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Biomarkers of clinical and radiological severity of a new coronavirus infection caused by SARS-CoV-2 virus, and their association with a severe variant of its course

Karnaushkina M.A.[1, 4], Topolyanskaya S.V.[1], Antonova E.V.[2], Matsyuk N.V.[2], Vasilyeva I.S.[1], Strutynskaya A.D.[3], Tyurin I.E.[3]

[1] I.M. Sechenov First Moscow State Medical University (Sechenov University)
8/2, Trubetskaya Str., Moscow, 119991, Russian Federation

[2] Hospital for War Veterans No. 3 of the Moscow City Health Department
4, Startovaya Str., Moscow, 129336, Russian Federation

[3] Russian Academy of Continuing Professional Education
2/1, build. 1, Barrikadnaya Str., Moscow, 125993, Russian Federation

[4] Peoples' Friendship University of Russia
6, Miklukho-Maklaya Str., Moscow, 1117198, Russian Federation

ABSRACT

Aim. To establish biomarkers for clinical, radiological, and laboratory severity of COVID-19 infection and to identify their relationships.

Materials and methods. A retrospective study was carried out which included 155 patients undergoing treatment at the Hospital for War Veterans No. 3 with a confirmed diagnosis of novel coronavirus infection caused by nCoV from April 6 to June 10, 2020. All patients underwent clinical and laboratory examination. An intergroup statistical analysis of clinical and laboratory parameters was carried out depending on the criteria of clinical severity and severity of radiological signs of chest organ pathology according to computed tomography (CT).

Results. Patients with mild COVID-19 showed a lower level of leukocytes, urea, creatinine, bilirubin, and aspartate dehydrogenase (AsAT), as opposed to the corresponding levels in patients with an extremely severe course of the disease. A lower level of calcium in the peripheral blood was found in patients with severe COVID-19, along with an increase in blood glucose.

Patients from the CT1 group as well as patients with a clinically mild course of the novel coronavirus infection had significantly lower levels of neutrophils, urea, creatinine, AsAT, and blood glucose and a higher level of blood calcium in comparison with patients with various CT patterns. In the group of patients with a lethal outcome, cardiovascular diseases were significantly more often detected, as opposed to the discharged patients.

Conclusion. A number of biomarkers characterizing the severity of the novel coronavirus infection caused by the SARS-CoV-2 virus have been identified. However, the revealed differences in the laboratory markers of the clinical and radiological severity of the disease do not currently allow to accurately characterize the nature of the relationship between the clinical severity of the disease, CT findings, and laboratory indicators of COVID-19 severity.

Key words: SARS-CoV-2, COVID-19, lymphocytes, D-dimer, glucose, calcium, CT scan, clinical severity.

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✉ *Vasilyeva Irina S.,* e-mail: emmans@rambler.ru.

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Биомаркеры клинической и рентгенологической тяжести новой коронавирусной инфекции, вызванной вирусом SARS-CoV-2, и их ассоциация с тяжелым вариантом ее течения

Карнаушкина М.А.[1, 4], Тополянская С.В.[1], Антонова Е.В.[2], Мацюк Н.В.[2], Васильева И.С.[1], Струтынская А.Д.[3], Тюрин И.Е.[3]

[1] Первый Московский государственный медицинский университет (МГМУ) имени И.М. Сеченова (Сеченовский Университет)
Россия, 119991, г. Москва, ул. Трубецкая, 8/2

[2] Госпиталь для ветеранов войн № 3 Департамента здравоохранения города Москвы
Россия, 129336, г. Москва, ул. Стартовая, 4

[3] Российская академия непрерывного профессионального образования
Россия, 125993, г. Москва, ул. Баррикадная, 2/1, стр. 1

[4] Российский университет дружбы народов
Россия, 117198, г. Москва, ул. Миклухо-Маклая, 6

РЕЗЮМЕ

Цель. Установление биомаркеров клинической, рентгенологической и лабораторной тяжести инфекции COVID-19 и выявление их взаимосвязи.

Материалы и методы. Выполнено ретроспективное исследование, в которое включены 155 пациентов, проходивших лечение в Госпитале для ветеранов войн № 3 с подтвержденным диагнозом «новая коронавирусная инфекция, вызванная SARS-CoV-2» с 6 апреля по 10 июня 2020 г. Пациентам выполнено клинико-лабораторное обследование. Проведен межгрупповой статистический анализ клинико-лабораторных показателей в зависимости от критериев клинической тяжести и выраженности рентгенологических признаков патологии органов грудной клетки по данным компьютерной томографии (КТ).

