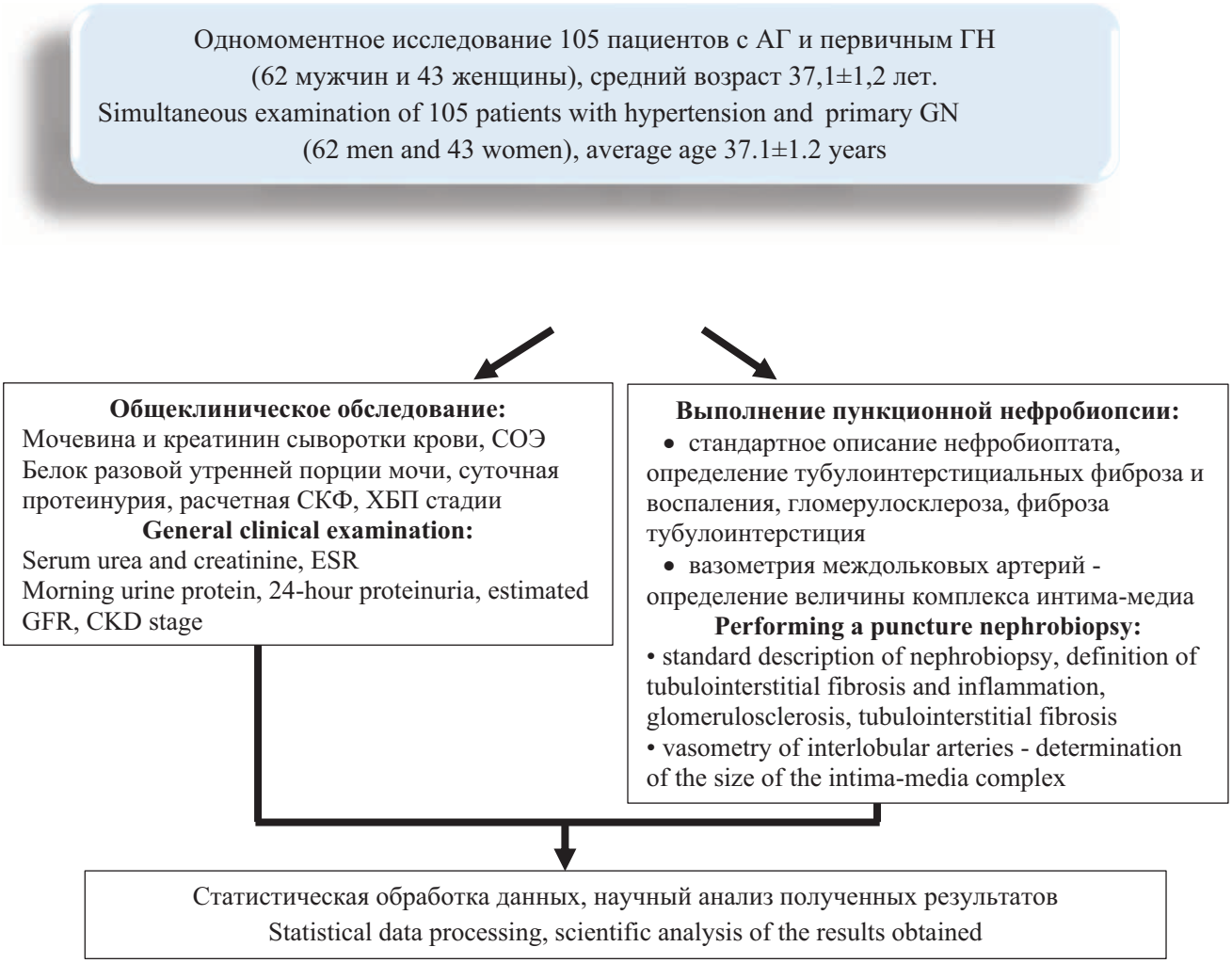

Figure 1. *Clinical study design*
Note: AH — arterial hypertension, GN — glomerulonephritis, ESR — erythrocyte sedimentation rate, GFR — glomerular filtration rate, CKD — chronic kidney disease

The inclusion criterion in this study was arterial hypertension and indication for needle renal biopsy (observation of any pathologic urine sediment in patients with GN (spot urine protein concentration over 0.033 g/L and over 150 g/day, erythrocyturia of over 3/HPF), stage 1–4 CKD). Exclusion criteria were secondary GN, inflammations of any origin, decompensated comorbidities.

All patients underwent a medical examination. Laboratory tests measured urea, serum creatinine, erythrocyte sedimentation rate (ESR), spot urine protein (SUP) and daily urine protein (DUP). Glomerular filtration rate (GFR) was calculated using the formula developed by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) [6]. Estimated GFR was used to determine the stage of chronic kidney disease (CKD) (KDIGO, 2012) [7]. Each CKD stage was graded. Grade 1 corresponded to stage 1 CKD, grade 2 — to stage 2 CKD, grade 3 — to stage 3a CKD, grade 4 — to stage 3b CKD, grade 5 — to stage 4 CKD. AH severity and stage were recorded; systolic (SBP) and diastolic (DBP) blood pressure were recorded during the first encounter with the patient; the highest SBP and DBP from the medical record were recorded as well. Clinical characteristics of study subjects are presented in Table 1.

At the time of enrolment, out of 105 patients, 75 patients had uncontrolled AH, BP in 17 patients corresponded to grade 1, in 44 patients — to grade 2, and in 14 patients — grade 3. 20 patients were diagnosed with stage III AH, 59 patients had stage II AH, and the rest were diagnosed with stage I AH. At the time of enrolment, all patients were taking antihypertensive medications.

All patients underwent needle renal biopsy and measurement of small renal vessels. Measurements of vessel diameter were performed using Leica DMD108 microscope (Leica Microsystems, Germany). Inner and outer diameter, thickness of vessel intima and media were measured. The intima-media complex (IMC) value was obtained by adding the values for intima and media. Of note, microtome sections of renal bioptate created various combinations of arteries (transverse, longitudinal). In order to establish the true diameter of a small renal artery, the rules of vascular geometry were used, and the smallest diameter was used as a true value.

Renal bioptate examination included standard description of changes in GN, which corresponded to the individual intensity of the pathological process. The presence of the signs of tubulointerstitial component of the damage (or tubulointerstitial component (TIC)) in the form of tubulointerstitial inflammation (TII), fibrosis (TIF) were evaluated. Table 2 shows the key results of renal biopsy in patients enrolled in the study.

Given that interlobular artery (IA) was the most common observation in renal bioptate analysis, it was decided to record remodelling results for IA only in order to ensure statistical homogeneity of the test data. IA IMC was recorded as a factor characterising the structural remodelling of IA. Mean IA IMC was 32.26 ± 1.34 μm. The study evaluated grade values of IA IMC based on the median value of 30.43 μm. IA IMC of less than 30.43 μm corresponded to grade 0, while a value of 30.43 μm or over — to grade 1.

Table 1. *Clinical and laboratory data of patients with glomerulonephritis and hypertension*

Criterion	Average value
SBP, mm Hg, Me [IQR]	128 [100; 200]
DBP, mm Hg, Me [IQR]	82,4 [60; 120]
SBP max, mm Hg, Me [IQR]	152,7 [90; 240]
DBP max, mm Hg, Me [IQR]	93,7 [60; 130]
Creatinine, μmol/l, Me [IQR]	104,0 [30,0; 232,7]
Urea, mmol/l, Me [IQR]	8,0 [1,8; 38,9]
eGFR, ml/min/1.73m^2, M+SD	87,1±3,9
CKD stage 1, abs (%)	52 (49,52)
CKD stage 2, abs (%)	31 (29,52)
CKD stage 3A, abs (%)	9 (8,57)
CKD stage 3B, abs (%)	9 (8,57)
CKD stage 4, abs (%)	4 (3,82)
ESR, mm/h, M+SD	24,6±18,6
Protein concentration in urine sample, g/l, Me [IQR]	2,8 [0; 32,0]
24h proteinuria, g/l, Me [IQR]	3,8 [0; 26,4]

Note: SBP — systolic blood pressure, DBP — diastolic blood pressure, SBP $_{max}$ — maximum values of the patient's SBP, DBP $_{max}$ — maximum values of the patient's DBP, eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease, ESR — erythrocyte sedimentation rate

Table 2. *Characterization of morphological changes in the nephrobioptate of patients with glomerulonephritis and hypertension*

Sign *	Prevalence, abs (%)
Mesangium expansion	77 (73,3)
Sclerosis of the mesangium	33 (31,4)
Glomerulus enlargement	41 (39,1)
Segmental sclerosis of capillary loops of the glomerulus	63 (60,0)
Segmental hyalinosis of capillary loops of the glomerulus	26 (24,8)
Fusion of capillary loops	89 (84,8)
Obliteration of capillary loops	6 (5,7)
Mesangial hypercellularity	62 (59,1)
Endothelial hypercellularity	9 (8,6)
Periglomerular focal fibrosis	77 (73,3)
Periglomerular focal hyalinosis	21 (20,0)
Glomerular hyalinosis	54 (51,4)
Glomerular fibrosis	41 (39,1)
Tubulointerstitial inflammation	64 (60,9)
Tubulointerstitial fibrosis	79 (75,2)
Tubulointerstitial component	86 (81,9)

Note: * — presence of a sign in the study cohort of patients

The study was conducted in accordance with the standards of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the Local Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Rostov State Medical University of the Ministry of Health of Russia. Before inclusion in the study, study subjects signed the informed consent form.

Statistical data analysis was performed using Statistica 10,0 (Stat Soft, USA). For normal distribution, data were presented as M ± SD (M is arithmetic mean, SD is standard deviation); otherwise — Me [Q1;Q3] (Me is the median value, Q1 and Q3 are the first and third quartiles). The probability of effect from a factor on a bipolar event was determined with logistic regression analysis with χ^2. The degree of correlation between test variables was evaluated with the use of Pearson correlation coefficient (r). The degree of correlation was interpreted on the basis of r value: with r = 0.01–0.29, the correlation was weak, with r = 0.3–0.69 — moderate, and with r = 0.7–1.0 — strong. Survival analysis was performed under the Kaplan–Meier method. The zero hypothesis on the absence of differences and correlations was discarded at $p < 0.05$.

Results and Discussion

The logistic regression analysis demonstrated that, among clinical and laboratory parameters, the risk of an increased IMC is statistically significantly impacted by higher SBP values, measured at the time of enrolment ($\chi^2 = 5.76$, $p = 0.016$), AH stage ($\chi^2 = 9.45$, $p = 0.002$), increased urine urea levels ($\chi^2 = 8.11$, $p = 0.004$), reduced eGFR ($\chi^2 = 5.0$, $p = 0.025$), and a higher CKD stage ($\chi^2 = 10.32$, $p = 0.001$).

The resulting data were used to generate a table of risk grading for small renal arteries (IA) remodelling in patients with GN and AH (Table 3). Of note, thickening of IA IMC was recorded where the result was equal or exceeded the median IA values (30.43 μm) in the study group (a graded parameter). The resulting logistic regression equations were used to calculate the risk of an increased IA IMC values with account of clinical and laboratory parameters.

The correlation analysis demonstrated that the IA IMC value is in direct weak correlation with the SBP values ($r = 0.29$, $p = 0.005$), AH severity ($r = 0.25$, $p = 0.01$) and moderate correlation with AH stages ($r = 0.39$, $p = 0.0001$) and CKD ($r = 0.4$, $p = 0.00008$). Also, an inverse weak correlation with eGFR was found ($r = -0.26$, $p = 0.01$).

Interestingly, higher ESR value and the degree of proteinuria did not have any statistically significant effect on IA remodelling ($p > 0.05$).

In order to achieve the objective of the study, we conducted an analysis of the effect of renal tissue changes on the risk of small renal artery remodelling. It has been shown that, among all studied parameters, a statistically significant effect on an increase of the risk of a higher IA IMC value was observed in the presence of hyaline degeneration of glomerulus anses capillaires, focal periglomerular hyaline degeneration and glomerulus sclerosis. The probability that IA IMC will be above 30.43 μm in the presence of hyaline degeneration of glomerulus anses capillaires was 31.28 % ($\chi^2 = 7.56$, $p = 0.006$), periglomerular hyaline degeneration — 33.78 % ($\chi^2 = 6.96$, $p = 0.008$), glomerulus sclerosis — 20.4 % ($\chi^2 = 3.9$, $p = 0.048$). Besides, the effect of the presence of hyaline degeneration of glomerulus anses on the risk of higher IMC values with account to GN duration (Gehan's Wilcoxon Test WW = -305.0, Test statistic = -2.097, p = 0.036, Cox-Mantel Test U = -5.66, Test statistic = -2.28, p = 0.02, Log-Rank Test WW = 5.66, Test statistic = 2.3, p = 0.02) and periglomerular hyaline degeneration (Gehan's Wilcoxon Test WW = -239.0, Test statistic = -2.07, p = 0.038, Cox-Mantel Test U = -4.67, Test statistic = -2.28, p = 0.02, Log-Rank Test WW = 4.67, Test statistic = 2.29, p = 0.02) has been established. Figures 2 and 3 show Kaplan–Mayer graphs.

An important result of the study was identification of a significant probability of an increase in IA IMC values with higher incidence of TIF ($\chi^2 = 12.16$, $p = 0.0005$) (Figure 4), and directly proportional moderate correlation between IMC and TIF ($r = 0.38$, $p = 0.0001$).

Table 3. *Stratification of the risk of an increase in the thickness of IMC MA in GN occurring with AH based on clinical and laboratory parameters*

Risk of increased IMC	Signs			
	SBP mmHg			
	100	140	160	180
Risk, %	30,7	60,6	74,1	84,2
	Hypertension, stages			
	I	II	III	
Risk, %	38,1	54,7	70,3	
	BUN, mmol/l			
	2	4	6	8
Risk, %	31,6	38,35	45,6	53,0
	eGFR, ml/min/1,73 м²			
	100	80	60	40
Risk, %	45,3	52,1	58,8	65,2
	eCKD, Ranks			
	1	2	3	4	5
Risk, %	37,3	52,6	67,5	79,5	87,9

Note: GN — glomerulonephritis, IMC MA — interlobular artery intima-media complex, SBP — systolic blood pressure, AH — arterial hypertension, eGFR — estimated glomerular filtration rate, CKD — chronic kidney disease
The table presents the risk of IMC MA thickening, expressed as a percentage, depending on changes in clinical and laboratory parameters

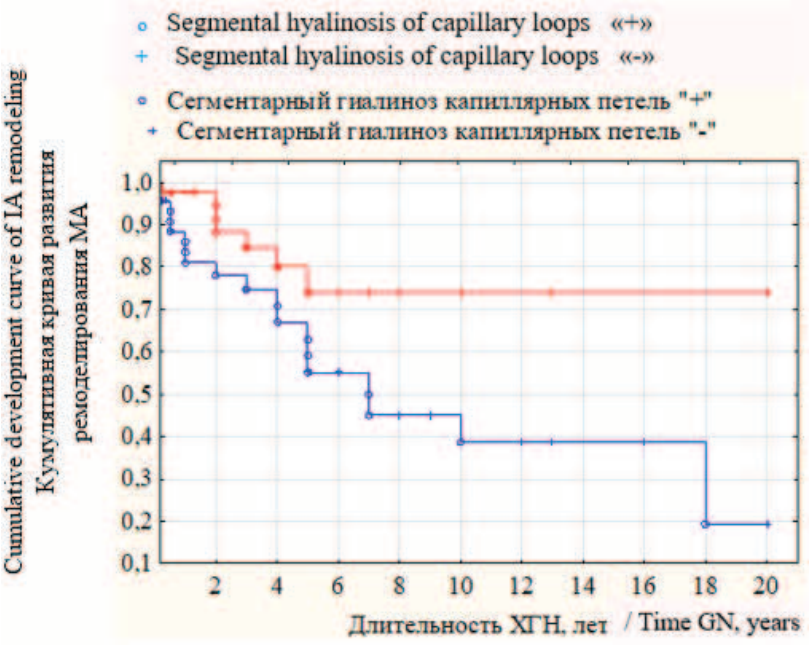

Figure 2. *Cumulative curve of MA remodeling development based on the presence or absence of segmental hyalinosis of glomerular capillary loops*

Note: the blue line is the presence of segmental hyalinosis of the glomerular capillary loops, the red line is the absence of segmental hyalinosis of the glomerular capillary loops. GN — chronic glomerulonephritis, IA — interlobular artery

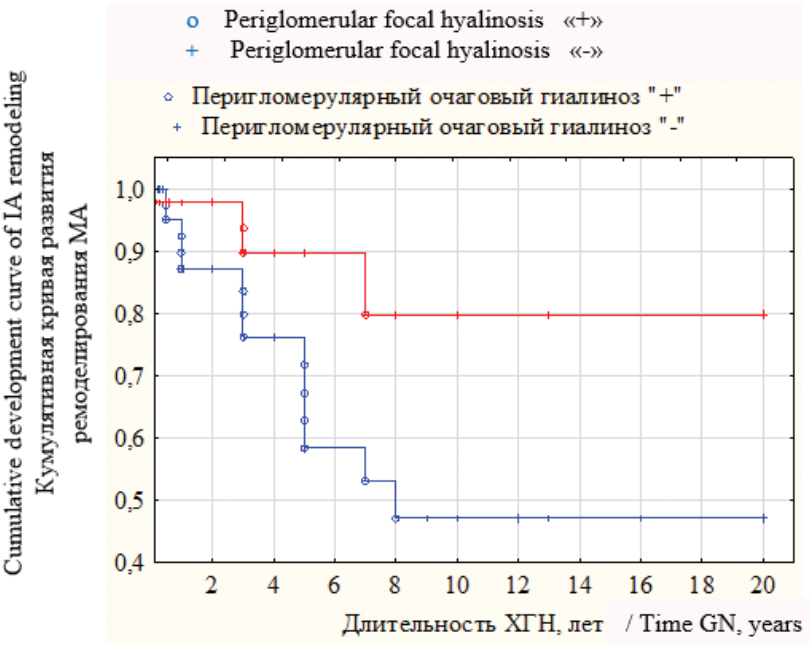

Figure 3. *Cumulative curve of IA remodeling development based on the presence of periglomerular focal hyalinosis.*

Note: blue line — presence of periglomerular focal hyalinosis, red stripe — absence of periglomerular focal hyalinosis. GN — chronic glomerulonephritis, IA — interlobular artery

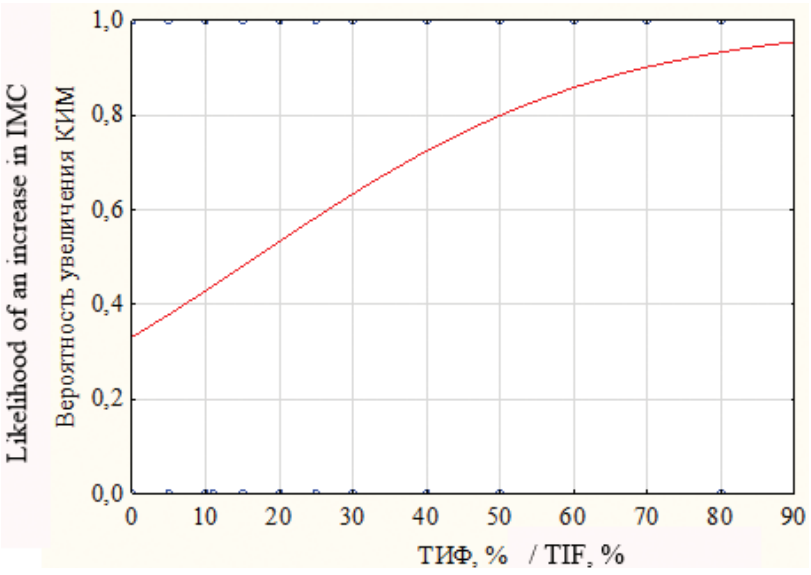

Figure 4. *Graph of non-linear logistic regression of the probability of increasing the value of intima-media complex of the interlobular artery depending on the prevalence of tubulointerstitial fibrosis and the logistic regression equation. Risk of increased intima-media complex (IMC) = exp * (-0,7 + [0,04 * tubulointerstitial fibrosis (TIF) (%)]) / (1 + exp * (-0,7 + [0,04 * tubulointerstitial fibrosis (%)])*

Note: IMC — intima-media complex, TIF — tubulointerstitial fibrosis

This study demonstrated that a condition for small artery remodelling in GN is a systemic haemodynamic factor. First, AH causes damage to arterial intima and media in any vascular pool, while systemic hypertension is an adverse prognostic factor of progressive renal tissue remodelling in numerous diseases [6, 7]. Second, it has been proven that prognosis of end-stage kidney disease in GN depends not only on glomerular damages, but also on the presence of tubular and vascular interstitial damage [8]. Numerous studies demonstrate high significance of AH as a determinant factor in the development and progression of CKD [9, 10]. However, publications on AH as a predictor of small artery remodelling in GN are scant [8, 11, 12, 13].