Результаты. У больных с легким течением COVID-19 отмечался более низкий уровень лейкоцитов, мочевины, креатинина, билирубина и аспартатдегидрогеназы (АсАТ) по сравнению с соответствующим уровнем показателей у пациентов с крайне тяжелым течением заболевания. Выявлен более низкий уровень кальция в периферической крови у пациентов с тяжелым течением COVID-19 и повышение в этой группе уровня глюкозы крови. Пациенты из группы КТ1, как и больные с клинически легким течением новой коронавирусной инфекции, имели достоверно более низкое содержание нейтрофилов, мочевины, креатинина, АсАТ и глюкозы крови и более высокий уровень кальция крови в сравнении с пациентами с различными КТ-паттернами. В группе пациентов с летальным исходом значимо чаще выявлялись сердечно-сосудистые заболевания по сравнению с выписанными больными.

Заключение. Установлено наличие ряда биомаркеров, характеризующих тяжесть течения новой коронавирусной инфекции, вызванной вирусом SARS-CoV-2. Однако выявленные различия в лабораторных маркерах клинической и рентгенологической тяжести заболевания не позволяют в настоящий момент дать однозначный ответ на вопрос о характере взаимосвязи между клинической тяжестью течения, КТ-картиной и лабораторными показателями тяжести COVID-19.

Ключевые слова: SARS-CoV-2, COVID-19, лимфоциты, D-димер, глюкоза, кальций, компьютерная томография, клиническая тяжесть.

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Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. От каждого из включенных в исследование участников было получено информированное добровольное согласие. Исследование одобрено Первым МГМУ им. И.М. Сеченова (протокол № 19-20 от 02.07.2020).

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INTRODUCTION

In March 2020, the World Health Organization announced the beginning of a pandemic of a novel coronavirus infection (COVID-19) caused by the SARS-CoV-2 virus, predominantly affecting the respiratory tract [1]. Pathological exposure to SARS-CoV-2 leads to the formation of a hyperergic response of the immune system in some patients [2]. This entails the development of extensive damage to the pulmonary parenchyma, multiple organ failure, clinically reported as a septic shock, and cytokine storm [3–5]. Furthermore, in severely ill patients, viremia causes damage to the heart, liver, pancreas, and kidneys [5–7].

According to various studies, the severity of the clinical condition most significantly correlates with lymphopenia, increased number of neutrophils, C-reactive protein (CRP), ferritin, interleukins-1,6, and elevated D-dimer leading to intravascular hypercoagulation [6–10]. Several studies have recently been published demonstrating the relationship between hypocalcemia and hyperglycemia and a severe course of the disease [3–8].

Cases with multiple organ lesions and hyperactivation of the immune system demonstrate extremely high mortality. Current mortality rate from the novel coronavirus infection ranges from 3 to 10% [1, 2, 11–13]. Despite the large number of published studies investigating markers of a severe COVID-19 course, there is still a lack of reliable early clinical and radiological predictors of such a fatal condition. In addition, several cases reveal clinicoradiological dissociation, when there is a mismatch between the volume of the lesion on the computed tomography of the lungs (CT) and clinical data. Thus, studying the features of the severe and extremely severe clinical course of COVID-19 and searching for its early biological markers should be a priority direction in the current studies.

The aim of the study was to reveal biomarkers of clinical, radiological, and laboratory severity of COVID-19 and to analyze their relationships.

MATERIALS AND METHODS

A retrospective cross-sectional study was conducted. From April 6 to June 10, 2020, by a simple random selection method, 155 patients were included in the study: 82 (52.9%) men and 73 (47.1%) women, who underwent treatment at the Hospital for War Veterans No. 3 with a confirmed diagnosis of the novel coronavirus infection caused by SARS CoV-2. The average age of the patients was 64.0 (59.5–81.0) years.

The diagnosis of the novel coronavirus infection was confirmed by a positive polymerase chain reaction carried out upon admission of patients to the hospital and characteristic CT symptoms of the infection.

The study was carried out according to the principles of Declaration of Helsinki (2013), national guidelines for good clinical practice of the Russian Federation, and other corresponding ethical standards and approved by the local Ethics Committee at I.M. Sechenov First Moscow State Medical University (Protocol No. 19–20 of 02.07.2020).

After admission, all patients underwent clinical and laboratory examination (collection of anamnestic data, physical examination, clinical and biochemical blood tests, and a coagulation test) and chest CT. A follow-up CT scan was performed on the 10th day of the hospitalization, if no indications for earlier investigation were revealed. Chest

CT was performed with multidetector CT scanners (Toshiba Aquilion One 160 (Japan) and Toshiba CXL 64 (Japan)) using a standard CT protocol. The patients were treated according to the current national guidelines for preventing, diagnosing, and treating the new coronavirus infection (COVID-19) [1]. All patients were over 18 years, had no mental disorders, did not suffer from alcohol or drug abuse, and signed an informed consent.

To achieve the established aim, we carried out an intergroup statistical analysis of clinical and laboratory parameters depending on the criteria of clinical severity and the severity of the disease according to CT findings. As clinical criteria of COVID-19 severity, we used the criteria recommended in the methodological guidelines for preventing, diagnosing, and treating the novel coronavirus infection (COVID-19) [1]. As CT criteria of the disease severity, we used the X-ray criteria for diagnosing inflammatory changes in the chest organs in COVID-19 [2].

Statistical analysis was performed using Statistica 10.0 software (StatSoft Inc, USA). Comparisons among the groups were performed using the Kruskal – Wallis H test. Assessment of the differences in the mean values in pairwise independent samples was performed using the Mann – Whitney U test. Qualitative data are presented as absolute or relative (%) values. Quantitative variables are presented as $M \pm SD$, where M is the arithmetic mean, and SD is the standard deviation. The difference in values was considered statistically significant at $p < 0.05$. Correlation analysis with Spearman's correlation coefficient and one-way regression analysis were carried out to analyze the dependencies. The correlation was considered strong if the correlation coefficient was from ± 0.7 to ± 1; it was considered average if the coefficient was from ± 0.3 to ± 0.699; and weak if it ranged from 0 to ± 0.299.

RESULTS

The obtained data indicate a significantly lower level of neutrophils in the peripheral blood in patients with mild COVID-19 in comparison with patients with a severe and extremely severe course of the disease (Table 1).

Table 1

Comparative analysis of laboratory parameters in patients upon admission to the hospital, depending on the severity of COVID-19

Parameter	Clinical severity 1	Clinical severity 2	Clinical severity 3	Clinical severity 4	*p**
Leukocytes	6.3 ± 3.6	7.67 ± 3.9	8.52 ± 4.7	9.47 ± 4.8	0.007
Neutrophils	4.46 ± 3.2	5.55 ± 3.7	6.90 ± 4.5	8.10 ± 4.8	0.02
Total protein	65.3 ± 6.8	64.3 ± 5.2	63.2 ± 5.1	58.4 ± 4.6	0.02
Albumin	36.4 ± 4.1	33.9 ± 5.6	32.6 ± 5.4	29.1 ± 2.6	0.001
Urea	7.3 ± 2.4	6.9 ± 2.2	10.7 ± 3.8	15.3 ± 4.1	0.002
Creatinine	126.5 ± 31.2	114.8 ± 30.1	116.5 ± 29.6	176.1 ± 32.6	0.005
Bilirubin	13.5 ± 4.1	11.3 ± 3.9	13.4 ± 3.6	21.9 ± 5.2	0.007
AST	59.2 ± 26.2	51.9 ± 23.3	91.0 ± 59.3	102.8 ± 65.5	0.01
Calcium	0.98 ± 0.35	0.93 ± 0.24	0.85 ± 0.29	0.49 ± 0.16	0.002
Glucose	6.99 ± 2.7	7.46 ± 2.8	8.28 ± 3.2	11.9 ± 3.8	0.02

* Kruskal – Wallis test (here and in Table 2)

Further, some other statistically significant differences were found in a number of laboratory parameters among patients with a mild course and patients with an extremely severe course of the disease. So, in patients with mild COVID-19, there were lower levels of leukocytes, urea, creatinine, bilirubin, and aspartate aminotransferase (AST), as opposed to the group of patients with extremely severe disease. In addition, patients with a mild course of COVID-19 had significantly higher concentration of albumin than patients with a more severe disease course.

Patients with a severe course of COVID-19 had a significantly lower level of calcium and increased glucose concentration in blood (Table 1). No data on the significant differences in the levels of other electrolytes (sodium, potassium, chlorine, iron) between the groups were obtained.