A publication by Zhuang Y et al. (2020) discusses analysis of factors affecting intrarenal haemodynamics remodelling in secondary GN caused by viral hepatitis B [8]. Their study evaluated the degree of small artery damage found during a morphological examination of renal bioptate. The degree of structural remodelling of the small arterial bed was used for patient grading for inclusion in the study groups. It has been shown that the most significant small artery remodelling was associated with high BP levels, serum creatinine concentrations and tubulointerstitial damage. Besides, clinical outcomes of patients with secondary GN were evaluated over a period of 94.2 ± 47.1 months. Multivariate regression analysis was used to find out that higher serum creatinine levels (1.011, 1.007–1.016), presence of AH (1.767, 1.004–3.108) and small artery remodelling (2.194, 1.062–4.530) were independent predictors of unfavourable outcomes in patients.

Another study evaluated indirect data on the condition of the microcirculation using sonographic signs in patients with CKD, 82 % of which had glomerular nephritis [11]. The study demonstrated that an increase in the resistive index in segmental and interlobar arteries directly correlated with the age (r = 0.435, p = 0.0063), pulse pressure (r = 0.303, p = 0.022), renal tissue atrophy (r = -0,275, p = 0,038) and negative correlation with impaired renal function (r = -0.402, p = 0.0018). The authors conclude that tubulointerstitial changes and impaired filtration function are most significant in the increase of resistive index of small arteries.

Identification of the correlation between small renal artery remodelling and tubulointerstitial changes and AH was described in a number of other scientific research papers with comparable results [12, 13]. However, the objective of a majority of studies was identification of the fact of renal artery changes or comparison of non-invasive kidney biopsy methods, without analysis of the association between the degree of such changes and the degree of AH.

Also, the association between glomerular and tubulointerstitial changes and signs of IA IMC remodelling has been established. In particular, it was demonstrated that as long as hyaline degeneration of glomerulus anses capillaires, focal periglomerular hyaline degeneration and glomerulus sclerosis, as well as TIF develop and progress, IA IMC remodelling becomes more common. This fact is suggestive rather of addition of vascular remodelling in GN to the overall remodelling process in renal parenchyma and is not an evidence of the effect of immune-mediated factors in GN. Apparently, the presence of AH and the association between the incidence of IA remodelling and AH duration and severity (stage and grade) make the haemodynamic effect more important for IA remodelling in GN. To be on the safe side with this hypothesis, future studies will be necessary to evaluate the condition of IA IMC in patients with GN in the absence of AH. It is likely that less marked signs of vascular remodelling in this case would be another argument in favour of the significance of the haemodynamic factor in progressive IA remodelling in patients with GN.

Conclusions

The study demonstrated that in GN with AH, the risk of small renal artery remodelling depends on the severity and stage of AH as well as duration of the disease. Also, small artery remodelling is associated with manifestations of renal tissue remodelling in GN, in the form of tubulointerstitial and glomerular fibrosis. At the same time, it has been demonstrated that the degree of proteinuria does not correlate with changes in IA IMC.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication.

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ЧАСТОТА И ПРОГНОСТИЧЕСКОЕ ЗНАЧЕНИЕ ОСТРОГО ПЕРИПРОЦЕДУРНОГО ПОВРЕЖДЕНИЯ МИОКАРДА ПРИ ПЛАНОВЫХ ЧРЕСКОЖНЫХ КОРОНАРНЫХ ВМЕШАТЕЛЬСТВАХ

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Frequency and Prognostic Value of Acute Periprocedural Myocardial Injury in Elective Percutaneous Coronary Interventions

Резюме

Обоснование. Острое повреждение миокарда (ОПМ) является перипроцедурным осложнением чрескожных коронарных вмешательств (ЧКВ) у пациентов со стабильной ишемической болезнью сердца. Его частота и связь с прогнозом заболевания особенно важны в связи с низким риском ишемических событий в этой когорте пациентов. Тем не менее, по данным литературы существуют значительные различия в критериях ОПМ и инфарктом миокарда (ИМ) 4а типа, и, соответственно, их частоте и их прогностическом значении. **Цель.** Изучить частоту и величину ОПМ при плановых ЧКВ по уровню перипроцедурного повышения кардиоспецифических ферментов (КСФ), а также определить связь ОПМ с отдаленными неблагоприятными событиями у пациентов с хронической коронарной болезнью сердца. **Материалы и методы.** Проведено одноцентровое открытое ретроспективное когортное исследование, включившее 435 пациентов (367/84,4 % мужчин, средний возраст 58,3±8,6 лет) из регистра плановых ЧКВ, у которых была отслежена динамика КСФ в перипроцедурный период. ОПМ диагностировалось при повышении уровня МВ фракции креатинфосфокиназы (СК-МВ) или или сердечного тропонина I (cTn I) >1×99 перцентиль URL (Upper Reference Limit — верхний референтный предел), при этом регистрировался уровень повышения КСФ >1, 2, 3, 4 или >5×99 перцентиль URL. Повышение КСФ >5×99 перцентиль URL оценивалось как значительное ОПМ, а при наличии клинических и визуализирующих доказательств новой потери жизнеспособного миокарда — как перипроцедурный ИМ. Далее был рассчитан относительный риск (RR) отдаленных неблагоприятных сердечно-сосудистых осложнений, смерти, а также клинически значимых кровотечений и вновь диагностированных злокачественных онкологических заболеваний в течение 5 лет после индексных ЧКВ в зависимости от уровня пери процедурного повышения КСФ. Корреляция между ОПМ и вышеперечисленными конечными точками была обобщена с помощью анализа Каплана-Мейера. **Результаты.** Частота перипроцедурного ОПМ, диагностированного по повышению КСФ >1x99 перцентиль URL составила 40,2 %, >2×99 перцентиль URL — 9,7 %, >3×99 перцентиль URL — 6,7 %, >4×99 перцентиль URL — 4,8 %, >5×99 перцентиль URL — 3,5 %, ИМ 4а типа — у 2 пациентов (0,46 %). Выявлена ассоциация «большого» ОПМ (>5x99 перцентиль URL) с сердечно-сосудистыми осложнениями, в том числе и смертельными, в течение 3-х лет после планового ЧКВ: для острого инфаркта миокарда (ОИМ) RR составил 6,516, доверительный интервал (CI) [2.375-17.881]; для смерти от сердечно-сосудистых причин RR — 6,538, CI [1.695-25.227]. Показана ассоциация «умеренного» ОПМ (>3, но <5 ×99 перцентиль URL) с острыми ишемическими собы-

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тиями в течение 3-х лет после планового ЧКВ: для ОИМ RR составил 4,073, CI [1.598-10.378]. Выявлена ассоциация «незначительного» ОПМ (>1, но <3 ×99 перцентиль URL) с вновь диагностированными злокачественными онкологическими заболеваниями в течение 5 лет после индексного ЧКВ: RR 2,319; CI [1.248-4.310]. Выявлена ассоциация отдаленных тромботических событий, таких как тромбоз стентов (индексных и установленных при повторных вмешательствах), окклюзии стентов (индексных и неиндексных) как причины повторного вмешательства в течение 5 лет после индексного ЧКВ — с большинством подгрупп ОПМ. Анализ Каплана-Мейера выявил зависимость клинически значимых кровотечений в течение 5 лет после индексного ЧКВ от развития «умеренного» ОПМ (p=0,003), а также ассоциацию не сердечно-сосудистой смерти в течение 5 лет после индексного ЧКВ с «незначительным» ОПМ (p=0,007). **Заключение.** Регистрация уровня периппроцедурного повышения КСФ должна проводится при плановых ЧКВ не только с целью диагностики и прогнозирования острых и отдаленных ишемических событий, но и для оценки риска развития окклюзии стентов, клинически значимых кровотечений, прогностически важной сопутствующей патологии и смерти в отдаленный (5-летний) период с целью выделения групп пациентов, требующих активного наблюдения, дополнительного обследования и подбора схемы оптимального лечения на амбулаторном этапе реабилитации.

Ключевые слова: *ишемическая болезнь сердца, чрескожное коронарное вмешательство, периппроцедурное повреждение миокарда, МВ фракция креатинфосфокиназы, сердечный тропонин*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Источники финансирования

Авторы заявляют об отсутствии финансирования при проведении исследования

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Abstract

Background. Periprocedural myocardial injury (PMI) is an acute complication of percutaneous coronary interventions (PCI) in patients with stable coronary artery disease. Its frequency and relationship with the prognosis of the disease are especially important in elective interventions due to the low risk of ischemic events in this cohort of patients. However, according to the literature, there are significant differences in the criteria for PMI and type 4a myocardial infarction (MI), and, accordingly, their frequency and their prognostic value. **Aim.** To study the frequency and magnitude of PMI during elective PCI in terms of the level of periprocedural increase in cardiospecific biomarkers, as well as to determine the relationship of PMI with long-term adverse events in patients with chronic coronary artery disease. **Materials and methods.** A single-center open retrospective cohort study was conducted, which included 435 patients (367/84.4 % men, mean age 58.3±8.6 years) from the elective PCI registry. PMI was diagnosed with an increase in the level of creatine phosphokinase MB fraction (CK-MB) or or cardiac troponin I (cTn I) >1×99 percentile URL (Upper Reference Limit), while the level of increase in biomarkers >1, 2, 3, 4 or >5×99 percentile URL was recorded. An increase in biomarkers >5x99 URL percentile was assessed as a large PMI, and in the presence of clinical and imaging evidence of new loss of viable myocardium, as periprocedural MI type 4a. Depending on the level of periprocedural increase in biomarkers, the relative risk (RR) of developing long-term (within 5 years after index PCI) adverse cardiovascular events, death, as well as clinically significant bleeding and newly diagnosed malignant oncological diseases was calculated. In addition, the correlation between PMI and the above endpoints was summarized using Kaplan-Meier analysis. **Results.** The frequency of periprocedural PMI diagnosed by increased biomarkers >1×99 percentile URL was 40.2 %, >2×99 percentile URL — 9.7 %, >3×99 percentile URL — 6.7 %, >4×99 percentile URL — 4.8 %, >5×99 percentile URL — 3.5 %, type 4a MI — in 2 patients (0.46 %). An association of "major" PMI (>5x99 percentile URL) with cardiovascular complications within 3 years after elective PCI, including fatal ones, was revealed: for acute myocardial infarction (AMI), RR — 6.516, confidence interval (CI) [2.375-17.881]; for death from cardiovascular causes RR — 6.538, CI [1.695-25.227]. An association of "moderate" PMI (>3, but <5 ×99 URL percentile) with acute ischemic events within 3 years after elective PCI was shown: for AMI, RR was 4.073, CI [1.598 — 10.378]. An association of "minor" AKI (>1, but <3 ×99 URL percentile) with newly diagnosed malignant oncological diseases within 5 years after index PCI was revealed: RR 2.319; CI [1.248-4.310]. An association of late thrombotic events, such as stent thrombosis (index and re-interventions), stent occlusion (index and non-index) as a reason for re-intervention within 5 years after index PCI, was found with most PMI subgroups. Kaplan-Meier analysis of the dependence of clinically significant bleeding within 5 years after index PCI on the development of "moderate" PMI (p=0.003), as well as the association of non-cardiovascular death within 5 years after index PCI with "minor" PMI (p= 0.007). **Conclusion.** Registration of periprocedural increase in cardiac biomarkers should be carried out during planned PCI not only for the purpose of diagnosing and predicting acute and late ischemic events, but also for assessing the risk of developing stent occlusion, clinically significant bleeding and prognostically important comorbidities in the long-term (5-year) period in order to identification of groups of patients requiring active monitoring, additional examination and selection of an optimal treatment regimen at the outpatient stage of rehabilitation.

Key words: *ischemic heart disease, percutaneous coronary intervention, periprocedural myocardial injury, creatine kinase-MB, cardiac troponin*

Conflict of interests

The authors declare no conflict of interests

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sAMI — significant acute myocardial injury, IHD — ischemic heart disease, MI — myocardial infarction, CI-AKI — contrast-induced acute kidney injury, CSF — cardio-specific ferments, HB — heart bypass, mAMI — minor acute myocardial injury, LBO — lateral branch occlusion, AMI — acute myocardial infarction, ACS — acute coronary syndrome, ACVA — acute cerebrovascular accident, AMIn — acute myocardial injury, AKI — acute kidney injury, CVD — cardiovascular death, modAMI — moderate acute myocardial injury, CCS — chronic coronary syndrome, PCI — percutaneous coronary intervention, ecoCG — echocardiography, Adj OR — adjusted odds ratio, CABG — Coronary Artery Bypass Graft Surgery, CI — confidence interval, CPK-MB — MB fraction of creatine phosphokinase, cTn I — cardiac troponin I, cTnT — cardiac troponin T, KDIGO (Kidney Disease: Improving Global Outcomes) — a global non-profit organisation which develops and implements evidence-based clinical guidelines in kidney diseases, MACCE — major adverse cardiac or cerebrovascular event, PACE — patient centred endpoint, PMI — periprocedural myocardial injury, UDMI — universal definition of myocardial infarction, URL — upper reference limit, RR — relative risk

Introduction

Percutaneous coronary intervention (PCI) is gradually becoming the primary method of coronary artery revascularisation and is believed to be a safe procedure with a low level of serious procedural complications [1], which can be performed even in outpatient settings. PCI complications, for instance, acute stent thrombosis, coronary perforation, stroke and death, are critical, but rare. On the contrary, periprocedural acute myocardial injury (AMIn) is a common complication caused by distal embolisation, lateral occlusion, dissection, blood clot and no-reflow [2-4]. Although major AMIn are caused by technical procedural complications in PCI, a majority of patients with higher biomarker levels do not present with any signs of procedural complications [5]. According to heart magnetic-resonance tomography, there are two various locations of procedural myonecrosis, where the average area of infarction is approximately 5 % of the left ventricle weight; their incidence is similar: the first location is adjacent to the intervention site and is caused by lateral epicardial occlusion, whereas the second one is below the intervention site and is likely to be associated with impaired microcirculation [6].

Several academic groups presented their consensus-based expert definitions of periprocedural myocardial injury and infarction, including various biomarkers, such as MB fraction of creatine phosphokinase (CPK-MB) or cardiac troponin T (cTn), their thresholds and need/no need to perform heart imaging assessment, causing significant differences in terms of sensitivity and specificity of proposed diagnostic methods [7-10]. According to the selected definition, recent studies reported high variability in the incidence of periprocedural AMIn or periprocedural myocardial infarction (MI), which is also called type 4a MI [11, 12], which were [3, 9, 11] or were not associated [13, 14] with unfavourable ischemic events and long-term mortality.

Classification of threshold rise in biomarkers with or without additional criteria as a major AMIn or periprocedural MI has potential consequences for patients and healthcare providers, when it is used as a measure of the quality of care, and also for the development and adequate evaluation of new therapies in clinical trials. However, predictive power of an increase in cardio-specific ferments (CSF) in terms of recurrent cardiovascular events and long-term mortality is still discussed. Several studies demonstrated a close association between high CPK-MB after PCI with subsequent cardiovascular events [8]. Unfortunately, CPK-MB is no longer used in a majority of medical institutions. The fourth Universal Definition of the myocardial infarction working group [9] included cTn as a biomarker of choice, since it is a more specific and sensitive CSF for early detection of myocardial necrosis and, therefore, facilitates early diagnosis and triage of patients with acute chest pain. Thus, it has become the only biomarker which is routinely used in periprocedural settings. Higher sensitivity can help in identifying the tiniest differences in devices in clinical trials. However, attempts to understand the prognostic value of higher troponin levels associated with coronary surgery, either individually or together with other criteria, give contradicting results. Moreover, although a majority of researchers agree that the definition of periprocedural MI should be related to early and late mortality, it is still a matter of argument whether this relation is causal or just reflects predictive power of more severe atherosclerosis.

Patients with stable ischemic heart disease (IHD) referred to elective endovascular myocardial revasculisation make up the largest population undergoing this procedure. They have a relatively low risk of ischemic events as compared to other patients who need PCI, therefore, it is essential to assess the risk of periprocedural AMIn in this group of patients [15].

The objective of this study was to evaluate the incidence and extent of AMIn in elective PCI using periprocedural increase in CSF, such as MB fraction of creatine phosphokinase (CPK-MB) or cardiac troponin T (cTn), and also to determine the association between AMIn and late unfavourable events in patients with chronic ischaemic heart disease.

Materials and Methods

A single-centre open-label retrospective cohort study was conducted in 435 patients from the register of elective PCIs, performed in the Rehabilitation Department

of the Scientific Research Institute of Cardiology of the Tomsk National Research Medical Centre at the Russian Academy of Sciences. 367 subjects (84.4 %) were males; the patient mean age was 58.3 ± 8.6 years. The primary inclusion criterion was the availability of in-patient examination and therapy results, including changes in cardio-specific ferments. The exclusion criterion was urgent interventions related to the confirmed diagnosis of acute coronary syndrome (ACS). This study was approved by the Local Ethics Committee at the Scientific Research Institute of Cardiology of the Tomsk Scientific Centre at the Siberian Branch of the Russian Academy of Sciences (No. 126 dated December 14, 2008). The study was conducted in accordance with the Declaration of Helsinki. All patients included in the register provided their consent for long-term follow-up.

PCI was performed under the standard method. A drug-eluting stent, technique and the use of additional devices and drugs were selected by the operator. Before PCI, all patients received aspirin and P2Y12 inhibitor (clopidogrel or ticagrelor). During the procedure, unfractionated heparin or bivalirudin were used as anticoagulants.

The baseline characteristics of patients and performed index endovascular interventions are presented in Table 1.

Involvement of index areas of coronary arteries in the study group was in the form of atherosclerosis de novo — 360 (82.7 %) patients, stent restenosis and occlusion — 31 (7.1 %) patients, restenosis and occlusion of previously installed stents — 24 (5.5 %) patients. For 38 (8.7 %) patients, the index PCI was a second step in myocardial revascularisation.

Blood for CSF (CPK-MB and cTn I) was drawn at baseline, 12, 24, 48 hours after the intervention. CPK-MB was quantified photometrically using analyser Konelab 60i, cTnI — using ELISA system (Biomerica, USA). The 99th percentile of the upper reference level (URL) for CPK-MB was 25 U/L, for cTnI — 1.0 ng/mL. AMIn was diagnosed at CPK-MB or Tn I > 1 x 99th percentile of URL; an increase in CSF of >1, 2, 3, 4 or > 5 x 99th percentile of URL was observed.An increase in CSF of > 5 x 99th percentile of URL was suggestive of a major AMIn, and in the presence of clinical and imaging evidence of a new loss of a healthy myocardium — as periprocedural IM [7, 9]. The number of acute periprocedural complications classified as technical (close to the target coronary artery), local (at the site of peripheral arterial access) and clinical (chest pain, blood pressure response, cardiac rhythm disturbances, allergies, acute kidney injury (AKI) etc.) was recorded. Periprocedural AKI was diagnosed in accordance with KDIGO 2012 criteria [16].

Five years after the index PCI, disease outcomes were evaluated: a phone interview was conducted, and medical records were analysed. Primary endpoints were 5-year survival rate, incidence of cardiovascular deaths (CVD) and all-cause mortality. Secondary endpoints were acute periprocedural complications; diagnosed thrombosis and stent restenosis, including stents deployed during the follow-up period; incidence of adverse cardiovascular complications, such as acute myocardial infarction (AMI), acute coronary syndrome (ACS), acute cerebrovascular accident (ACVA); and the incidence of clinically significant bleeding and newly diagnosed malignancies. Combined endpoints were MACCE (major adverse cardiac or cerebrovascular events), including CVD, ACS and ACVA, as well as PACE (patient centred endpoint), including all-cause mortality, AMI and ACVA. Also, the number of repeated interventions in patients from the study groups one and five years after the index PCI was evaluated; and primary causes of the damage to areas of coronary arteries, which required repeated interventions, were analysed.

Continuous data were presented as mean ± standard deviation (M±SD), or as a median value with interquartile range (Me (Q1-Q3) (depending on the normality of distribution). Categorial data were given in percent. Differences in continuous data were verified using t-test for independent samples (normal data) or Mann–Whitney U test (asymmetric data). Similarly, paired variables were verified using t-test for paired samples (normal data) or Wilcoxon criterion (asymmetric data). Proportional differences in categorial data were compared using chi-square or Fisher's exact test (Fisher's exact test was used when the frequency of one or several cells was less than five). Relative risk (RR) was calculated using cross tables, with the calculation of 95 % confidence interval (CI). Correlation between AMIn and endpoints was summarised using Kaplan-Meier analysis. All probability values were two-sided; $p < 0.05$ was significant.

Results

The incidence of periprocedural AMIn diagnosed on the basis of increased CSF of > 1 x 99th percentile of URL was 40.2 %, > 2 x 99th percentile of URL — 9.7 %, > 3 x 99th percentile of URL — 6.7 %, > 4 x 99th percentile of URL — 4.8 %, > 5 x 99th percentile of URL — 3.5 %. Type 4a periprocedural MI (as per the 4-th universal definition of MI) [9] was diagnosed in 2 patients (0.46 %).