In order to identify the differences in clinical and laboratory parameters in patients stratified according to the severity of COVID-19 following CT findings, an intergroup comparative analysis was carried out (Table 2).

As it is shown in Table 2, patients from the CT1 group, similarly to patients with a clinically mild course of the disease, had significantly lower levels of neutrophils, urea, creatinine, AST, and blood glucose and a higher level of blood calcium than other participants. Additional laboratory markers were established (lymphocytes, eosinophils, lactate dehydrogenase (LDH), D-dimer, and C-reactive protein (CRP)), according to which the patients in the groups differed and patients with different clinical severity of the disease did not differ. From the data presented in Table 2, it can be seen that patients from the group with less pronounced changes in the lung tissue had a higher level of lymphocytes in the peripheral blood and lower levels of LDH, D-dimer, and CRP.

Table 2

Comparative analysis of laboratory parameters in patients with COVID-19 upon admission to the hospital, depending on the degree of changes detected by CT of the chest organs (CT0–CT4), *M* ± *SD*

Parameter	CT1	CT2	CT3	CT4	*p**
Neutrophils	4.78 ± 3.3	5.98 ± 3.7	5.73 ± 3.6	7.46 ± 3.9	0.01
Leukocytes	1.66 ± 0.62	1.18 ± 0.71	1.29 ± 0.9	0.94 ± 0.32	0.001
Albumin	36.9 ± 4.6	33.3 ± 3.7	33.6 ± 5.2	30.4 ± 2.8	0.001
Urea	6.3 ± 5.2	8.1 ± 3.6	8.5 ± 4.7	12.1 ± 8.3	0.001
Creatinine	123.4 ± 78.1	130.3 ± 65.4	103.5 ± 56.9	152.1 ± 90.0	0.01
AST	43.6 ± 12.5	62.3 ± 24.9	75.2 ± 28.7	77.1 ± 30.8	0.02
LDH	563.4 ± 102.5	826.2 ± 259.4	866.9 ± 234.9	1,103.0 ± 522.4	0.003
Calcium	1.06 ± 0.46	0.94 ± 0.21	0.84 ± 0.32	0.703 ± 0.18	0.01
Glucose	6.49 ± 2.3	7.41 ± 2.7	8.12 ± 2.5	10.0 ± 4.2	0.001
D-dimer	583.2 ± 132.4	1,780.9 ± 1,446.9	1,663.6 ± 1,165.4	1,750.3 ± 1,240.8	0.001
CRP	48.4 ± 23.7	125.8 ± 82.2	127.4 ± 73.5	171.0 ± 90.4	0.001

* Kruskal – Wallis test

The next stage of the statistical analysis included a comparative analysis of the clinical and laboratory parameters in patients with deterioration according to CT, who were divided into groups depending on the outcomes (discharge from the hospital / death). Out of 104 patients with negative CT dynamics, the outcome was fatal in 82 patients. Upon admission, the condition of the patients with subsequent lethal outcome was assessed as severe in 61 (73.8%) cases and as extremely severe in 21 (26.2%) individuals. However, CT patterns upon admission were distributed as follows: CT2 was detected in 19 (23%) patients, CT3 – in 44 (54%) patients, and CT4 – in 19 (23%) patients. Pairwise comparison (Mann – Whitney test) revealed significant differences in the levels of lymphocytes, eosinophils, LDH, D-dimer, and CRP between the CT2 and CT3–4 groups ($p < 0.01$). However, between patients of CT3 and CT4 groups, only insignificant differences ($p < 0.05$) in the concentrations of lymphocytes and urea were revealed.

We also obtained data indicating that a part of the participants (15 (9.6%) patients) with CT3–4 lesions had a mild clinical course of the disease and / or had no pathological changes in the clinical laboratory data at the time of the discharge.

At the next stage of the work, we looked closer at the patients with lethal outcome. All these participants underwent a postmortem examination, so it was possible to establish particular complications of COVID-19 and causes of death with certainty. The postmortem examination data analysis confirmed acute respiratory distress syndrome (ARDS) as a complication of the disease in 80 (97.5%) patients who had died. Pulmonary embolism (PE) was detected in 8 (9.8%) patients, sepsis – in 2 (2.4%) cases, and ischemic stroke – also in 2 (2.4%) patients. Concomitant bacterial infection was found in 58 (70.7%) people, which was confirmed by intravital tracheobronchial aspiration and the presence of areas of neutrophil infiltration in the lung parenchyma upon the postmortem exa – mination.

We studied the distribution of concomitant pathologies in patients with different outcomes of the disease (discharge from the hospital / death). The data between the groups are presented in Table 3.

Table 3

Distribution of comorbidities in patients with different outcomes of COVID-19

Parameter	Discharged patients, *n* = 73	Patients with the lethal outcome, *n* = 82
Arterial hypertension	38 (52%)	67 (81.7%)
Ischemic heart disease	33 (45%)	52 (63.4%)
Chronic heart insufficiency	9 (12%)	44 (54%)
Diabetes	29 (40%)	29 (35.4%)
Malignancy (in the medical history)	44 (60%)	13 (16%)
Chronic lung diseases	47 (64%)	26 (32%)
No comorbidity	26 (36%)	12 (14.6%)

In the group of patients with the lethal outcome, cardiovascular diseases were significantly more often detected in comparison with discharged patients. At the same time, a concomitant pathology in this group was absent only in 14.6% of patients, in contrast to the group of individuals discharged from the hospital, where the concomitant pathology was absent in almost 1/3 of observations. This may indicate that the concomitant cardiovascular pathology to a greater extent is associated with an unfavorable outcome of the disease.

Analysis of the relationships between the data of clinical and laboratory studies and the clinical and radiological severity of COVID-19 showed a strong positive correlation with the levels of neutrophils, albumin, creatinine, urea, and calcium. A strong negative correlation was found between lymphocyte counts and the radiological severity. A moderate positive correlation was found between the level of D-dimer, glucose, and CRP and the radiological severity. These data confirm the value of the comprehensive analysis of laboratory parameters, clinical examination data, and a CT pattern of the disease.

DISCUSSION

The results of our study of clinical biomarkers of severe and extremely severe courses of COVID-19 do not contradict with the data published in the literature. We demonstrated that serum levels of neutrophils, lymphocytes, albumin, urea, creatinine, D-dimer, calcium, glucose, and CRP are associated with the severity and outcome of the disease in patients with COVID-19. Some researchers also revealed the influence of concomitant bacterial infection (leukocytosis, neutrophilia, and increased CRP levels) on aggravation of the course of COVID-19 [5, 6, 9]. According to the same researchers, elevated levels of CRP, AST, LDH, D-dimer, and lymphocytopenia were almost not registered in patients with mild COVID-19, in contrast to patients with a severe course of infection [6, 7]. These findings emphasize rare concomitant bacterial infection and development of multiple organ failure in patients with a mild course of the novel coronavirus infection.

In some other studies, hypocalcemia was used as a prognostic marker of the severe and extremely severe course of COVID-19 [7–9]. Low serum calcium concentration can result from decreased absorption of electrolyte in the intestine, dysregulation of calcium metabolism against the background of hyperparathyroidism and a decrease in vitamin D level, and direct viral exposure. It was shown that in various viral infections calcium is required for penetration of the virus in the host cells, its maturation, and replication. For example, with similar infection caused by a virus of the same SARS-CoV family, intracellular impairment of calcium homeostasis promoted the activation of pro-inflammatory mechanisms and an increase in the levels of IL-1, IL-6, and tumor necrosis factor α. This pathological state resulted in damage to the lung tissue [13].

Hypoalbuminemia and increased serum creatinine and urea may be considered as biomarkers of the development of multiple organ failure [7, 9]. What is more, several studies demonstrated the

connection between hypoproteinemia and hypocalcemia in the acute phase of COVID-19 and their association with the lethal outcome of the disease [5, 10].

Our analysis revealed an increased blood glucose level in patients in the acute phase of COVID-19. Glucose values were significantly higher in the severe and extremely severe course of the disease. Diabetes mellitus is considered one of the most frequent concomitant pathologies that aggravate the course of COVID-19 [14, 15]. In our group of patients, 58 (37.4%) people had had the diagnosis of diabetes mellitus before admission to the hospital. At the same time, hyperglycemia during hospitalization was registered in 72 (46.5%) patients. Since in the majority of patients who had no history of diabetes mellitus, hyperglycemia was transient and resolved at the time of discharge from the hospital, the diagnosis of diabetes mellitus was not made upon discharge.