The incidence of major acute complications from the index PCI is presented in Figure 1.

According to angiography results performed within 5 years after the index PCI, obliterating atherosclerosis of coronary arteries de novo was diagnosed in 123 (29.4 %) patients. Subacute thrombosis (up to 30 days after PCI) of stents (index or deployed during repeated interventions) was observed in 5 (1.15 %) patients; late thrombosis (30 days to 1 year after PCI) — in 18 (4.1 %) patients; very late thrombosis (over one year after PCI) — in 22 (5.1 %) patients.

One year after the index PCI, haemodynamically relevant restenosis of index stents were recorded in 15 (3.5 %) patients, and index stent occlusions — in 5 (1.2 %) patients. Five years after the index PCI, their number was 30 (7.1 %) and 14 (3.3 %) patients, respectively.

Repeated interventions within a year after the index PCI were performed in 85 (19.9 %) patients, within five years — in 154 (36.5 %) patients. 18 (4.3 %) patients underwent heart bypass (HB) procedure and 139 (32.9 %) patients had endovascular interventions. Causes of repeated revascularisation procedures are presented in Figure 3.

Then, we evaluated the risk of late adverse events each year during 5 years after the index PCI, depending on the rate of periprocedural AMIn. The most relevant associations are given in Table 2.

Hence, we can see that AMIn > 1, but ≤ 3 x 99th percentile of URL is not associated with late ischemic complications of elective PCI, i.e. it is a minor event of increased CSF and is negligible for prognosis. Moderate AMIn (> 3, but ≤ 5 x 99th percentile of URL) is associated with ACS and AMI during 3 years after the index PCI. Major AMIn (> 5 x 99th percentile of URL) is associated not inly with late adverse ischemic events, but also with cardiovascular death during midterm follow-up. Therefore, we were able to single out three main groups of AMIn: minor (miAMIn), moderate (moAMIn) and major (maAMIn).

Then we compared survival curves using Kaplan–Meier method for primary and secondary endpoints (AMI, ACS, CVD, all-cause mortality, non-CDV, MACCE, PACE, clinically significant bleeding) which were plotted during the 5-year follow-up after the index PCI, depending on the AMIn group. The zero (baseline) group was a group of patients without periprocedural AMIn. The most important results of this analysis are presented in Figures 4 to 8.

Analysis results demonstrate that miAMIn is associated with non-cardiovascular death, modAMIn — with clinically significant bleeding, and maAMIn — with major adverse ischemic events during the late (5 years) period after the index PCI.

Discussion of Results

In this study, the incidence of periprocedural AMIn was 40.2 %, with an increase in CSF of > 1 × 99th percentile of URL, and 3.5 % with an increase of > 5 x 99th percentile of URL. Type 4a periprocedural MI (as per the 4-th universal definition of MI) [9] was diagnosed in 2 patients (0.46 %).

Despite the absence of any clear evidence, in accordance with the 2007 universal definition of myocardial infarction (UDMI), type 4a MI is diagnosed, when CSF values (cTn or CPK-MB) are 3 times higher than the respective URL [17]. This rigorous position was softened in the recent versions (UDMI versions 3 and 4) [7, 9]: type 4a MI is diagnosed, if cTn values are at least 5 times higher than 99th percentile of URL in patients with normal baseline cTn levels, or if there is a 20 % increase in patients with a high, but stable pre-PCI cTn level, associated with additional criteria, such as signs of a new myocardial infarction, or changes on ECG, imaging, or the presence of procedural complications, which cause reduction in coronary blood flow (coronary dissection, occlusion of a large epicardial artery or lateral occlusion/blood clot, impaired collateral blood flow, slow flow or no-reflow, distal embolisation). A post-procedure increase in CSF values without any additional criteria is required in order to diagnose procedural myocardial injury.

In 2013, the Society for Cardiovascular Angiography and Interventions (SCAI) released an expert consensus paper to argue the definition of periprocedural MI proposed by the UDMI working group [8]. Since there were no post-PCI threshold cTn values, the exceeding of which impacts the long-term prognosis, the paper favoured CPK-MB for the assessment of clinically significant post-PCI events. According to the document, clinically significant MI during post-PCI period was MI with an increase in CPK-MB values of > 10 × 99th percentile of URL, or a lower threshold (> 5 × 99th percentile of URL) in patients with new pathologic Q-waves in more than two adjacent leads (or a new stable post-PCI left bunch branch block).

In 2018, the Academic Research Consortium-2 (ARC-2) [18] published a consensus document, noting that over the past several years, cTn has been gradually replacing CPK-MB as a preferable biomarker of myocardial damage in clinical practice; and the authors proposed the cTn value of ≥ 35 × 99th percentile of URL as a reasonable value for PCI-associated periprocedural MI. Also, one more auxiliary criterion was required in addition to an absolute increase in cTn of ≥ 35 in order to confirm periprocedural MI (flow-limiting angiographic complications in a large epicardial vessel or a branch of > 1.5 mm in diameter, new procedure-associated significant Q-waves (or equivalent), or a significant new abnormal procedure-associated wall movement seen on echoCG).

Therefore, the incidence of periprocedural MI in endovascular myocardium revascularisation in patients with chronic coronary syndrome (CCS) varies depending on the definition and the cardiac biomarker used. According to UDMI version 3, the incidence of type 4a MI was 7 % when using highly sensitive cTnT [3] and 10 % when using cTnT [12], whereas when the SCAI guidelines were used to define periprocedural MI, the incidence was just 1.5–2.9 % [3, 11]. Recent literature demonstrates that among 4,404 patients with CCS who underwent PCI [19], periprocedural MI defined as per UDMI versions 3 and 4, ARC-2 и SCAI was recorded in 18.0 %, 14.9 %, 2.0 % and 2.0 % of patients, respectively.

Table 1. *Baseline Patient Characteristics, Coronary Lesions, and Index PCI*

Parameters	Group n=435
Age, years, M±SD (min-max)	58,3±8,6 (32-81)
Body mass index, Me (Q1-Q3)	28,6 (25,8-31,7)
Family history of cardiovascular diseases, n/%	198 / 46,2
Smoking, n/%	141 / 32,4
Diabetes mellitus, n/%	101 / 23,3
History of acute cerebrovascular accident, n/%	32 / 7,4
Arterial hypertension, n/%	391 / 89,9
Atrial fibrillation, n/%	72 / 16,6
Glomerular filtration rate (CKD-EPI) ≤ 60 ml/min/1.73 m^2, n/%	33 / 7,7
Chronic obstructive pulmonary disease, n/%	54 / 12,4
Multifocal atherosclerosis, n/%	92 / 21,2
Charlson Comorbidity Index, Me (Q1-Q3)	3 (2-4)
Previous myocardial infarction, n/%	309 / 71
Previous myocardial revascularization, n/%	134 / 30,8
– PCI	94 / 21,6
– CABG	31 / 7,1
– PCI + CABG	9 / 2,1
Chronic heart failure, NYHA functional class, n/%	
– 1	279 / 64,1
– 2	140 / 32,2
– 3	16 / 3,7
Number of affected areas of the coronary arteries, n/%	
– 1	116 / 26,7
– 2	155 / 35,6
– 3	164 / 37,7
Anatomy of a coronary lesion: n/%	
– Main left coronary artery	22 / 5,06
– Anterior descending artery	336 / 77,2
– Circumflex artery	269 / 61,8
– Right coronary artery	300 / 68,9
Index SYNTAX, Me (Q1-Q3)	11 (7-16,5)
Left ventricular ejection fraction according to ECHO-CG, %, Me (Q1-Q3)	62 (56-66)
n/% ≥ 50 %	386 / 89,15
40-49 %	35 / 8,08
< 40 %	12 / 2,8
Target vessel, n/% – Main left coronary artery	11 / 2,5
– Anterior descending artery	211 / 48,5
– Circumflex artery	145 / 33,3
– Right coronary artery	197 / 45,3
Intervention on chronic occlusion, n/%	110 / 25,3
Drug-eluting stents, n/%	565 / 86
Index stent length, мм, M±SD (min-max),	33±16,1(12-107)
Me (Q1-Q3)	28 (23-38)
Index stent diameter, мм, M±SD (min-max),	3,15±0,3 (2,5-5)
Me (Q1-Q3)	3 (3-3,5)
Complete revascularization, n/%	252 / 58,1
Volume of injected contrast, мл, Me (Q1-Q3)	250 (200-300)

Note: M±SD — mean ± standard deviation; min-max — minimum and maximum value of the parameters; Me (Q1-Q3) — median with interquartile range; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration is a research group with interests in measurement and estimation of GFR (Glomerular Filtration Rate); PCI — percutaneous coronary interventions; CABG — Coronary Artery Bypass Graft Surgery; NYHA — stage of chronic heart failure according to the functional classification of the New York Heart Association; Index SYNTAX — scale developed based on the results of the SYNTAX study (Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery); ECHO-CG — echocardiography

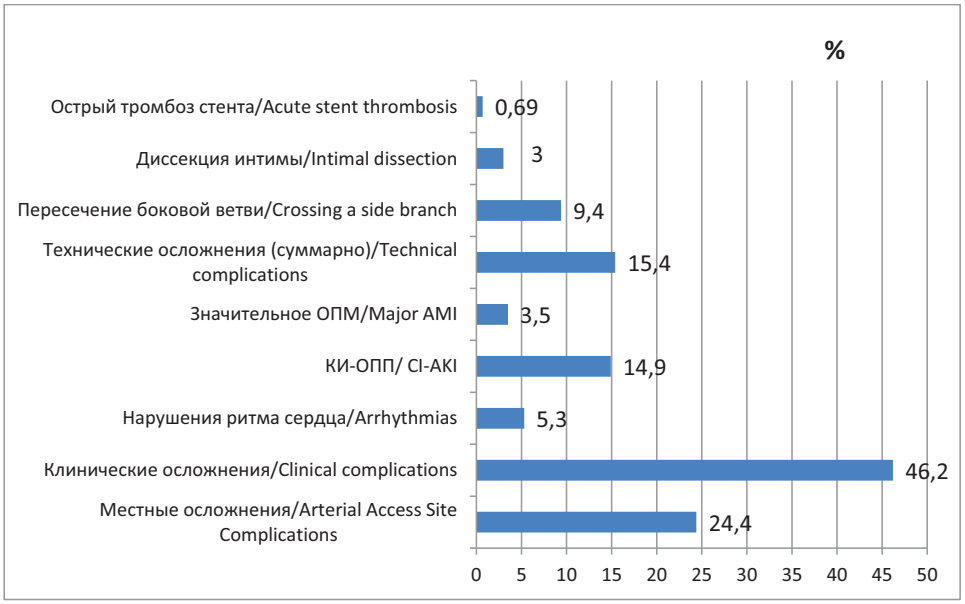

Figure 1. *Acute complications of index percutaneous coronary interventions*

Note: AMI — acute myocardial injury; CI-AKI — contrast-induced acute kidney injury

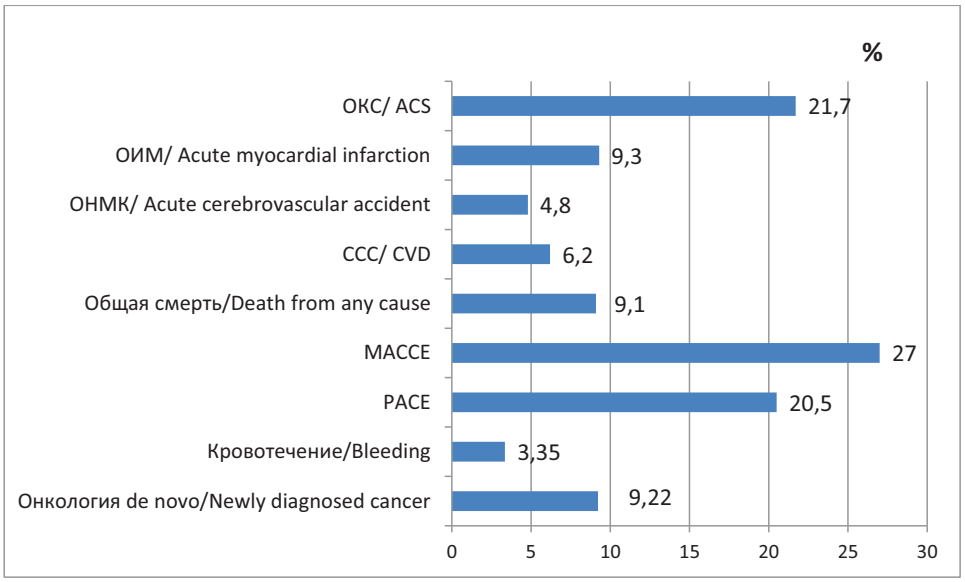

Figure 2. *Long-term adverse events within 5 years after index percutaneous coronary interventions*

Note: ACS — acute coronary syndrome; CVD — death from cardiovascular causes; MACCE — Major Adverse Cardiac or Cerebrovascular Events; PACE — patient centered endpoint.

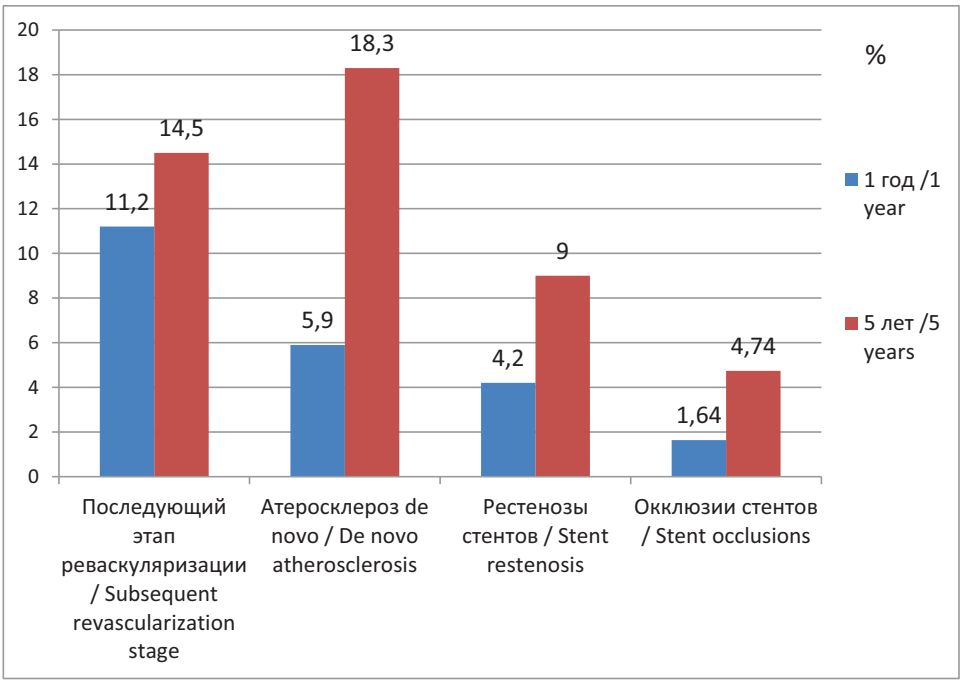

Figure 3. *Causes of repeat revascularizations 1 year and 5 years after index PCI*

Table 2. *The risk of development of long-term adverse events depending on the magnitude of acute periprocedural myocardial injury during elective PCI*

	RR	CI	S	P
PMI >5x99 percentile URL				
MACCE within 3 years after index PCI	4,486	[1.680-11.977]	0,501	0,006
CVD within 3 years after index PCI	6,538	[1.695-25.227]	0,689	0,046
AMI within 3 years after index PCI	6,516	[2.375-17.881]	0,515	0,003
PACE within 3 years after index PCI	3,850	[1.371-10.809]	0,527	0,024
Thrombosis of stents (index and non-index) during 5 years of follow-up	3,158	[1.307-7.629]	0,450	0,037
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	5,143	[1.702-15.539]	0,564	0,024
PMI >4x99 percentile URL				
MACCE within 4 years after index PCI	2,359	[1.009-5.517]	0,433	0,045
AMI within 3 years after index PCI	4,073	[1.598-10.378]	0,477	0,011
PACE during 5 years of follow-up	2,046	[1.154-3.627]	0,292	0,042
Thrombosis of stents (index and non-index) during 5 years of follow-up	2,658	[1.165-6.062]	0,421	0,042
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	5,482	[1.659-18.110]	0,610	0,024
Second-stage revascularization as a reason for re-intervention within 1 year after index PCI	2,907	[1.404-6.021]	0,372	0,017
PMI >3x99 percentile URL				
AMI within 3 years after index PCI	2,715	[1.113-6.622]	0,455	0,040
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	3,657	[1.314-10.183]	0,522	0,032
Second-stage revascularization as a reason for re-intervention within 1 year after index PCI	2,433	[1.203-4.919]	0,359	0,038
PMI >2x99 percentile URL				
Occlusion of stents (index and non-index) as a reason for re-intervention during 5 years of follow-up	4,042	[1.331-12.273]	0,567	0,029
PMI >1x99 percentile URL				
Newly diagnosed malignant oncological diseases during 5 years of follow-up	2,319	[1.248-4.310]	0,316	0,0062
Second-stage revascularization as a reason for re-intervention within 1 year after index PCI	1,933	[1.137-3.323]	0,274	0,0059

Note: RR — relative risk; CI — confidence interval; S — standard error of relative risk; p — significance level; PMI — periprocedural myocardial injury; URL — upper reference limit; MACCE — Major Adverse Cardiac or Cerebrovascular Events including cardiovascular death, acute coronary syndrome and acute cerebrovascular accident; CVD — death from cardiovascular causes; AMI — acute myocardial infarction; PCI — percutaneous coronary interventions; PACE — patient centered endpoint, including death from any cause, acute myocardial infarction and acute cerebrovascular accident.