Such an increase in blood glucose levels detected in our patients is consistent with the results of other studies [8, 16]. Hyperglycemia in COVID-19 patients is likely associated with damage to the pancreas. Pancreatic damage, with increased levels of amylase and lipase in blood, was also reported in the study by D.J. Drucker (2020). According to this author, a moderate increase in glucose levels was found in more than 2/3 of patients [16]. Impairment of carbohydrate metabolism may develop due to tropism of SARS-CoV-2 to two receptors (ACE2 (angiotensin-converting enzyme-2) and DPP-4 (dipeptidylpeptidase-4)), which are involved in various stages of carbohydrate metabolism. In addition, these receptors can be involved in the regulation of inflammatory reactions and the functional state of the cardiovascular system and kidneys. Thus, the expression of ACE2 in both endocrine and exocrine pancreatic tissue can cause the development of pancreatitis in a number of patients against the background of COVID-19, which contributes to the exacerbation or *de novo* emergence of diabetes mellitus in the severe course of this infection [16].

Since the assessment of the clinical severity of the course of COVID-19 is based not only on the results of clinical and laboratory research methods, but also on the radiological characteristics of the pulmonary lesion, several researchers attempted to use CT as a prognostic criterion for the clinical disease severity [2].

In the course of the study, no significant relationship between the clinical and radiological characteristics of COVID-19 and its outcomes was found. Thus, we identified statistically significant differences in the markers of the infectious and inflammatory process, lymphocytes, urea, creatinine, LDH, AST, calcium, glucose, and D-dimer between the groups of patients with different radiological severity at initial CT scanning. These differences were not found in the groups of patients divided according to the same classification upon discharge; even though upon discharge, a lot of patients retained radiological changes corresponding to both CT 1–2 and CT 3–4 grades. There were only minor differences in the lymphocyte and urea levels between the patients from the CT3 and CT4 groups.

In May 2020, an article was published, where the authors point out that older age and high LDH are independent risk factors for a severe course of COVID-19 even in patients with a mild course of the disease [17]. These data also correlate with our results.

CONCLUSION

Our results indicate several biomarkers of the severity of the course of the novel coronavirus infection caused by the SARS-CoV-2 virus. However, the revealed differences in laboratory markers of the clinical and radiological severity of the disease do not currently allow to accurately characterize the nature of the relationship between the clinical severity of the disease course, CT changes, and laboratory parameters of COVID-19 severity.

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Authors contribution

Karnaushkina M.A. – conception and design, drafting of the article, final approval of the manuscript, integrity of all sections of the article. Topolyanskaya S.V. – critical revision of the manuscript for important intellectual content. Antonova E.V. – collection and analysis of the material, drafting of the manuscript. Matsyuk N.V. – analysis and interpretation of data, statistical processing of the results. Vasilyeva I.S. – collection and analysis of the material, drafting of the manuscript. Strutynskaya A.D. – statistical processing of the results, drafting of the manuscript. Tyurin I.E. – conception and design of the study, drafting of the manuscript, editing.

Authors information

Karnaushkina Maria A., Dr. Sci. (Med.), Professor, Department of Advanced-Level Therapy No. 2, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation. ORCID 0000-0002-8791-2920.

Topolyanskaya Svetlana V., Dr. Sci. (Med.), Associate Professor, Department of Advanced-Level Therapy No. 2, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation. ORCID 0000-0002-4131-8432.

Antonova Elena V., Phthisiologist, Hospital for War Veterans No. 3 of the Moscow City Health Department, Moscow, Russian Federation.

Matsyuk Natalya V., Head of the Consultative and Diagnostic Department, Hospital for War Veterans No. 3 of the Moscow City Health Department, Moscow, Russian Federation.

Vasilyeva Irina S., Cand. Sci. (Med.), Assistant, Department of Advanced-Level Therapy No. 2, I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation. ORCID 0000-0003-2654-1561.

Strutynskaya Anastasia D., Post-Graduate Student, Department of X-Ray Radiography and Radiology, Russian Academy of Continuing Professional Education, Moscow, Russian Federation. ORCID 0000-0001-9325-5587.

Tyurin Igor E., Dr. Sci. (Med.), Chief Freelance Specialist in Radiation and Instrumental Diagnostics of the Ministry of Health of Russia, Head of the Department of X-Ray Radiography and Radiology, Russian Academy of Continuing Professional Education of the Ministry of Health of the Russian Federation, Moscow, Russian Federation. ORCID 0000-0003-3931-1431.

(✉) **Vasilyeva Irina S.,** e-mail: emmans@rambler.ru.

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