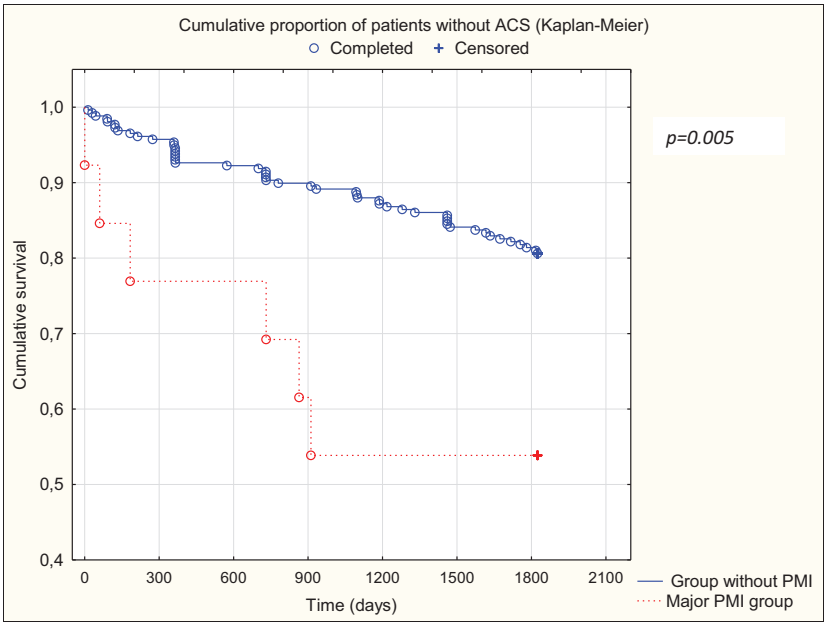

Figure 4. *Kaplan-Meier curves for new cases of ACS up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «major» PMI group (>5×99 percentile URL), p=0.005*

Note: ACS — acute coronary syndrome; PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

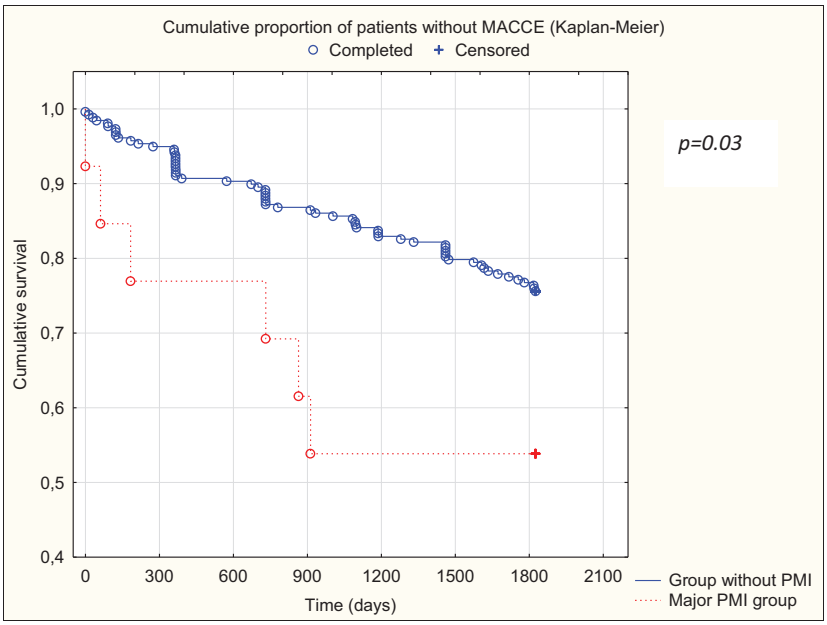

Figure 5. *Kaplan-Meier curves for new cases of MACCE up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «major» PMI group (>5×99 percentile URL), p=0.03.*

Note: MACCE — Major Adverse Cardiac or Cerebrovascular Events including cardiovascular death, acute coronary syndrome and acute cerebrovascular accident; PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

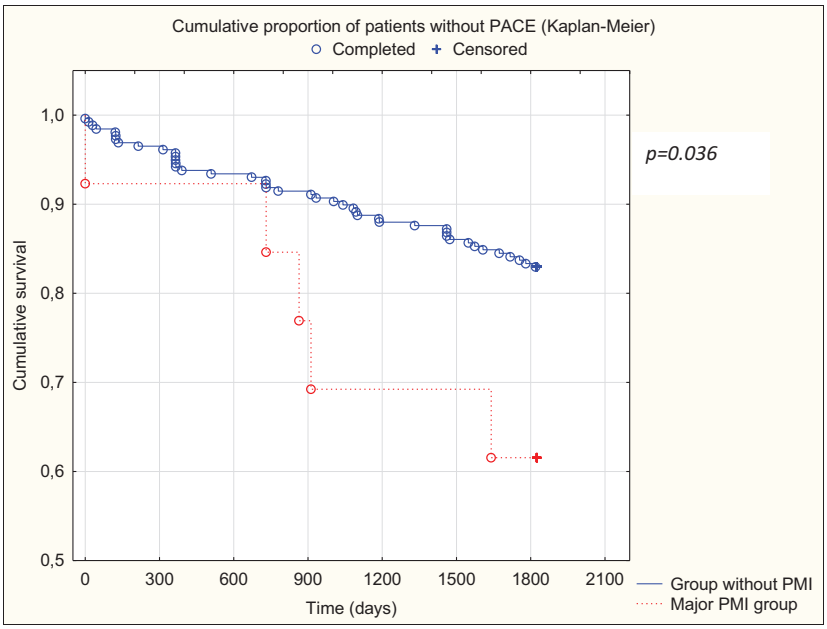

Figure 6. *Kaplan-Meier curves for new cases of PACE up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «major» PMI group (>5×99 percentile URL), p=0.036.*

Note: PACE — patient centered endpoint, including death from any cause, acute myocardial infarction and acute cerebrovascular accident; PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

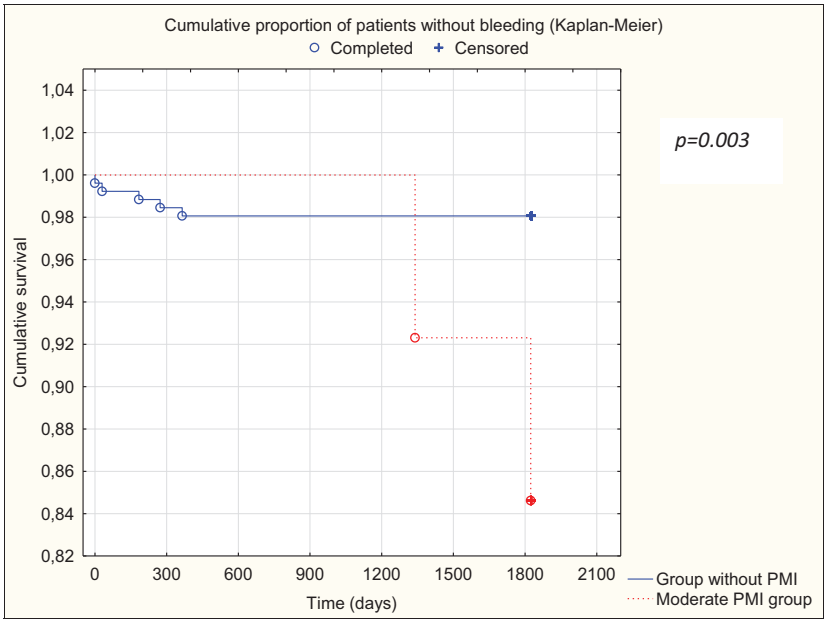

Figure 7. *Kaplan-Meier curves for clinically significant bleeding up to 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with the «moderate» PMI group (>3, but ≤5 ×99 percentile URL), p=0.003.*

Note: PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

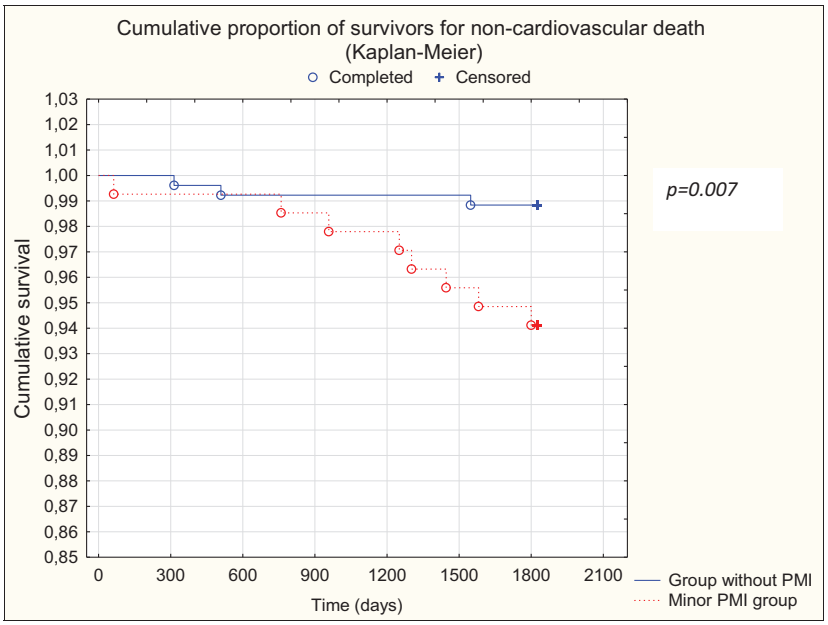

Figure 8. *Survival curves for non-cardiovascular death at 5 years after index PCI in 2 groups: comparison of no cardiac biomarkers elevation group (group 0) with «minor» PMI group (>1 but ≤3 ×99 percentile URL), p=0.007.*

Note: PCI — percutaneous coronary intervention; PMI — periprocedural myocardial injury; URL — upper reference limit

Similar to type 4a MI, there are various definitions of periprocedural myocardial injury in patients with CCS who underwent PCI. UDMI version 4 [9] defines periprocedural AMIn as any post-PCI increase in cTn of > 1 × 99th percentile of URL in patients with normal baseline values (before PCI). According to ARC-2, a major periprocedural myocardial injury is diagnosed at significantly higher increase in post-PCI cTn (≥ 70 × 99th percentile of URL) [18]. Predictably, the incidence of periprocedural myocardial injury is also dependent on the definition and the cardiac biomarker used: 2.9 % as per ARC-2 criteria [11] — 20 to 43 % for cardiac troponin T (cTnT) [20], 14 to 52 % for cTnI [21] and 78 to 85 % for highly sensitive cTnT [22].

Thus, currently there is no consensus on the definition of periprocedural myocardial infarction and injury; the definitions by SCAI and ARC-2 set forth significantly higher thresholds for post-PCI CSF increases as compared to UDMI version 4.

According to UDMI version 4 [7], one of the key criteria for diagnosing type 4a MI in patients with CCS after PCI is new myocardial ischemia seen on coronary angiography scans, suggestive of periprocedural flow-limiting complications, such as coronary dissection, occlusion of a large epicardial artery or lateral occlusion/blood clot, impaired collateral blood flow, slow flow or no-reflow, distal embolisation. ARC-2 [18] presented detailed criteria for the definition of flow-limiting coronary angiographic complications in patients undergoing PCI and suspected periprocedural MI.

According to study results, the key causes of periprocedural AMIn and type 4a MI are lateral branch

occlusion (LBO) and distal embolisation. LBO is the most common cause of type 4a MI in patients with CCS undergoing PCI [23, 24], and its effects on the intervention outcome depend on the size of occluded lateral branches. The incidence of LBO can be associated with the stent type selected, type of procedure (e.g. chronic total occlusion, rotational atherectomy, etc.) and target segment — mid-LAD with the highest density of lateral branches [25]. Distal coronary embolisation with an intracoronal clot and atheromatous material can result in no-reflow/slow-flow during PCI in patients with CCS. It has been shown that, as of now, embolisation cannot be completely prevented, despite the use of anticoagulant and antiplatelet adjunctive therapy and the use of aspirating or protective devices [26].

However, according to the modern idea, PCI complications seen during angiography are not always associated with higher cardiac biomarker levels, and increased CSF can be caused by plaque degradation and local vascular damage without any apparent coronary angiographic complications [10]. Intravascular imaging methods can be used as an addition to coronary angiography in order to better understand the pathophysiology of PCI complications [27].

In our study, technical complications confirmed by angiography results, including acute stent thrombosis (0.7 %), intima dissection (3 %), lateral branch transfixion (9.4 %), etc., were observed in 15.4 % of patients. Significant AMIn of > 5 × 99th percentile of URL was recorded just in 3.5 % of patients.

Besides, chronically elevated highly sensitive cTnT/I can be seen in 30 % of patients due to comorbidities and risk factors, such as chronic kidney disease, diabetes mellitus, structural heart diseases, skeletal muscle diseases, malignancies and elderly age [28, 29].

A recently published meta-analysis demonstrated that higher post-PCI CPK-MB and cTn levels were independently associated with all-cause mortality within one year; and the following combinations of an increase in CSF were significant for the outcome: CPK-MB ≥ 5 and cTn ≥ 35, CPK-MB ≥ 10 and cTn < 70, and CPK-MB ≥ 5 and cTn ≥ 70 × 99th percentile of URL [11].

Silvain J. et al. (2021) [30] also conducted a pooled analysis to assess increased post-PCI cTn levels (they analysed a pool of studies other than a study by Garcia-Garcia HM et al. (2019) [11]) in 9,081 patients with CCS who underwent PCI. The incidence of type 4a MI in a group of 2,316 patients with CCS who underwent PCI and had normal baseline cTn values, was 12.7 %, and its presence was a strong independent predictor of all-cause death in a year (adjusted odds ratio (Adj OR) 3.21, 95 % CI [1.42–7.27], p = 0.005). These results confirm predictive power of the cuttoff threshold of > 5 × 99th percentile of URL in elevated post-PCI cTn, selected by UDMI version 4 for the definition of type 4a MI. The incidence of periprocedural myocardial injury (seen as elevated post-PCI cTn of > 1 × 99th percentile of URL as per UDMI version 4) in patients with CCS and normal baseline cTn values was 52.8 % (79.8 %, if highly sensitive cTn was used); however, periprocedural myocardial injury was not associated with all-cause death during one year [30]. Besides, a study by Silvain J. et al. demonstrated that elevated post-PCI cTn of > 3 × 99th percentile of URL was also an independent predictor of all-cause death within a year in patients with ACS who underwent PCI, suggesting that even a slight increase in post-PCI cTn has predictive power.

On the contrary, in a consensus document published in 2021 by the working group of the European Society of Cardiology, patients with elevated post-PCI cTn levels of > 1, but ≤ 5 × 99th percentile of URL were found to have a minor periprocedural myocardial injury. A significant prognostic or major periprocedural myocardial injury (in the consensus paper, it is elevated post-PCI cTn of > 5 × 99th percentile of URL) was recorded in 18.2 % of patients with normal baseline cTn values and was an independent predictor of all-cause damage one year later (Adj OR 2.29, 95 % CI [1.32–3.97], p = 0.004) [10].

A recent study by Ueki Y. et al. (2022) [19] evaluated AMIn in accordance with the criteria set forth in UDMI version 3 and 4, ARC-2 and SCAI using highly sensitive cTn in patients with stable coronary disease who underwent PCI and were included in the Bern PCI Register. This analysis is the first detailed evaluation of up-to-date definitions of AMIn in patients undergoing elective PCI, which is based on routine measurements of highly sensitive cTn and routine assessment of additional criteria in a large real-life population of PCI patients. The primary endpoint was cardiac death after one year. In patients with AMIn, one year mortality in accordance with UDMI version 3, UDMI version 4, ARC-2 and SCAI was 2.9 %, 3.0 %, 5.8 % and 10.0 %, respectively. ARC-2 (hazard ratio (HR): 3.90; 95 % CI: 1.54–9.93) and SCAI (HR: 7.66; 95 % CI: 3.64–16.11) criteria were more relevant in comparison with UDMI version 3 (HR: 1.76; 95 % CI: 1.04–3.00) and UDMI version 4 (HR: 1.93; 95 % CI: 1.11–3.37) for cardiovascular death within one year after the index PCI.

Therefore, a majority of published studies evaluated the association between AMIn and 1-year disease outcome after elective PCI procedures; and there is no general expert consensus on this matter. Nevertheless, the clinical significance of diagnosing maAMIn is stated in the current guidelines on endovascular myocardial revascularisation.

We have evaluated the incidence and association between AMIn and midterm and late adverse events 1–5 years after index endovascular intervention for chronic coronary syndrome and found out an association between a major AMIn and late post-PCI cardiovascular complications, including fatal ones. At the same time, we have demonstrated the predicative power of moderate

Table 3. *Association of periprocedural myocardial injury with complications and patient survival within 5 years after elective PCI*

Name	Level of increase in cardiac biomarkers	Association with outcomes
1. **Minor** periprocedural myocardial injury	>1, but ≤3 ×99 percentile URL	– no association with long-term ischemic complications and cardiovascular death after elective PCI; – there is an association with non-cardiovascular death in the long-term (5-year) period; – there is an association with newly diagnosed malignant cancers within 5 years after the index PCI; – there is an association with index stent occlusions as a cause of re-interventions during 5 years of follow-up;
2. **Moderate** periprocedural myocardial injury	>3, but ≤5 ×99 percentile URL	– there is an association with acute ischemic events (ACS, AMI, MACCE) 3 years after the index elective PCI; – there is an association with clinically significant bleeding within 5 years after elective PCI; – there is an association with stent thrombosis (index and non-index) and index stent occlusions as a cause of re-interventions during 5 years of follow-up;
3. **Major** periprocedural myocardial injury	>5 ×99 percentile URL	– there is an association with long-term ischemic events, as well as cardiovascular death within 3 years after the index PCI.

Note: PCI — percutaneous coronary intervention; URL — upper reference limit; ACS — acute coronary syndrome; AMI — acute myocardial infarction; MACCE (Major Adverse Cardiac or Cerebrovascular Events) — a composite endpoint including cardiovascular death, acute coronary syndrome and acute cerebrovascular accident.

and minor AMIn in relation not only to cardiovascular events, but also to clinically significant bleeding, as well as non-cardiovascular death and newly diagnosed malignancies during 5 years after elected PCI (Table 3).

Conclusions

Periprocedural increase in CSF values should be recorded during elective PCI not only for diagnosis and prediction of acute and late ischemic events, but also for evaluation of the risk of stent occlusion, clinically significant bleeding, significant predicative comorbidity and death during the late (5-year) period in order to identify groups of patients requiring active follow-up, additional observation and selection of an optimal outpatient rehabilitation regimen.

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Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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Repin A.N. (ORCID ID: https://orcid.org/0000-0001-7123-0645): scientific consultation, manuscript text editing

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ПРЕДИКТИВНАЯ ДИАГНОСТИКА ФАКТОРОВ РИСКА РАЗВИТИЯ САРКОПЕНИИ У ПОЖИЛЫХ ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА

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Predictive Diagnostics of Risk Factors for the Development of Sarcopenia in Early Patients with Type 2 Diabetes

Резюме

Обоснование. Своевременная диагностика саркопении у пациентов с нарушениями углеводного обмена позволит повысить качество и продолжительность жизни. **Цель:** проанализировать наличие основных факторов риска развития саркопении у пациентов с пресаркопенией и СД 2 типа. **Материалы и методы.** Участвовало 82 пациента с СД 2 типа, которые были разделены на 2 группы: с пресаркопенией и группу сравнения. Проведены: анкетирование с помощью опросников (краткая форма оценки здоровья (Health Status Survey (SF-36)), оценка саркопении и качества жизни (Sarcopenia and Quality of Life — SarQoL), сила, помощь при ходьбе, подъем со стула, подъем по лестнице и падения — Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls — SARC-F), определения физической активности (International questionnaire on physical activity — IPAQ), оценка скорости ходьбы, динамометрия, биоимпедансометрия, анализ лабораторных показателей. Статистическая обработка проводилась с помощью программного обеспечения Statistica IBM (русская версия). Достоверными различия считались при p <0,05. **Результаты.** Чаще пациентов с пресаркопенией беспокоят онемение нижних конечностей, головокружение, снижение памяти, лабильность артериального давления, одышка при физической нагрузке. В обеих группах регистрировалось ожирение I ст. В основной группе снижена скорость ходьбы — 1,63 м/сек, по сравнению с группой сравнения — 1,25. Показатели гликемии у лиц с пресаркопенией выше -7,6 ммоль/л, чем в группе сравнения — 7,2. Уровень физической активности в основной группе ниже и составил 40 мин/ в сутки, а также снижен общий показатель качества жизни до 34,99. Пациенты с пресаркопенией чаще принимают: бигуаниды — 46 %, иНГЛТ-2 — 27 %, препараты сульфанилмочевины — 26 %, 46 % получают инсулинотерапию (p<0,05). В группе с пресаркопенией снижена жировая масса, площадь и процентное содержание висцерального жира по сравнению с группой сравнения. Индекс аппендикулярной мускулатуры в 1-ой группе составил 7,0 кг/м², во второй 7,5 кг/м². В 1-ой группе снижено содержание протеинов, минералов и общего количества воды. В лабораторных показателях в группе с пресаркопенией зарегистрированы дислипидемия, гипокальциемия, более высокие значения HbA1c, по сравнению с группой сравнения. **Заключение.** Для первичного скрининга саркопении у больных с СД 2 типа можно использовать динамометрию и биоимпедансометрию. Поддержание целевых параметров гликемии, коррекция дислипидемии, компенсация недостатка витамина Д и гипокальциемии способствует сохранению мышечной массы и силы.

Ключевые слова: *пресаркопения, биоимпедансометрия, сахарный диабет 2 типа, кистевая динамометрия*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Objective. **Materials and methods:** 82 patients with type 2 diabetes mellitus participated, which were divided into 2 groups: probable sarcopenia and comparison groups. Conducted: questionnaire surveys (Health Status Survey (SF-36)), Sarcopenia quality and life assessment (SarQoL)), strength, assistance with walking, getting up from a chair, climbing stairs and falling — Strength, Assisted walking, getting up from a chair, Climbing stairs and Falls (SARC-F)), assessment of walking speed and physical activity, carpal dynamometry, bioimpedancemetry, analysis of laboratory parameters. **Results**: the difference between the conducted questionnaires is statistically insignificant. According to bioimpedansometry, obesity of the 1st degree was recorded in the lesions. In the group with presarcopenia, the main decrease in body composition parameters decreases. In addition, in the main group, the rate of intake is reduced, and decompensation of carbohydrate and lipid metabolism occurs. Differences were considered significant at $p < 0.05$. **Conclusion.** Dynamometry and bioimpedance can be used for primary screening of sarcopenia in patients with type 2 diabetes. Maintaining the main indicators of glycemia, correction of dyslipidemia, compensation for obesity D and hypocalcemia of obesity in muscle mass and mass.

Key words: *presarcopenia, bioimpedancemetry, type 2 diabetes mellitus, hand dynamometry*

Conflict of interests

The authors declare no conflict of interests

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DM — diabetes mellitus, EWGSOP- European Working Group on Sarcopenia in Older People, SarQoL– Sarcopenia and Quality of Life, SARC-F — Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls, SF-36 — Health Status Survey

Introduction

Type 2 diabetes mellitus (DM) is one of the most common chronic non-infectious diseases. Over the past decade, the number of patients with DM globally grew 2-fold; by the end of 2021, the number of patients with this condition exceeded 537 million people. According to forecasts by the International Diabetes Federation, by 2030, the number of patients with DM will reach 643 million people, by 2045 — 784 million people [1]. A majority of patients with type 2 DM have obesity or overweight [2]. In the results of the study titled NATION (2013–2015), the highest incidence of type 2 DM was recorded at the age of 65–69 years old [3]. Also, type 2 DM is associated with a high risk of cardiovascular disease and sarcopenia. With age, elderly people have less muscle bulk and strength. This condition is called sarcopenia and is more common in patients with type 2 DM [4]. Insulin resistance, dyslipidemia, hyperglycemia, oxidative stress contribute to faster reduction in muscle bulk, causing reduction and worsening of the quality of life of elderly people [4]. Diabetic polyneuropathy can also cause reduced muscle bulk and functions as a result of a reduced number of functional motor neurons and impaired coordination of muscle contraction. It has been found out that patients with type 2 DM and diabetic polyneuropathy have progressing reduction in muscle strength of lower limbs, whereas patients without diabetic polyneuropathy had their muscle strength preserved [5]. Nevertheless, currently available information whether diabetic polyneuropathy or age-associated reduction in the number of motor neurons have higher impact on reduced muscle strength is controversial.

Development and progression of sarcopenia in type 2 DM can cause vitamin B_{12} deficiency. Vitamin a B_{12} deficiency results in neurogenic disorders including muscle weakness, which increases the risk of falls. Approximately 25 % of cases of reduced vitamin B_{12} levels are accounted for metformin therapy [6]. However, metformin has a reliable evidence base and is a drug of choice in patients with type 2 DM for insulin resistance reduction [7].

Data on the incidence of sarcopenia are controversial, since there are no uniform diagnostic criteria. The results of a study conducted in the Moscow Region during examination of patients with type 2 DM of middle and elderly age (n = 42, mean age: 64 [60;70] years old) with the use of X-ray densitometry showed that 97.6 % of patients met

the criteria for sarcopenia [8]. In another clinical trial conducted at the Federal Bureau for Medical and Social Assessment of the Ministry of Labour of Russia in and for Moscow, among 66 subjects over 50 years of age, 17 % were patients with sarcopenia, the screening of which used handgrip test, Short Physical Performance Battery (SPPB) and bioimpedansometry [9]. Based on the results of several large studies in a large population, Korean and Japanese researches found out that the incidence of sarcopenia in patients with DM is 15.7 % [4]. According to the latest guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP, 2019), handgrip test, Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls (SARC-F) questionnaire, 4 m walking test, appendicular mass calculations used X-ray densitometry or bioimpedansometry are optimal for initial sarcopenia screening [10].

In the revised guidelines (EWGSOP2, 2019), low muscle bulk is the primary parameter of sarcopenia. Potential sarcopenia (pre-sarcopenia) is diagnosed when muscle strength is reduced. Sarcopenia is confirmed if muscle bulk is inadequate. Sarcopenia is considered severe in the presence of low muscle bulk, strength and poor function [10].

There are a number of instrumental methods to diagnose reduced muscle bulk, such as magnetic resonance imaging (MRI), computer tomography (CT), ultrasound, X-ray densitometry, bioimpedansometry. Each method has its advantages and disadvantages. In clinical practice, X-ray densitometry and bioimpedansometry are more common. The main parameters included in X-ray densitometry are assessment of bone mineral density, mineral ratio and lean muscle bulk [11]. It has been established that, unlike total muscle bulk, the results of appendicular mass measurements using densitometry significantly correlate with skeletal muscle CT and MRI results [11]. However, densitometry has its drawbacks: mean values used as control values can differ from mean values in the general population, depending on the region and ethnicity. Besides, it is impossible to identify adipose infiltration inside and around muscle fibres, hence the diagnostic value of densitometry in diagnostics of sarcopenia is reduced drastically [11]. The use of bioimpedansometry to verify reduced muscle bulk has been studied for over 10 years. It has been demonstrated that under standard conditions, bioimpedansometry results have positive correlation with MRI forecasts. Thus, bioimpedansometry can be used instead of densitometry for screening of reduced muscle bulk [11]. According to available information, bioimpedansometry is one of the most accessible methods in clinical medicine for the assessment of the compositional body analysis in elderly patients with type 2 DM [12].

A combination of reduced muscle bulk and strength in patients with DM reduces life expectancy [13]. Sarcopenia in patients with DM is associated with a higher frequency of hospitalisations and cardiovascular accidents [14]. Insulin resistance and oxidative stress are components of the pathophysiological foundation of sarcopenia [15]; on the other hand, they are associated with development of endothelial dysfunction [16], chronic inflammation [17] and lipid infiltration in muscles in DM patients.

The objective of the study is to analyse the presence of the primary risk factors of sarcopenia in patients with pre-sarcopenia and type 2 DM.

Materials and Methods

Study designs: cross-sectional observational comparative study. The study was conducted in accordance with the clinical practice standards and Declaration of Helsinki. The study protocol was approved by the Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Siberian State Medical University of the Ministry of Health of the Russian Federation No. 8888 dated November 29, 2021. All in all, the study included 82 patients with type 2 DM aged 50 to 85 years old (41 men, 41 women, mean age: 69 [67.5;72] years old), who signed an informed consent form and did not meet any exclusion criteria. DM was diagnosed on the basis of criteria set forth in the Algorithm of Specialised Care for Patients with Diabetes Mellitus (2021) [1]. Exclusion criteria were: decompensated cardiovascular, respiratory, musculoskeletal, GIT diseases, stage 4–5 chronic kidney disease (CKD), a history of limb amputation, vitamin B12 deficiency, alcohol abuse, cardiac pacemaker, large metal prosthetic devices or structures, marked lymphostasis of lower limbs.

Potential sarcopenia (pre-sarcopenia) was diagnosed in accordance with the algorithm recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2, 2019), with muscle bulk reduction of less than 27 kg in men and less than 16 kg in women [10]. Unlike the EWGSOP2 2019 algorithm, handgrip test and not SARC-F [18] was used for group differentiation during initial screening.

Patients were divided into two groups: the main group (reduced muscle bulk) — 55 patients (27 men, 28 women, mean age: 71 [67–71] years old) and control group (no reduction in muscle bulk and strength) — 27 patients (14 men, 13 women, mean age: 67 [68–73] years old). The protocol stipulated measurement of hand strength using handgrip test: recording of the three highest values obtained with both hands in isometric contraction (the standard position was sitting, with elbow extended at 90°). The quality of life was assessed using SF-36 (Health Status Survey, 2006) and SarQol (Sarcopenia and Quality of Life, 2019); for sarcopenia severity, SARC-F (Strength, Assistance with walking, Rise from a chair, Climb stairs and Falls, 2018) was used. The

degree of physical activity was assessed with the help of questionnaires (Physical Activity Questionnaire (PAQ 23), 2013) [19], recording the time of physical activity (min/day) and 4 m walking test (severe sarcopenia was diagnosed if the speed reduced by ≤ 0.8 m/s) [10]. All subjects underwent bioimpedansometry at Inbody 770 (Korea) with the body mass index assessment, analysis of extracellular and intracellular fluid, total body water, body fat, fat mass percent, visceral fat area, and muscle bulk. The obtained data were used to calculate the appendicular index of the skeletal mass as the ratio between lean muscle mass and height in square meters. According to EWGSOP (2019), low muscle bulk was skeletal mass index of < 7.0 kg/m^2 for men and < 5.5 kg/m^2 for women [10]. Carbohydrate metabolism compensation was assessed on the basis of glycaemia (blood biochemistry). Laboratory blood parameters (total protein, albumin, AST (aspartate aminotransferase), ALT (alanine aminotransferase), total bilirubin, urea, uric acid, creatinine, AP (alkaline phosphatase), fats (cholesterol, triglycerides, high-density lipoproteins (HDLP), low-density lipoproteins (LDLP)) were assessed.

Statistical data processing was performed using IBM SPSS Statistics 23 (Russian version 23.0). Parameters were assessed for correspondence to normal distribution; and Shapiro-Wilk's test was used. Data are presented as the median value with interquartile range Me [Q25; Q75] for parameters with distribution other than normal. Categorical variables are presented as absolute values and percent. Qualitative parameters of groups were compared using chi square (χ^2); for quantitative comparison of samples, one-way analysis of variance was used. Correlation analysis was performed using Spearman's or Pearson's test, depending on the distribution of parameters. Results with $p < 0.05$ were statistically significant.

Results:

When medical records of patients were evaluated, patients from the group of potential sarcopenia (n = 55) significantly more often complained of numbness in their lower limbs — 39 (70 %), dizziness — 18 (33 %), difficulty remembering — 13 (24 %), unstable blood pressure — 18 (33 %), dyspnoea during physical activities — 17 (31 %) vs. controls (p = 0.0001).

The characteristics of subjects are presented in Table 1.

When evaluated, BMI of patients in the groups differed: stage I obesity was recorded in 30 (65.2 %) patients, stage II — in 6 (13 %) patients in the main group; in the control group, stage I obesity was observed in 18 (72 %) of subjects and stage II obesity was recorded in 7 (28 %) patients. Also, patients in the main group had weaker muscle function and fewer points in the physical activity test.

Patients in the main group demonstrated reduced walking speed vs. controls. The main group had statistically significant signs of reduced daily physical activity (PAQ 23).

There were no statistically significant differences in SARC-F (Figure 1) and SF-36 (Figure 2) between groups (Figure 1). The low sensitivity of these questionnaires is likely to be related to the small number of patients in the study, elderly age, chronic comorbidities in both groups (Table 2).

When comorbidities in patients with sarcopenia were assessed, thyroid pathologies, a history of cancer, chronic anaemia and DM complication — polyneuropathy ($p \le 0.05$) were significantly more common (see Table 2).

Analysis of SarQol results (Table 3) did not show any statistical significance.

According to medical records, subjects of the study were taking the following medications (Table 4). Patients with pre-sarcopenia took insulins, as well as incretin tablets (dipeptidyl peptidase inhibitors) more often than controls. The frequency of the use of sulfonylureas was similar in both groups. Sodium-glucose linked cotransporter 2 inhibitors (SGLC-2), biguanides were used more often in patients with type 2 DM from the control group.

Table 5 presents the information on the patients' body composition based on bioimpedansometry results. Analysis of data shows reduced fat mass in the main group vs. controls. Also, in the group of pre-sarcopenia, skeletal muscle mass and appendicular muscle index are below the normal value.

Laboratory data (Table 6) show that the patients in the main group had lower total protein, ALT and calcium levels ($p \le 0.05$).

Of note, in a majority of cases, patients with pre-sarcopenia had antihypertensives, whereas in the control group, menopausal hormone therapy, multivitamins, including vitamin D (Table 7), were more common.

The correlation analysis demonstrated that potential sarcopenia is associated with higher fat mass ($r = 0.526$, $p = 0.001$) and BMI ($r = 0.587$, $p = 0.001$), reduced skeletal muscle mass ($r = -0.296$, $p = 0.007$).

Discussion

Improved medical care resulted in a higher number of diagnostic methods to screen pre-sarcopenia and risk factors in patients with impaired carbohydrate metabolism; however, currently, there is no unified model for verification of reduction in muscle bulk and strength [20]. In this paper, SARC-F did not show any statistical significance of results, which can cause inability to identify reduced muscle bulk. SF-36 score in the groups did not have any statistical significance. Since there is no consensus on its interpretation among researchers, very often results are controversial and can require its use together with physical examination results [21, 22].

Table 1. Characteristics of the main and comparison groups

Parameters	Main group (n=55)	Control group (n=27)	p
Age, years	71 [67-71]	67 [68-73]	0,771
Hight, centimeters	161 [159- 163]	168[164,3- 171]	0,384
Weights, kilograms	81 [76-86]	93 [87-99]	0,198
Waist circumference, cm	104 [98-114]	110 [104-115]	0,490
Hip circumference, cm	110 [105-120]	112 [107-120]	0,329
Body mass index, kg/m^2	31,1 [29,4-32,9]	33,2 [31,2-35,1]	0,011
Waist circumference to hip circumference ratio	0,93[0,93- 0,94]	0,97[0,96-0,97]	0,231
Right arm dynamometry, kg	13 [11-15]	23 [19-27]	0,003
Left arm dynamometry, kg	12 [10-14]	22 [19-25]	0,002
Walking speed, m/s	1,63 [1,47-1,79]	1,25 [1,13 — 1,37]	0,090
Glycemia, mmol/L	7,6 [7,0- 8,1]	7,2 [6,6-7,7]	0,573
Physical activity, points	40 [34- 45]	61 [45-77]	0,040

Note: Data are presented as median with interquartile range.

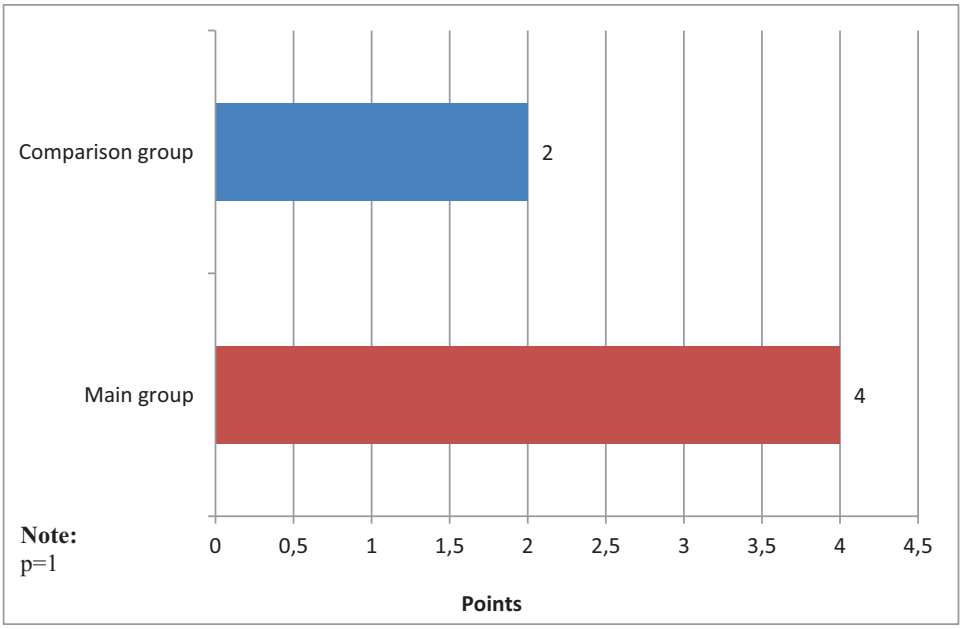

Figure 1. *Results of the SARC-F questionnaire*

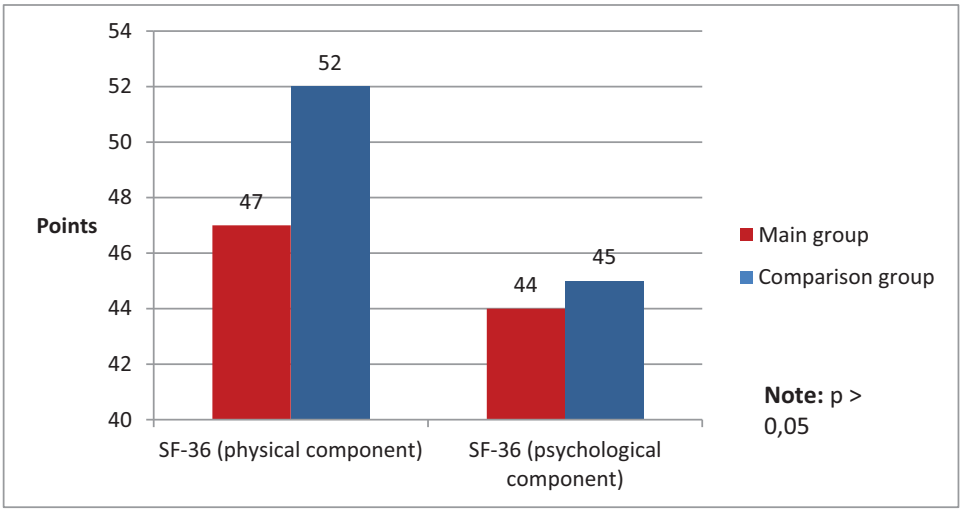

Figure 2. *Results of the SF-36 questionnaire*

Table 2. *Frequency of occurrence of concomitant diseases in the main group and comparison group*

Diseases	Main group (n=55)	Control group (n=27)	p
Cholelithiasis	15 (33 %)	2 (8,%)	0,858
Pathology of the thyroid gland	10 (22 %)	2 (%)	0,046
Arterial hypertension	44 (96 %)	23(92 %)	0,668
Cardiac ischemia	24 (52 %)	12 (48 %)	0,592
History of stroke/heart attack	8 (17 %)	9 (36 %)	0,099
Atrophic gastritis	8 (17 %)	2 (8 %)	0,747
Non-alcoholic fatty liver disease	26 (57 %)	15 (60 %)	0,382
History of cancer	6 (13 %)	1 (4 %)	0,007
Chronic anemia	4 (9 %)	2 (8 %)	0,01
History of coronavirus infection	19 (41 %)	7 (28 %)	0,296
Complications of diabetes			
Diabetic polyneuropathy	40 (73 %)	51,8 (56 %)	0,039
Diabetic nephropathy	25 (45,4 %)	14 (51,8)	0,142
Diabetic retinopathy	29 (52,7 %)	16 (59,2)	0,428
Macroangiopathy of the lower limbs	17 (30 %)	5 (18 %)	0,227

Note: Data are presented as median with interquartile range; GSD — cholelithiasis, IHD — coronary heart disease, CKD — chronic kidney disease

Table 3. *Assessment of parameters of the SarQol questionnaire*

Parameters, points	Main group (n=55)	Control group (n=27)	r	p
SarQoL general (/100)	34,99 [34,95-45,17]	43,87 [43,9-55,0]	-,184	0,970
Physical and mental health (/100)	31,77 [31,1-41]	47,77 [47,77-52,2]	,703	0,055
Ability to move (/100)	25 [25-31,25]	30 [30-38,89]	,445	0,790
Body composition (/100)	30 [29,17-33,33]	45,83 [45,83-50]	-,008	0,069
Functionality (/100)	32,14 [32,14-36,54]	42,31[42,31-71,15]	-,194	0,768
Daily activities (/100)	18,34 [16,67-35]	50 [50-52,78]	-1,072	0,757
Leisure (/100)	3, 33[0 -16,62]	0 [0 -33,25]	0,739	0,529
Fears (/100)	0 [10-75]	75 [75-87,5]	-,454	0,511

Note: Data are presented as median with interquartile range

Table 4. *Antihyperglycemic therapy used in patients with presarcopenia and in the comparison group*

Parameters, drugs	Main group (n=55)	Control group (n=27)	p
Insulin therapy	18 (32 %)	6 (22 %)	0,242
Insulin therapy, basal therapy	40 (72,7%)	13 (48,1)	0,004
Metformin	25 (45,5 %)	20 (74 %)	0,002
and DPP-4 inhibitors	44 (80 %)	6 (22,2 %)	0,001
and GLP-1 — агонист	0	1 (4 %)	0,164
and iNGLT-2 type	8 (14,5 %)	23 (85,1 %)	0,001
Sulfonylureas	36 (65,4 %)	12 (33 %)	0,008

Note: i DPP-4 — dipeptidyl peptidase 4 inhibitors (Gliptins), a GLP-1 — glucagon-like peptide-1 receptor agonists, i SGLT-2 — inhibitor of sodium-glucose cotransporter type 2 (Gliflozins)

Table 5. *Bioimpedancemetry parameters in the main group and in the comparison group*

Parameters	Main group (n=55)	Control group (n=27)	p
Fat mass, kg	33,5 [30- 37]	39,3 [34,5- 44]	0,036
Fat mass, %	40 [38- 43]	42 [38- 45]	0,679
Visceral fat area, cm^2	176 [158- 194]	200 [177- 223]	0,177
Skeletal muscle mass, kg	25,6 [24,4- 27]	29,4 [27,3-31,5]	0,045
Index of appendicular skeletal muscle, kg/m^2	7,0 [6,7-7.3]	7,5 [7,1-7.9]	0,011
Protein, kg	9,2 [8,8- 9,6]	10,4 [9,7-11]	0,869
Minerals, kg	3,2 [3,1- 3,4]	3,7 [3,5-3,9]	0,998
Total amount of water in the body, l	35 [33-37]	40 [37-42]	0,862
Intracellular fluid, l	21[20-22]	24[23-26]	0,951
Extracellular fluid, l	14[13-14]	16[14,5-17]	0,672
Cell mass, kg	30[29-32]	34,5[32-37]	0,941

Note: Data are presented as median with interquartile range

Table 6. *Biochemical parameters in the main group and the comparison group*

Parameters	Main group (n=55)	Control group (n=27)	p
Total cholesterol, mmol/L	5,1 [4,6- 5,6]	4,9 [4,4- 5,4]	0,567
HDL, mmol/L	1,3 [1,2- 1,4]	1,2 [1,1- 1,3]	0,762
LDL, mmol/L	3,8 [2,1- 5,5]	2,8 [2,4- 3,2]	0,628
Triglycerides, mmol/L	3,7 [0,8- 6,3]	2,5 [1,9- 3,1]	0,496
Total bilirubin, mmol/L	13,9 [11,5-16,3]	11,4 [9,7-13.1]	0,238
Total protein, mmol/l	68 [67- 70]	70 [68-72]	0,005
AST, U/L	23 [20- 27]	27 [19-36]	0,057
ALT, U/L	24 [19-29]	37 [21-52]	0,001
Alkaline phosphorus, U/L	64 [54-73]	66 [50-82]	0,523
Creatinine, μmol/L	90 [82-97]	87 [78-95]	0,090
Sodium, mmol/L	135 [128-143]	141 [140-141]	0,331
Potassium, mmol/L	3,8 [3,5-4,0]	4 [3,8-4,0]	0,849
Calcium, mmol/L	1,1 [1,0-1,2]	1,2 [1,1-1,3]	0,001
Uric acid, μmol/L	318 [290-346]	310 [263-357]	0,719
Albumin, g/l	38 [35-41]	33 [26-40]	0,607
Glycated hemoglobin, %	8,2 [7,4-9]	7,6 [6,3-9]	0,200

Note: Data are presented as median with interquartile range; ALT — alanine aminotransferase, AST — aspartate aminotransferase, HDL — high density lipoproteins, LDL — low density lipoproteins, ALP — alkaline phosphatase

Table 7. *Additional drug therapy in patients with presarcopenia and in the comparison group*

Parameters, drugs	Main group (n=55)	Группа сравнения/ Control group (n=27)	p
Antihypertensive therapy	54 (98%)	16 (59,2%)	0,001
Antiarrhythmics	54 (98%)	25 (92,5%)	0,198
Disaggregants	39 (85%)	20 (80%)	0,080
Statins	33 (71,74%)	18 (72,00%)	0,259
Thyroxine	3(5,4%)	1 (3,7%)	0,966
Menopausal hormone therapy	1 (1,8%)	6 (22,2%)	0,001
Vitamin D	3(5,4%)	8 (29,6%)	0,006
Hepatoprotectors	9 (16,3%)	5 (18,5%)	0,747
Bronchodilators	5 (9%)	2 (7,4%)	0,198
Glucocorticosteroids	2 (3,6%)	1 (3,7%)	0,122
Multivitamins	0	5 (18,5%)	0,014

An Iranian study (2012) of the quality of life of elderly and old patients with type 2 diabetes mellitus using SF-36 and WHOQoL–BREF (World Health Organization's Quality of Life) demonstrate that SF-36 and WHOQoL–BREF are reliable clinical questionnaires; however, WHOQoL–BREF results were more specific than SF-36 [23]. According to the study results, it can be suggested that SF-36 can have moderate screening capability to assess the quality of life of patients with type 2 DM and reduced muscle strength. The efficiency of this questionnaire in middle-aged subjects without carbohydrate metabolism disorders requires verification in other clinical trials [24].

Handgrip test results were worse in the main group; it is caused by reduced secretion of anabolic hormones, mitochondrial dysfunction induced by chronic hyperglycemia and inflammatory reaction under the influence of cytokines and free radical [25].

According to some authors, reduced walking speed in patients with potential sarcopenia can be associated with diabetic polyneuropathy and atherosclerosis of lower limb arteries, as well as high glycaemia values. Long-lasting hyperglycemia is known to cause glycosilation of myelin sheath of nerves and neuron death, resulting in reduced muscle fibre innervation and reduced walking speed [26]. Reduced walking speed in patients with type 2 DM can be caused by long-term use of metformin, resulting in cyanocobalamine deficiency and reduced myelin synthesis [27]. Although this study did not find any difference between the use of biguanides in the groups, the fact of the use of this medication was associated with reduced muscle bulk. Timely prevention of complications at early stages of type 2 DM (alpha-lipoic acid and cyanocobalamine) will improve neural trophism and facilitate slower reduction in mass bulk in patients with type 2 DM due to better endoneurial blood flow and higher glutathione values [28].

According to the data obtained during the study, there were no significant differences in glycaemia and HbA1c. However, it is well-known that chronic hyperglycaemia is caused by an increase in the number of glycation end-products, which accumulate in cartilages and skeletal muscles and lead to reduced muscle strength and joint elasticity [29]. Earlier studies revealed that high levels of glycation end-products are associated with low values of handgrip tests and walking speed in elderly people [29]. Based on the results, maintenance of the target glycaemia levels in patients with type 2 DM will help to prevent reduction in muscle bulk and strength [30].

Assessment of the body composition using bioimpedansometry demonstrated that the fat mass percentage was high in both groups; however, in the pre-sarcopenia group, fat mass and BMI were higher. The results are comparable with the study conducted by the Federal Bureau for Medical and Social Assessment of the Ministry of Labour of Russia (2017) [9]. Allegedly, this variant of fat mass distribution can correspond to sarcopenic obesity, which contributes to reduced muscle bulk [9].

In serum of patients with potential sarcopenia, protein levels were reduced as compared to controls, which causes reduction in skeletal muscle mass [9]. This trend is a result of physical inactivity as one of the leading causes of reduced muscle bulk and strength [31] and is confirmed with the results of reduced physical activity in the main group. These results can be associated with the unbalanced diet in the modern population: high levels of simple carbohydrates, saturated fats and trans fats, low intake of protein-rich products. Diet should further be evaluated with the use of bioimpedansometry. In order to prevent sarcopenia, controlled physical aerobic activities for at least 20 minutes and daily intake of 1–1.2 g/kg of protein (depending on pathology) are recommended; it can facilitate better synthesis of muscle protein, reduce fat mass and preserve normal bone mineralisation [31].

Later reduced mineral density will increase the risk of osteosarcopenia and spontaneous fractures in patients with type 2 DM [32, 33]. Therefore, intake of an adequate amount of protein will improve calcium reabsorption and reduced production of parathyroid hormone [34], thus reducing the risk of osteoporosis. Among chronic diseases, severe chronic kidney disease (CKD) should be mentioned, where daily protein intake is reduced to 0.2–0.5 g/kg (at GFR of < 30 mL/min/1.73 m^2) in order to prevent metabolic acidosis [35]. Inadequate mineral density can be a result of vitamin D deficiency and diabetic kidney disease [36]. Preventive doses of vitamin D will likely facilitate bone mass preservation [37]. In this paper, patients with pre-sarcopenia presented took lower amounts of multivitamins and vitamin D; however, there were no differences in the incidence of chronic complications of DM between groups.

Various effects of antidiabetic medications on the quality of muscles flag that selection of medications should account for the risk of sarcopenia, in addition to comprehensive monitoring of glycaemic status and cardiovascular complications. It has been demonstrated that sulfonylureas, insulin and metformin can promote skeletal muscles loss, unlike SGLC-2 inhibitors and DPP-4 [38]. In this study, patients with pre-sarcopenia were more often treated with insulin, DPP-4, while SGLC-2 inhibitors and biguanides were used less often, and it needs further investigation. Also, development of sarcopenia in elderly people is affected by arterial hypertension, e.g. in some studies, angiotensin-converting-enzyme inhibitors show positive protective effect [39]. Another preventive approach can be menopausal hormone therapy, which was prescribed more often to women in the control group; according to some researchers, if combined with physical activities, it may result in muscle building [40].

The limitations of this study were non-assessment of efficacy and lack of a healthy population, who would not have glucose metabolism disorders, with a similar BMI (30 and 35 kg/m^2), in order to compare groups with similar body composition; small sample size, absence of multivariative analysis and evaluation of the nutritional status of patients. These factors will be taken into account and applied in our future study in a larger population.

Conclusion

Thus, an initial screening of reduced muscle bulk and strength in patients with type 2 DM can be performed with the use of handgrip test and bioimpedansometry. Handgrip test is used to diagnose reduced muscle strength, while body composition assessment (bioimpedansometry) can identify reduced muscle and appendicular mass as long as the disease evolves. Despite numerous studies and relevance of the problem, there are no marketed medications to preserve muscle bulk. Prevention measures in patients with type 2 DM aimed at preservation of muscle bulk and strength are: stable target glycaemia levels, prevention of physical inactivity, adequate intake of proteins and preventive doses of vitamin D. The identified risk factors can be red flags of sarcopenia; but their statistical value should be verified in a larger population.

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ВЛИЯНИЕ УРОВНЯ ВИТАМИНА D И ПОЛИМОРФИЗМА ГЕНА ЕГО РЕЦЕПТОРА (BSMI, FOKI) НА ТЯЖЕСТЬ COVID-19-АССОЦИИРОВАННОГО ПОРАЖЕНИЯ ЛЕГКИХ

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Effect of Vitamin D Receptor Gene Polymorphism (BsmI, FokI) and its Concentration on the Severity of Covid-Associated Lung Damage

Резюме

Цель. Выявить взаимосвязь между сывороточным содержанием витамина D и полиморфизмом гена рецептора витамина D с тяжестью течения COVID-19-ассоциированного поражения легких. **Материалы и методы.** В работе представлены результаты обследования 200 человек через 1 месяц после перенесенного COVID-ассоциированного поражения легких в период с 01 июня по 31 октября 2020 года. Пациенты разделены на группы по 50 человек в зависимости от степени поражения легких по результатам проведения компьютерной томографии: 1-я группа (КТ-1), медиана по возрасту составила 51,5 [50,5; 54,8]; 2-я группа (КТ-2), медиана по возрасту 57,0 [53,1; 57,0]; 3-я группа (КТ-3), медиана по возрасту 52,5 [51,9; 55,0]; 4-я группа (КТ-4), медиана 55,0 [53,2; 56,4]. В группу контроля вошли 56 человек относительно здоровых лиц, не болевших коронавирусной инфекцией, медиана по возрасту составила 55,0 [51,1; 55,0]. Все группы были сопоставимы по возрасту и полу. В сыворотке крови исследовали концентрацию общего 25-гидроксивитамина D (25(OH)D). Также проведено молекулярно-генетическое исследование гена рецептора витамина D: 283 A>G (BsmI) и 2 A>G (FokI). **Результаты.** Учитывая полученные результаты у пациентов, перенесших COVID-19-ассоциированное поражение легких, можно предположить, что недостаточное содержание в крови общего 25-гидроксивитамина D может являться одним из факторов, способствующих осложненному течению коронавирусной инфекции, а также фактором риска ухудшения течения COVID-19-ассоциированного поражения легких. Анализ полиморфизма гена рецептора витамина D VDR: 283 A>G показал преимущественное наследование аллели A и гомозиготы A/A у пациентов с большим уровнем повреждения легочной ткани на фоне COVID-19 инфекции — КТ-3, 4. Изучение полиморфизма гена рецептора витамина D VDR: 2 A>G показало преимущественное наследование гомозиготы A/A среди заболевших по сравнению с группой контроля. При изучении концентрации витамина D у пациентов с COVID-19-ассоциированным поражением легких в зависимости от полиморфизма генов рецептора витамин D VDR: 283 A>G (BsmI) и VDR: 2 A>G (FokI) отличий не выявлено. **Заключение.** Недостаточное содержание в крови 25(OH)D может являться одним из факторов, способствующих осложненному течению коронавирусной инфекции. Анализ полиморфизма гена рецептора витамина D VDR: 283 A>G показал преимущественное наследование аллели A и гомозиготы A/A у более тяжелой категории пациентов — с объемом повреждения легочной ткани более 50 % (КТ-3, 4) на фоне COVID-19 инфекции. Изучение полиморфизма гена рецептора витамина D VDR: 2 A>G выявило среди заболевших наиболее распространенное носительство гомозиготы A/A по сравнению с группой контроля.

Ключевые слова: *COVID-19-ассоциированное поражение легких, полиморфизм гена рецептора витамина D: 283 A>G (BsmI) и 2 A>G (FokI)*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Objective. To identify the relationship between the serum vitamin B content and the polymorphism of the vitamin B receptor gene with the severity of the course of COVID-19-associated lung damage.

To identify the relationship between serum vitamin D content and polymorphism of the vitamin D receptor gene with the severity of COVID-19-associated lung damage. **Materials and methods.** The paper presents the results of an examination of 200 people, after 1 month suffering COVID-associated lung damage in the period from June 1 to October 31, 2020. The patients were divided into groups of 50 people depending on the degree of lung damage based on the results of computed tomography: group 1 (CT-1), median by age was 51.5 [50.5; 54.8]; group 2 (CT-2), median by age 57.0 [53.1; 57.0]; group 3 (CT-3), median by age 52.5 [51.9; 55.0]; group 4 (CT-4), median 55.0 [53.2; 56.4]. The control group included 56 relatively healthy people who did not have coronavirus infection; the median age was 55.0 [51.1; 55.0]. All groups were comparable in age and gender. The concentration of total 25-hydroxyvitamin D (25(OH)D) was studied in blood serum. A molecular genetic study of the vitamin D receptor gene was also carried out: 283 A>G (BsmI) and 2 A>G (FokI). **Results.** It was revealed that insufficient levels of 25(OH)D in the blood are one of the risk factors for the development of COVID-19 infection, as well as a risk factor for worsening the course of COVID-19-associated lung damage. Analysis of the polymorphism of the vitamin D receptor gene VDR: 283 A>G showed the predominant inheritance of allele A and homozygote A/A in patients with a high level of damage to lung tissue due to COVID-19 infection — KT-3, 4. Study of polymorphism of the vitamin D receptor gene VDR: 2 A>G showed preferential inheritance of homozygote A/A among patients compared to the control group. When studying the concentration of vitamin D in patients with COVID-19-associated lung damage depending on the polymorphism of the vitamin D receptor genes VDR: 283 A>G (BsmI) and VDR: 2 A>G (FokI), no differences were found. **Conclusion.** Insufficient levels of 25(OH)D in the blood may be one of the factors contributing to the complicated course of coronavirus infection. Analysis of the vitamin D receptor gene polymorphism VDR: 283 A>G showed preferential inheritance of the A allele and homozygote A/A in a more severe category of patients — with more than 50 % damage to the lung tissue (CT-3, 4) against the background of COVID-19 infection. A study of the polymorphism of the vitamin D receptor gene VDR: 2 A>G revealed the most common carriage of the A/A homozygote among patients compared to the control group.

Key words: *COVID-19-associated lung damage, vitamin D receptor gene polymorphism: 283 A>G (BsmI) and 2 A>G (FokI)*

Conflict of interests

The authors declare no conflict of interests

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Introduction

Vitamin D is one of the key immunity regulators [1, 2]. Vitamin D deficiency observed in 80 % of the Russian citizens is associated with impaired innate and acquired immunity, resulting in a high risk of viral and bacterial infections. Patients with vitamin D deficiency have significantly reduced resistance to bacterial and viral diseases (ARVI, flu, rhinitis, obstructive pulmonary diseases) [2, 3].

Recent studies conducted during and after the COVID-19 pandemic demonstrated that vitamin D deficiency can contribute to the morbidity rates and aggravate SARS-CoV-2 infection [4-6]. It has been shown that there are several mechanisms of how vitamin D can reduce the risk of bacterial and viral infections by creating a barrier and affecting the innate cellular and humoral immunity [7]. An active form of vitamin D (calcitriol 1.25(OH)2D3) facilitates the reduction in pro-inflammatory cytokine (IL-6, TNFα, CXCL8, CXCL10) levels, stimulates synthesis of antimicrobial peptides (cathelicidin, defensin), which have antiviral effects [3, 8]. Also, one of the vitamin D functions is related to pathogen identification by macrophages, it being innate immune response. Besides, vitamin D suppresses IL-2 and IFγ production by type 1 T-helper cells and stimulates cytokine production by type 2 T-helper cells [9]. Given that vitamin D takes part in the activity of the renin-angiotensin-aldosterone system, it is assumed that it controls the amount of mRNA (messenger ribonucleic

acid) and expression of angiotensin-converting enzyme-2, responsible for the protective against various respiratory infections [10]. As for SARS-CoV-2, it is worth mentioning that vitamin D can suppress supposed adhesive molecules (DPP-4/CD26) for viral penetration to the cell [6, 10]. Vitamin D affects the body with the help of the VDR (vitamin D receptor), localised on chromosome 12, locus 12q13.11 [11]. VDR is specifically activated by calcitriol and causes changes in expression of over 2,700 human genes [2, 3]. A genome-wide biological system analysis by Gromova OA et al. to study the VDR binding made it possible to systematise biological roles of vitamin D for further treatment and prevention of a wide array of diseases [12]. It has been found out that the antiviral immunity is supported by at least 155 proteins, the expression of which is regulated by vitamin D receptor [3, 12].

Vitamin D receptor is characterised by polymorphism, i.e. various allelic variants of this gene in a population [13, 14]. *VDR* gene localised on chromosome 12q13.11 contains a number of single nucleotide polymorphisms, including polymorphism 283 A>G (BsmI) (rs1544410), polymorphism 2 A>G (FokI) (rs2228570). The Russian scientific literature does not contain any data on the study of the correlation between respiratory pathologies and polymorphisms BsmI and FokI of the *VDR* gene; however, there are foreign studies discussing this correlation with bronchopulmonary diseases [11].

Study Objective

To find the correlation between serum vitamin D levels and polymorphism of the vitamin D receptor gene and the severity of COVID-19-associated lung involvement.

Materials and Methods

The study included 200 patients with a history of COVID-19-associated lung involvement during the period from June 1 to October 31, 2020 one month after discharge from in-patient clinics in Chita. All patients were divided into groups of 50 people, depending on the degree of pulmonary involvement as seen on CT scans: group 1 (CT1) — median age was 51.5 [50.5; 54.8]; group 2 (CT2) — median age was 57.0 [53.1; 57.0]; group 3 (CT3) — median age was 52.5 [51.9; 55.0]; group 4 (CT4) — median age was 55.0 [53.2; 56.4]. The study enrolled patients with confirmed novel coronavirus infection, where SARS-CoV-2 (Severe Acute Respiratory Syndrome-relate Coronavirus 2) RNA was identified with real-time polymerase chain reaction. Exclusion criteria were: lymph and myeloproliferative disorders, system diseases requiring immunosuppression therapy, HIV infection, chronic alcoholism, pregnancy, intake of vitamin D.

The control group included 56 healthy volunteers without a history of coronavirus infection and other respiratory diseases within the past three months; median age was 55.0 [51.1; 55.0]. All study groups were similar in sex and age composition.

Serum vitamin D (total 25-hydroxyvitamin D) was measured by an immunoassay after collection of serum samples from all study subjects. Serum 25(OH)D levels were measured using commercially available kits and Access 2 analyser (Beckmancoulter, USA). Molecular genetic testing of vitamin D receptor gene 283 A>G (BsmI) (rs1544410) and 2 A>G (FokI) (rs 2228570) was performed using polymerase chain reaction with allele-specific primer (LEGEND plex™). DNA was isolated with real-time PCR (PCR-RT) and PCR with electrophoretic result detection (DNA Technology).

The study was approved by the Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Chita State Medical Academy of the Ministry of Health of the Russian Federation. Before any assessments, patients provided their voluntary informed consent; all activities were performed in accordance with the World Health Organisation's Declaration of Helsinki (2013).

Statistical processing of study results was performed with IBM SPSS Statistics Version 25.0 (licence No. Z125-3301-14, IBM, USA). Statistical analysis followed the principles of the International Committee of Medical Journal Editors (IC MJE) and the Statistical Analysis and Methods in the Published Literature (SAMPL) guidelines. Normality of parameter distribution in groups of over 50 subjects was assessed using the Kolmogorov–Smirnov test. Given that the parameter distribution in all study groups was not normal, obtained data were presented as a median value, first and third quartiles: Me [Q_1; Q_3]. Kruskal-Wallis test was used to compare quantitative parameters in three independent groups. Results were statistically significant at $p < 0.05$. Pair-wise comparison of two independent groups using one quantitative parameter, Bonferroni modified Mann–Whitney U test was used. Correlation relationships between study parameters were identified with the help of the Spearman's coefficient. The degree of correlation between study parameters was found using Chaddock scale. Ratings were described with absolute values and percentages. Study ratings were compared with the use of Pearson's χ^2 which allows assessing the significance of differences between the actual number of outcomes or qualitative characteristics of a group in each category and the theoretical number which can be expected in the study groups if the zero hypothesis is true. For smaller groups, likelihood-adjusted Pearson's chi-squared test was preferable. Cramer's factor (V) was used to measure the degree of correlation between the risk factor and outcome. The distribution of the frequency of vitamin D genotypes 283 A>G (BsmI) and 2 A>G (FokI) corresponded to Hardy-Weinberg equilibrium [14].

Results and Discussion

Analysis of vitamin D concentration in the study groups demonstrated lower levels in patients with COVID-19-associated lung involvement vs. controls. Difference vs. group 1 was 1.2-fold [1.14; 1.22] ($p < 0.001$), group 2 — 1.3-fold [1.22; 1.31] ($p < 0.001$), group 3 — 1.4 fold [1.29; 1.38] ($p < 0.001$), and group 4 — 1.4 -fold [1.34; 1.45] ($p < 0.001$) (Table 1). Also, lower levels of vitamin D were found in patients with an extensive pulmonary tissue involvement: in groups 3 (CT-3) and 4 (CT-4) vs. group 1 (CT-1) — 1.12-fold [1.09; 1.17] and 1.17-fold [1.13; 1.23], respectively ($p < 0.001$); in group 4 (CT-4) vs. group 2 (CT-2) — 1.12-fold [1.06; 1.15] ($p < 0.001$) (Table 1).

According to the 2021 Vitamin D Deficiency Guidelines [16] in adults, measurement of vitamin D levels in patients corresponded to the following criteria: vitamin D deficiency — blood 25(OH)D level of < 20 ng/mL, inadequate vitamin D level — blood 25(OH)D level between ≥ 20 and < 30 ng/mL, with the target value of 30–60 ng/mL. In our study, low vitamin D levels were recorded in 184 patients (92 %): group 1 (CT-1) — 41 (82 %) subjects, group 2 (CT-2) — 46 (92 %) subjects, group 3 (CT-3) — 48 (96 %) subjects, group 4 (CT-4) — 49 (98 %) subjects. Besides, vitamin D deficiency was diagnosed in 2 patients in group CT-3 (4 %) and 7 patients (14 %) in group CT-4. The majority of controls had target 25(OH)D levels (87.5 %), unlike patients who had coronavirus infection. This value was 4.9 times higher than in group 1 ($p < 0.001$), 10.9 times higher than in group 2 ($p < 0.001$), 21.9 times higher than in group 3 ($p < 0.001$), 43.8 times higher than in group 4 ($p < 0.001$) (Table 2).

In analysis of the group of patients, depending on the severity of COVID-19-associated lung involvement, target vitamin D levels in group 1 (CT-1) vs. group 3 (CT-3) and 4 (CT-4) were found 4.5 times ($p = 0.03$) and 9 times ($p = 0.02$) more often (Table 2).

The correlation analysis demonstrated that there is moderate inverse relationship ($V = -0.46$, $p < 0.001$) between 25(OH)D level and extent of lung tissue involvement.

Therefore, it can be assumed that lower serum vitamin D levels are a risk factor of coronavirus infection and a risk factor of aggravated COVID-19-associated lung involvement.

Table 1. *The concentration of vitamin D in the blood of patients of the studied groups*

Groups		Vitamin D concentration, ng/ml Me [Q1; Q3]	Statistics		
			Kruskal-Wallis	Manna-Whitney	
				Comparison with control group	Comparison of groups studied
Control group, n=56	к	33,17 [32,46; 33,53]	H=130,53, df=4, P <0,001.	**$U_{к-1}$=397,5, $p_{к-1}$<0,001; $U_{к-2}$=172,0, $p_{к-2}$<0,001; $U_{к-3}$=96,5, $p_{к-3}$<0,001; $U_{к-4}$=73,5, $p_{к-4}$<0,001.**	**U_{1-2}=907,0, p_{1-2}=0,02; U_{1-3} =512,0, p_{1-3}<0,001; U_{1-4} =421,0, p_{1-4}<0,001; U_{2-3} =861,0, p_{2-3}=0,007; U_{2-4} =702,0, p_{2-4}<0,001;** U_{3-4} =1010,0, p_{3-4}=0,1.
Group 1, n=50	1	27,53 [27,41; 28,43]			
Group 2, n=50	2	26,41 [25,65; 26,61]			
Group 3, n=50	3	24,54 [24,23; 25,11]			
Group 4, n=50	4	23,51 [23,17; 24,19]			

Note: the statistical significance of the differences between: $p_{к-1}$ — control group and group 1; $p_{к-2}$ — control group and group 2; $p_{к-3}$ — control group and group 3; $p_{к-4}$ — control group and group 4; p_{1-2} — between 1 and 2 groups of patients; p_{1-3} — between 1 and 3 groups of patients; p_{1-4} — between 1 and 4 groups of patients; p_{2-3} — between 2 and 3 groups of patients; p_{2-4} — between 2 and 4 groups of patients; p_{3-4} — between 3 and 4 groups of patients

Table 2. *Characteristics of patients depending on the level of vitamin D concentration*

Groups		Number of patients with low 25(OH)D levels (less than 30 ng/ml)	Number of patients with target level 25(OH)D (from 30 to 60 ng/ml)	Statistics P χ^2
Control group, n=56	к	12,5 % (7/56)	87,5 % (49/56)	**$\chi^2_{к-1}$=51,5; $p_{к-1}$<0,001; $\chi^2_{к-2}$=66,8; $p_{к-2}$<0,001;**
Group 1, n=50	1	82 % (41/50)	18 % (9/50)	**$\chi^2_{к-3}$=24,1; $p_{к3}$<0,001; $\chi^2_{к-4}$=23,58; $p_{к-4}$<0,001.**
Group 2, n=50	2	92 % (46/50)	8 % (4/50)	χ^2_{1-2}=1,4; p_{1-2}= 0,14; **χ^2_{1-3}=5,01; p_{1-3}=0,03;**
Group 3, n=50	3	96 % (48/50)	4 % (2/50)	**χ^2_{1-4}=5,4; p_{1-4}=0,02.** F_{2-3}=0,7; p_{2-3}=0,68
Group 4, n=50	4	98 % (49/50)	2 % (1/50)	F_{2-4}=1,47; p_{2-4}=0,21 F_{3-4}=0,6p_{3-4}=0,62

Note: see table 1

Scientific literature contains similar information that higher serum vitamin D concentrations are associated with a reduced risk and milder COVID-19 infection [17]. Also, there is evidence that vitamin D activates immune cells, which are then used to produce immune peptides and proteins — cathelicidins and defensins, which have an array of antimicrobial and antiviral effects [18, 19].

In turn, it would be interesting to study the association between the levels of vitamin D with known polymorphisms of vitamin D gene depending on the severity of COVID-19-associated lung involvement. We managed to perform a genetic testing of 156 patients; thus, groups 1, 2 (CT-1,2) — group I were compared with groups 3, 4 (CT-3,4) — group II.

Analysis of polymorphism of vitamin D receptor gene VDR: 283 A>G in patients with COVID-19-associated lung involvement demonstrated that allele G is 1.2 times more common in patients with less extended pulmonary tissue involvement (CT-1,2) vs. controls ($p < 0.03$; OR = 0.6). Also, it was found out that patients with less extended pulmonary tissue involvement (CT-1,2) have allele G 1.4 times more often ($p < 0.001$; OR = 2.5) than controls (CT-3,4). Patients with more extended lung tissue involvement (CT-3,4) have allele A 1.8 times more often ($p < 0.001$; OR = 0.4). Analysis of polymorphism genotypes of vitamin D receptor gene VDR: 283 A>G demonstrated that polymorphism G/G is 1.7 times more common in groups CT-1,2 vs. controls ($p = 0.01$; OR = 0.4). The study of polymorphism A/G showed that it is 1.6 times more common in controls vs. groups CT-1,2 ($p = 0.02$; OR = 2.3) and 1.3 times more common vs. groups CT-3,4 ($p = 0.12$; OR = 1.7). Polymorphism A/A is observed mostly in more severe cases of COVID-19-associated lung involvement (group II) (2.8 times more common) ($p = 0.006$; OR = 0.3) vs. patients with less extended lung involvement (group I) (Table 3).

The study of polymorphism of vitamin D receptor gene VDR: 2 A>G in patients with lung involvement associated with past COVID-19 infection demonstrated predominant inheritance of homozygote A/A in groups I and II: 2.6 times more common ($p = 0.04$; OR = 0.3) and 2.5 times more common ($p = 0.04$; OR = 0.4) vs. controls, respectively. Analysis of genotype A/G of the studied polymorphism demonstrated its predominance in the control group: 1.7 times more common than in group I ($p = 0.007$; OR = 2.7) and 1.6 times more common than in group II ($p = 0.009$; OR = 2.5) (Table 3).

Table 3. *Distribution of the frequency of alleles and genotypes of the vitamin D receptor gene polymorphism VDR:283 A>G (BsmI), VDR:2 A>G (FokI) in patients with COVID-19-associated lung damage*

Gene	Genotypes and alleles	Control group n=56	Group		Statistics	Pairwise comparison of study groups
			I (KT-1, 2) n=74	II (KT-3,4) n=82		
VDR: 283 A>G	G	60,7 % (68/112)	73,6 % (109/148)	53 % (87/164)	**χ^2=14,21 df=2 p<0,001**	**$\chi^2_{к-1}$=4,91; $p_{к-1}$=0,03;** $\chi^2_{к-2}$=1,59; $p_{к-2}$=0,21; **χ^2_{1-2}=14,13; p_{1-2}<0,001;**
	A	39,3 % (44/112)	26,4 % (39/148)	47 % (77/164)		
	G/G	33,9 % (19/56)	56,8 % (42/74)	32,9 % (27/82)		**$\chi^2_{к-1}$=6,67; $p_{к-1}$=0,01;** $\chi^2_{к-2}$=0,02; $p_{к-2}$=0,90; **χ^2_{1-2}=8,96; p_{1-2}=0,003;**
	A/G	53,6 % (30/56)	33,8 % (25/74)	40,2 % (33/82)	**χ^2=17,24 df=4 p=0,002**	**$\chi^2_{к-1}$=5,11; $p_{к-1}$=0,02;** $\chi^2_{к-2}$=2,38; $p_{к-2}$=0,12; χ^2_{1-2}=0,69; p_{1-2}=0,41;
	A/A	12,5 % (7/56)	9,5 % (7/74)	26,8 % (22/82)		$\chi^2_{к-1}$=0,07; $p_{к-1}$=0,79; **$\chi^2_{к-2}$=4,12; $p_{к-2}$=0,04; χ^2_{1-2}=7,78; p_{1-2}=0,006;**
VDR:2 A>G	A	39,3 % (44/112)	41,2 % (61/148)	40,9 % (67/164)	χ^2=0,11 df=2 p=0,95	$\chi^2_{к-1}$=0,09; $p_{к-1}$=0,75; $\chi^2_{к-2}$=0,07; $p_{к-2}$=0,79; χ^2_{1-2}=0,004; p_{1-2}=0,95;
	G	60,7 % (68/112)	58,8 % (87/148)	59,1 % (97/164)		
	A/A	8,9 % (5/56)	23,0 % (17/74)	22 % (18/82)		**$\chi^2_{к-1}$=3,53; $p_{к-1}$=0,04; $\chi^2_{к-2}$=3,18; $p_{к-2}$=0,04;** χ^2_{1-2}=0,02; p_{1-2}=0,88;
	A/G	60,7 % (34/56)	36,5 % (27/74)	37,8 % (31/82)	**χ^2=10,38 df=4 p=0,035**	**$\chi^2_{к-1}$=7,51; $p_{к-1}$=0,007; $\chi^2_{к-2}$=7,01; $p_{к-2}$=0,009;** χ^2_{1-2}=0,03; p_{1-2}=0,87;
	G/G	30,4 % (17/56)	40,5 % (30/74)	40,2 % (33/82)		$\chi^2_{к-1}$=1,43; $p_{к-1}$=0,23; $\chi^2_{к-2}$=1,41; $p_{к-2}$=0,24; χ^2_{1-2}=0,001; p_{1-2}=0,97;

Note: statistical significance of differences between: $p_{к-1}$ — control group and group 1; $p_{к-2}$ — control group and group 2; p_{1-2} — between groups 1 and 2 of patients

Table 4. *Vitamin D concentration in carriers of different genetic polymorphisms of the vitamin D receptor gene VDR: 283 A>G (BsmI), VDR: 2 A>G (FokI)*

Gene	Genotypes	Concentration of 25(OH) D, ng/ml Me [Q1; Q3]	Statistics	
			Kruskal-Wallis	Manna-Whitney
				Comparison of study groups
VDR: 283 A>G	A/A n=29	26,2 [26,2; 28,3]	H=0,6 df=2 p=0,74	U_{1-2}=807,5, p_{1-2}=0,86; U_{1-3}=915,0 p_{1-3}=0,44; U_{2-3}=1763,0 p_{2-3}=0,26.
	A/G n=58	27,9 [27,3; 28,5]		
	G/G n=69	26,6 [26,6; 27,9]		
VDR:2 A>G	A/A n=35	26,0 [25,7; 27,1]	H=2,96 df=2 p=0,23	U_{1-2}=1011,5, p_{1-2}=0,98; U_{1-3}=1008,0, p_{1-3}=0,48; U_{2-3}=1741,5; p_{2-3}=0,66;
	A/G n=58	27,9 [27,5; 28,7]		
	G/G n=63	26,6 [26,6; 28,3]		

Note: p_{1-2} — statistical significance of differences between carriers of A/A polymorphism and A/G; p_{1-3} — statistical significance of differences between carriers of A/A polymorphism and G/G; p_{2-3} — statistical significance of differences between carriers of A/G polymorphism and G/G

No differences were found when studying vitamin D concentrations in patients with COVID-19-associated lung involvement, depending on polymorphism of vitamin D receptor gene VDR: 283 A>G (BsmI) and VDR: 2 A>G (FokI) (Table 4). Similar results were observed in other studies; for example, Smagina IV et al. studied patients with multiple sclerosis and found reduced serum concentrations of 25-hydroxyvitamin D25; however, there was no significant difference in plasma 25(OH)D levels in patients with various genotypes of these polymorphisms — 283 A>G (BsmI) and VDR: 2 A>G (FokI) [20].

Analysis of scientific literature on the study of genetic implications of the association between vitamin D deficiency and severity of the past COVID-19 infection shows ambiguous data; for instance, Shreiner EV, Petukhova SK, Khavkin AI et al. did not find out any association between the studied genotypes and severity of the past coronavirus infection [17]. At the same time, Protas VV et al. analysed information on various allele combinations of vitamin D receptor gene VDR: 2 A>G (FokI), including A>G, and summarised data on the association between such diseases as dengue fever, bronchopulmonary diseases (bronchial asthma, TB), Parkinson disease, and hepatitis B [11,21-25]. Analyses by Li, Qian MM and other foreign researchers mention some association between inheritance of certain polymorphisms of vitamin D receptor gene VDR, particularly rs1544410 (BsmI), rs 2228570 (FokI), and sepsis in various pathologies [26]. In their metaanalysis, Palshina AM et al. found out that in Caucasian patients in France, who carry FF frequency of genotype FokI, rheumatoid arthritis is much more common [27, 28]. A study of the Russian population of patients with arterial hypertension to analyse the distribution of genotypes FokI of VDR gene, encoding vitamin D receptor, demonstrated that in subjects with genotypes FokI FF and Ff of gene VDR, the disease onsets in younger age [27, 29]. A metaanlysis of VDR gene polymorphism, in particular of FokI and BsmI, in type 1 diabetes mellitus (79 studies) and type 2 diabetes mellitus (44 studies) showed a high risk of type 1 diabetes mellitus in the presence of allele B BsmI and type 2 diabetes mellitus in the presence of allele f FokI [27, 30]. In studies by Kostik MM et al., genotype bb of BsmI of a gene VDR polymorphous marker manifested as a marker of poor prognosis in boys with juvenile idiopathic arthritis [31].

Meanwhile, according to various estimates, the genotype contribution to fluctuation of serum 25(OH)D levels is 23–43 % to 77–80 % [32, 33]. If the patient's genotype has "risk alleles", i.e. genotype variants that cause a reduction in the amount or function of VDR receptors, vitamin D will not be fully absorbed by respective cells from the blood. A metabolic disorder will develop, similar to vitamin deficiency. At the same time, blood vitamin D level can remain normal. These genotypes account for 48 %, approximately 7–11 % of them have 2 "risk alleles" at once [32, 33].

Currently, only an incomplete list of genes, mutations of which impact vitamin D status, has been compiled [32]. Our idea of the genetic structure of 25(OH)D levels may be expanded as a result of large-scale genetic testing, analysis of "gene-gene" and "gene-environment" interactions, epigenetic observations, etc. Further studies in this area are likely to ensure better understanding of the mechanisms behind vitamin D metabolism regulation. How identified genetic polymorphisms affect vitamin D metabolism is not clearly known [32]. A majority of authors believe that serum 25(OH)D concentrations depend on both gene polymorphism and environmental factors (UV index, skin exposure to sunlight, nutritional path), therefore, they should be considered together.

Nevertheless, features of polymorphism of vitamin D receptor gene VDR can have an indirect impact on the function of innate and acquired immunity. It is essential to undertake a further study of the peculiarities of the genetic status of patients with COVID-19-associated lung involvement and search for haplotypes (including a study of cytokine gene polymorphisms, etc.) that affect disease severity, including sepsis.

Conclusions

Therefore, given the available results for patients with past COVID-19-associated lung involvement, it can be assumed that low blood levels of total 25-hydroxyvitamin D can contribute to a more severe course of coronavirus infection. Analysis of polymorphism of vitamin D receptor gene VDR:283 A>G demonstrated predominant inheritance of allele A and homozygote A/A in patients with a more severe disease, where pulmonary tissue involvement is over 50 % (CT-3, 4) associated with COVID-19 infection. Study of polymorphism of vitamin D receptor gene VDR: 2 A>G showed that most patients were homozygote A/A carriers vs. controls.

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РАСПРОСТРАНЕННОСТЬ СИНДРОМА РАННЕГО СОСУДИСТОГО СТАРЕНИЯ У МУЖЧИН, РАБОТАЮЩИХ В УСЛОВИЯХ ВОЗДЕЙСТВИЯ ШУМА

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Prevalence of Early Vascular Aging Syndrome in Men Working Under Noise Exposure

Резюме

Шум может быть одним из факторов, провоцирующих преждевременное развитие изменений в стенке артерий, ассоциированных с возрастом. **Цель:** оценить жесткость сосудистой стенки и распространенность синдрома раннего сосудистого старения у мужчин трудоспособного возраста в зависимости от контакта с шумом, статуса курения и наличия артериальной гипертензии. **Материалы и методы.** Обследовано 148 мужчин, работавших в шуме и 90 мужчин, для которых уровень всех вредных производственных факторов на рабочем месте не превышал допустимых нормативов. Средний возраст обследованных составил 41,6 ± 9,9 лет, 133 человека (55,9 %) являлись курильщиками, 43 человека (18,1 %) страдали ожирением, 47 человек (19,7 %) имели отягощенную по сердечно-сосудистой патологии наследственность, у 132 человек (55,5 %) была выявлена гиперхолестеринемия, 37 человек (15,5 %) страдали артериальной гипертензией (АГ). Каждый из пациентов, страдавших АГ, получал антигипертензивную терапию. Существенных различий структуры антигипертензивной терапии в сравниваемых группах пациентов не было. Группы обследованных были сопоставимы между собой по возрасту, индексу массы тела, распространенности курения, ожирения и артериальной гипертензии. Всем пациентам была проведена объемная сфигмография по стандартной методике в первой половине дня на аппарате VaSera 1500N (FukudaDenshi, Япония), прибором автоматически определены сердечно-лодыжечный сосудистый индекс (СЛСИ) справа и слева, расчетный возраст артерий. За синдром раннего сосудистого старения (EVA — синдром) принимали клиническое состояние, ассоциированное с превышением расчетным возрастом артерий паспортного возраста пациента на 4 года и более (критерии VaSera). **Результаты и их обсуждение.** После исключения из анализа курильщиков и гипертоников и коррекции на возраст индекс жесткости сосудистой стенки справа и слева в основной группе пациентов значимо превышал указанный показатель в группе сравнения. СЛСИ справа составил 7,2 [6,9; 7,9] и 7,05 [6,05; 7,45] соответственно, p=0,02; СЛСИ слева — 7,3 [7,0; 7,9] и 6,85 [6,05; 7,65] соответственно, p =0,007. В группе лиц, работавших в шуме, расчетный возраст артерий достоверно превышал паспортный возраст пациентов (p=0,004), тогда как в контрольной группе указанные показатели были сопоставимы (p=0,27). Распространенность EVA — синдрома в основной группе пациентов составила 14 случаев (27,5 %,) что в 8,6 раза превышало распространенность EVA — синдрома в группе сравнения — 1 случай (3,2 %); p=0,004. Сопоставимость групп пациентов по основным факторам кардиоваскулярного риска и критерии исключения из исследования позволили предположить, что выявленные изменения состояния сосудистой стенки были связаны с воздействием шума на организм обследованных. **Заключение.** Шум может быть фактором, ускоряющим сосудистое старение. Необходим контроль состояния сердечно-сосудистой системы у лиц, работающих в шуме.

Ключевые слова: *раннее сосудистое старение, сосудистая жесткость, шум*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Noise can be one of the factors provoking the premature development of changes in the artery wall associated with age. **Aim:** to assess the stiffness of the vascular wall and the prevalence of early vascular aging syndrome in men of working age, depending on contact with noise, smoking status and the presence of hypertension. **Materials and methods.** 148 men worked in noise and 90 men for whom the level of all harmful production factors in the workplace did not exceed the permissible standards were examined. The average age of the examined patients was 41.6 ± 9.9 years, 133 people (55.9 %) were smokers, 43 people (18.1 %) were obese, 47 people (19.7 %) had a complicated heredity, 132 people (55.5 %) had hypercholesterolemia, and 37 people (15.5 %) suffered from arterial hypertension (AH). Each of the patients suffering from hypertension received antihypertensive therapy. There were no significant differences in the structure of antihypertensive therapy in the compared groups of patients. The groups of surveyed were comparable in age, body mass index, prevalence of smoking, obesity and hypertension. All patients underwent volumetric sphygmography according to the standard procedure in the morning on the VaSera 1500N device (FukudaDenshi, Japan), the device automatically determined the cardio-ankle vascular index on the right and left (R/L — CAVI), the estimated age of the arteries. The syndrome of early vascular aging (EVA syndrome) was considered to be a clinical condition associated with an excess of the estimated age of the arteries of the patient's passport age by 4 years or more (VaSera criteria). **Results and discussion.** After exclusion of smokers and hypertensive patients from the analysis and correction for age, the vascular wall stiffness index on the right and left in the main group of patients significantly exceeded the indicated indicator in the comparison group. R — CAVI was 7.2 [6.9; 7.9] and 7.05 [6.05; 7.45], respectively, p=0.02; L — CAVI was 7.3 [7.0; 7.9] and 6.85 [6.05; 7.65], respectively, p =0.007. In the group of people working in noise, the estimated age of the arteries significantly exceeded the passport age (p=0.004), whereas in the control group these indicators were comparable (p=0.27). The prevalence of EVA syndrome in the main group of patients was 14 cases (27.5 %), which was 8.6 times higher than the prevalence of EVA syndrome in the comparison group — 1 case (3.2 %); p=0.004. The comparability of the patient groups according to the main cardiovascular risk factors and the exclusion criteria from the study suggested that the identified changes in the state of the vascular wall are associated with the effects of noise on the body of the examined. **Conclusion.** Noise can be a factor that accelerates vascular aging. It is necessary to monitor the state of the cardiovascular system in persons working in noise.

Key words: *early vascular aging, vascular stiffness, noise*

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AH — arterial hypertension, BBA — beta-blocking agents, CCB — calcium channel-blocking agents, ARB — angiotensin II receptor blockers, ACEi — angiotensin converting enzyme inhibitors, BMI — body mass index, CAVI — cardio-ankle vascular index, RHS — routine health screening, EVA-syndrome — early vascular ageing syndrome

Introduction

The concept of early vascular ageing (EVA) syndrome includes early development of age-associated mechanical and functional changes in arterial walls. The main pathogenetic aspects of EVA-syndrome are epithelial dysfunction, thickening of intima-media complex, more rigid vascular walls, impaired elastic artery dilatation, and higher pulse wave velocity. Recently, the vascular age has been considered as an important predictor of cardiovascular risk [1, 2]. According to researchers, the incidence of early vascular ageing syndrome in the population varies a lot and depends on the assessment method used and the age-sex group of subjects. For instance, the incidence of EVA-syndrome in a population of citizens of St. Petersburg aged 25 to 65 years old (VaSera method) was 13.5 % to 37.5 % [3].

Vascular wall rigidity and the rate of vascular ageing are affected by numerous factors. To begin with, sex and genetic differences in cardiovascular system ageing should be emphasised [4]. Also, the incidence of EVA-syndrome is higher in persons with carbohydrate metabolism disorders [5, 6]. Arterial hypertension (AH) also adversely affects vascular wall condition [7]. On the other hand, vascular ageing is impacted by exogenous factors. Smoking is known to significantly increase arterial rigidity [8]. Some studies describe a possible increase in vascular wall rigidity when the body is exposed to such common environmental factors as air pollution and noise [9-11]. However, at the moment, the role of noise exposure in early vascular ageing is not completely clear. Since the level of noise affecting the patient can be easily modified, it is very important to assess how this harmful factor changes the rate of vascular ageing.

Currently, numerous methods are available for the assessment of the patient's vascular age [1, 3]. One of the most accessible and representative methods of non-invasive EVA-syndrome diagnosis is 3D sphygmography. During this assessment, the pulse wave velocity is used to calculate the vascular wall rigidity index (CAVI). Automated determination of CAVI correspondence to the available age standards is used to generate a conclusion whether the patient has early vascular ageing syndrome or not. It has been shown that 3D sphygmography can be used in the assessment of the impact of various endogenous and exogenous factors on the rate of vascular ageing [12].

The objective of the study is to assess vascular wall rigidity and the incidence of early vascular ageing syndrome in men of working age, depending on exposure to noise, smoking status and presence of arterial hypertension.

Materials and Methods

We have conducted a cross-sectional study in 238 men aged 21–65 years old, who were undergoing a routine health screening (RHS) in the medical centre of the Federal Budgetary Scientific Institution Nizny Novgorod Scientific Research Institute of Hygiene and Occupational Pathologies. Inclusion criteria in this study were the age of over 18 years old; male sex; exposure to occupational noise at work or work outside industrial health hazards; possibility to perform 3D sphygmography; informed consent for the participation in the study. Exclusion criteria were the age of over 65 years old; BMI of over 40 kg/m^2; a history of a significant somatic pathology (diabetes mellitus, ischemic heart disease, arterial sclerosis of lower limbs; chronic obstructive pulmonary disease; bronchial asthma, chronic kidney disease); and hyperglycaemia diagnosed for the first time during RHS.

The study was performed in accordance with the Declaration of Helsinki (2000); it did not violate the rights and freedoms of subjects and did not jeopardise their safety . Each patient provided their voluntarily informed consent for the participation in the study. This study was approved by the Local Ethics Committee at the Federal Budgetary Scientific Institution Nizhny Novgorod Scientific Research Institute of Hygiene and Occupational Pathologies (meeting minutes No. 1 dated January 26, 2021).

Based on a special assessment of the working conditions provided by the employer, all subjects were divided into two groups. The main group included 148 males (mean age: 41 [35; 48] years old), at the working stations of which the noise level exceeded the maximum permissible level (80 dBA), whereas all other occupational factors were normal. Mean duration of working in conditions of noise exposure in the main group was 15.5 [10.0; 23.0] years. Controls were 90 males (mean age: 40 [34; 49] years old), the social and economic status of which was similar to that in the main group and at the working stations of which all hazardous occupational factors, including noise, were normal.

The clinical and demographic characteristics of patients are presented in the table (Table 1).

Table 1. *Clinical and demographic characteristics of patient groups*

	The main group (148 people)	**Comparison group (90 people)**	**Significance level p**
Age, years, Me [Q_{25}; Q_{75}]	41 [35; 48]	40 [34; 49]	0,86
The number of persons under the age of 40 inclusive, n (%)	68 (45,9)	44 (48,9)	0,66
The number of persons aged 55 and over inclusive, n (%)	15 (10,2)	15 (16,7)	0,14
The number of people with heredity burdened by cardiovascular pathology, n (%)	27 (19,6)	20 (22,5)	0,60
Number of smokers, n (%)	80 (54,1)	53 (58,9)	0,47
The number of people suffering from hypertension, n (%)	24 (16,2)	13 (14,4)	0,71
Body mass index, kg/m^2, M±SD	26,8±3,2	26,8±4,0	0,96
The number of obese people, n (%)	25 (16,9)	18 (20)	0,55
The number of people with total blood cholesterol≥5.0 mmol/l, n (%)	88 (59,5)	44 (48,9)	0,11

Table 2. Structure of antihypertensive therapy in patient groups, n (%)

Groups of medicines	The main group (24 people)	Comparison group (13 people)	Significance level (p)
ACE inhibitors or ARBs	13 (54,2)	7 (53,8)	0,74
ACE inhibitors or ARBs + diuretics	8 (33,3)	4 (30,8)	0,59
ACE inhibitors + CCB	2 (8,3)	1 (7,7)	0,72
ACE inhibitors or ARBs + beta blockers.	1 (4,2)	1 (7,7)	0,59

Notes: ACE inhibitors — angiotensin converting enzyme inhibitors, ARBs — angiotensin II receptor blockers, CCB — calcium channel blockers, beta-blockers — beta-adrenoceptor antagonists

According to the information presented, there were no statistically significant differences between groups in terms of the main cardiovascular risk factors: age, BMI, incidence of smoking, obesity, hypercholesterolemia and arterial hypertension (AH).

AH was diagnosed in accordance with the current clinical guidelines [13]. At the time of inclusion in the study, all patients with AH were taking antihypertensives: angiotensin converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), calcium channel-blocking agents (CCB), beta-blocking agents (BBA), diuretics. The structure of the antihypertensive therapy in groups of patients is presented in the table (Table 2).

According to the data presented, there were no major differences in the structure of the antihypertensive therapy in the study groups.

All patients underwent a comprehensive medical examination, which included physical examination with anthropometry and Quetelet body mass index calculation (BMI = body mass (kg)/ height (m^2)); chest X-ray; laboratory (complete blood count, urinalysis, blood glucose, total cholesterol) and functional (ECG) tests. Vascular wall condition was assessed using 3D sphygmography performed under a standard method before noon (VaSera — VS 1500N, FukudaDenshi, Japan). During 3D sphygmography, the following parameters were calculated automatically: cardio-ankle vascular index (CAVI) on the right and left sides, estimated vascular age. Early vascular ageing syndrome (EVA-syndrome) was a clinical condition, in which the estimated age of an artery was at least 4 years older than the real age of the patient (criteria VaSera) [3].

Resulting data were processed statistically using Statistica 6.1 (Stat Soft, USA). Normality of quantitative data distribution was checked using Shapiro-Wilk's test. The tabular data are given as a mean value (M) and standard deviation (SD) or a median value (Me) and interquartile range [Q_{25}; Q_{75}], depending on the type of distribution. When parameter values were compared in two unassociated groups, modified Student t-test (taking into account uneven dispersion) and Mann-Whitney u-test in non-parametric distribution were used. When parameter values were compared in two associated groups, Wilcoxon test was used. Where a frequency estimation was performed, tabular data were presented as an absolute and relative frequency of the parameter (n (%)). In order to compare frequencies of a parameter in two groups, χ^2, Yates corrected χ^2 or Fisher's exact test were used (depending on the absolute frequency of a parameter in the groups). Differences between groups were statistically significant at $p < 0.05$.

Results and Discussion

3D sphygmography results obtained during the study are presented in the table (Table 3).

Patients in the main group had statistically higher vascular wall rigidity index, both on the right and left sides. According to a number of studies, CAVI for patients of 31–40 years old is 7.4 ± 0.63 units, while in patients of 41–50 years old, it is 7.55 ± 0.7 units [14]. Therefore, neither in the main group not in controls, mean CAVI was higher than the age-associated normal value, thus indicating challenges in the identification of changes in a vascular was exposed to noise.

A higher estimated artery age in the main group could be indicative of impaired biological mechanisms, maintaining normal vascular wall elasticity. Besdies, in persons exposed to noise, the estimated artery age was 44 [39; 54] years and was statistically higher than the real age of patients (41 [35; 48] year) (Wilcoxon test, $p < 0.001$), whereas in controls these values were 39 [34; 39] years and 40 [34; 39] years, respectively, and were comparable (Wilcoxon test, $p = 0.52$). Over one forth of patients in the main group had early vascular ageing syndrome, while in controls the incidence of this syndrome was 3.6 times lower ($p = 0.003$).

Given comparability of groups in terms of main cardiovascular risk factors and exclusion criteria, it is impossible to rule out that the identified differences in D sphygmography results were associated with exposure of patients from the main group to noise.

Table 3. *Indicators of volumetric sphygmography in the study groups*

	The main group (148 people)	Comparison group (90 people)	Significance level (p)
R — CAVI, Me [Q_{25}; Q_{75}],	7,25 [6,8; 7,8]	7,1 [6,5; 7,6]	0,016
L — CAVI, Me [Q_{25}; Q_{75}],	7,2 [6,9; 7,8]	7,1 [6,6; 7,7]	0,025
Estimated age of the arteries, years, Me [Q_{25}; Q_{75}],	44 [39; 54]	39 [34; 39]	0,035
The number of people with EVA syndrome, n (%)	42 (28,4)	7 (7,8)	0,003

Notes: CAVI — cardio-ankle vascular index (R — on the right, L — on the left), EVA — syndrome — syndrome of early vascular aging

Table 4. *Indicators of volumetric sphygmography in the groups of patients, depending on arterial hypertension*

	with AH			without AH		
	The main group (24 people)	Comparison group (13 people)	Significance level (p)	The main group (124 people)	Comparison group (77 people)	Significance level (p)
R — CAVI, Me [Q_{25}; Q_{75}],	8,1 [6,8; 9,15]	7,9 [7,6; 8,4]	0,91	7,2 [6,8; 7,7]	7,0 [6,4; 7,4]	0,005
L — CAVI, Me [Q_{25}; Q_{75}],	7,9 [7,0; 8,85]	8,4 [7,7; 8,8]	0,90	7,2 [6,9; 7,6]	6,9 [6,5; 7,5]	0,007
Estimated age of the arteries, years, Me [Q_{25}; Q_{75}],	56,5 [44; 64]	59 [49; 64]	0,75	44 [34; 49]	39 [29; 44]	0,011
The number of people with EVA syndrome, n (%)	11 (45,8)	2 (15,4)	0,07	31 (25)	5 (6,5)	0,0005

Notes: CAVI — cardio-ankle vascular index (R — right, L — left), EVA syndrome — early vascular aging syndrome

However, some patients from both groups had confirmed AH, and each of them was taking antihypertensives. According to some researches, AH is a key determinant of early vascular ageing [3]. As for the effect of antihypertensives on vascular wall elasticity, currently there are evidences of reduced vascular rigidity with regular administration of products, which stabilise blood pressure [15, 16]. Despite the absence of significant differences in the structure of antihypertensive therapy in the study groups, it was necessary to account for the individual character of changes in vascular wall rigidity in response to the intake of antihypertensives. Besides, since the study was cross-sectional, it was impossible to reliably assess compliance with antihypertensive therapy and the degree of achievement of target blood pressure values. Therefore, analysis of 3D sphygmography values in patients with and without AH, depending on exposure to noise, seems to be more informative. Analysis of resulting values in presented in the table (Table 4).

An increase in the vascular wall rigidity index and estimated artery age in men exposed to noise was observed only in subjects without AH. EVA-syndrome was more common in subjects with AH who was exposed to occupational noise — 11 cases (45.8 %), and was rare in subjects with normal blood pressure who were not exposed to noise — 5 cases (6.5 %). The mean age of patients with AH in the main group was 48.3 ± 9.7 years old, in controls — 53.4 ± 8.2 years old. Subjects with AH exposed to occupational noise were slightly younger than subjects in the control group; however, the differences were not statistically significant (p = 0.12). Thus, intake of antihypertensives in AH concealed changes in vascular wall resulting from exposure to loud noise. Smoking was likely to have a similar effect. According to literature, smoking adversely affects the arterial wall condition. In studies conducted over 10 years ago, arterial rigidity was growing in regular smokers [17, 18]. A literature review of the effect of smoking on the pulse wave velocity and augmentation index demonstrated that acute, chronic and even passive smoking adversely affect the condition of vascular wall and increase its rigidity [19]. The negative impact of tobacco consumption on arterial rigidity can be observed at young age with a short smoking history [20]. The objective of this study was not to assess the

Table 5. *Indicators of volumetric sphygmography in the studied groups of people, depending on smoking*

	Smokers			Non-smokers		
	The main group (80 people)	**Comparison group (53 people)**	**Significance level (p)**	**The main group (68 people)**	**Comparison group (37 people)**	**Significance level (p)**
R — CAVI, Me [Q_{25}; Q_{75}],	7,15 [6,7; 7,65]	7,1 [6,6; 7,4]	0,60	7,45 [6,9; 8,35]	7,0 [6,1; 7,8]	0,004
L — CAVI, Me [Q_{25}; Q_{75}],	7,1 [6,7; 7,5]	7,1 [6,7; 7,6]	0,97	7,55 [7,0; 8,3]	7,0 [6,1; 7,7]	0,003
Estimated age of the arteries, years, Me [Q_{25}; Q_{75}],	39 [34; 49]	39 [34; 49]	0,65	44 [39; 59]	39 [24; 49]	0,002
The number of people with EVA syndrome, n (%)	19 (23,8)	6 (11,3)	0,12	23 (33,8)	1 (2,7)	0,0001

Notes: CAVI — cardio-ankle vascular index (R — right, L — left), EVA syndrome — early vascular aging syndrome

Table 6. *Volumetric sphygmography indicators depending on noise exposure in non-smoking patients without arterial hypertension*

	The main group (51 people)	**Comparison group (31 people)**	**Significance level (p)**
R — CAVI, Me [Q_{25}; Q_{75}],	7,2 [6,9; 7,9]	6,9 [5,9; 7,3]	0,002
L — CAVI, Me [Q_{25}; Q_{75}],	7,3 [7,0; 7,9]	7,1 [5,9; 7,5]	0,0009
Estimated age of the arteries, years, Me [Q_{25}; Q_{75}],	44 [39; 54]	34 [24; 44]	0,0003
The number of people with EVA syndrome, n (%)	14 (27,5)	1 (3,2)	0,004

Notes: CAVI — cardio-ankle vascular index (R — right, L — left), EVA syndrome — early vascular aging syndrome

impact of smoking on arterial rigidity, therefore, exclusion of smokers from analysis was considered informative. Results of 3D sphygmography comparison in the study groups, with account to the smoking status, are presented in the table (Table 5).

It has been found that a higher vascular rigidity index, higher estimated arterial age and higher incidence of early vascular ageing syndrome were observed only in non-smokers. The results demonstrated that smoking, a contributor to the arterial wall condition, could interfere with identification of changes in vascular rigidity caused by exposure to noise. Currently, literature sources confirm the ability of smoking to affect arterial rigidity. A large population-based study in 15,010 patients demonstrated that smoking facilitates an increase in arterial rigidity both in men and women [21]. Studies by Russian researchers show that CAVI is higher in a group of smoking patients [8] and correlates with the smoking history [22].

Thus, in order to understand the role of smoking in changes of the vascular wall condition, the most informative is an analysis of 3D sphygmography parameters in non-smokers who do not suffer from arterial hypertension. Analysis results are presented in the table (Table 6).

Given all results, it can be concluded that 3D sphygmography parameters presented in Table 6 were most representative of changes in vascular wall elasticity caused by exposure to noise. However, once non-smokers and subjects with AH were excluded from the study, the real age of patients in the main group was 42 [37; 48] years old, that is, statistically higher than the real age of controls — 36 [30; 45] years (p = 0.017). Therefore, the vascular rigidity index should have been adjusted depending on the age group of patients. According to the literature, average differences in vascular rigidity index between age groups of 31–40 years old and 41–50 years old is 0.15 units [13]. Available information was used for age-related correction of CAVI in controls. The obtained results are presented in the table (Table 7).

Despite the adjustment factor, CAVI on the right and left side in the main group was still higher than the value in controls. The estimated artery age in the study groups

Table 7. *Volumetric sphygmography scores in normotensive nonsmokers adjusted for age, Me [Q_{25}; Q_{75}]*

	The main group (51 people)	Comparison group (31 people)	Significance level (p)
R — CAVI	7,2 [6,9; 7,9]	7,05 [6,05; 7,45]	0,02
L — CAVI	7,3 [7,0; 7,9]	6,85 [6,05; 7,65]	0,007

Notes: CAVI — cardio-ankle vascular index (R — right, L — left)

did not require adjustments, since it could be compared with the real age of patients. In the groups of subjects exposed to noise, the estimated artery age was 44 [39; 54] years, and was statistically higher than the real age — 42 [37; 48] years (p = 0.004), whereas in the control group, these values similar: 34 [24; 44] years and 36 [30; 45] years, respectively (p = 0.27).

Analysis of the incidence of early vascular ageing syndrome also did not require adjustments, since in diagnosis of this syndrome, individual parameters of vascular rigidity were compared to the age-appropriate normal value. The incidence of EVA-syndrome in non-smokers who did not suffer from AH was significantly higher in men exposed to occupational noise: 14 cases (27.5 %) in the main group vs. 1 case (3.2 %) in the control group (p = 0.004).

Literature sources discuss a few studies containing information on the condition of vascular wall when the body is exposed to working-environment factors. Studies by Russian researchers demonstrated higher vascular rigidity in subjects exposed to industrial aerosols [23] and high copper concentrations in workplace air [24]. Foreign researchers showed an increased thickness of carotid intima-media complex when the body was exposed to loud noise [25]. However, changes in vascular rigidity in patients exposed to occupational noise have not been studied thoroughly. Therefore, this study allows suggesting a possible mechanism of the effect of noise on the cardiovascular system and emphasises the need for thorough follow-up of the heart and vessel condition in persons exposed to loud noise. In the future, it is advisable to study the correlation between the current noise level and the risk of late cardiovascular events.

Conclusions

Men exposed to occupational noise had a higher arterial wall rigidity index as compared to men who were not exposed to noise. The estimated arterial age values in subjects exposed to noise were significantly higher than the real age. The incidence of early vascular ageing syndrome in subjects exposed to occupational noise was 8.6 times higher vs. persons who were not exposed to hazardous occupational factors (after adjustment for the standard cardiovascular risk factors: age, smoking and arterial hypertension). Thus, exposure of the human body to higher than normal noise levels can be seen as a factor contributing to faster vascular ageing.

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