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ORIGINAL ARTICLE

VARYING SEVERITY COVID-19 EFFECTS ON THE BLOOD INDICATORS OF INSULIN-LIKE GROWTH FACTORS FAMILY IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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ABSTRACT

Purpose of the study. An analysis of IGF and their carrying proteins levels in blood serum of patients with non-small cell lung cancer (NSCLC), depending on the severity of the previous COVID-19 infection.

Materials and methods. 60 patients with histologically verified NSCLC $T_{2-3}N_xM_0$ receiving treatment at the Thoracic Department (National Medical Research Centre for Oncology, 2020–2021), were included in the study. The control group included 30 NSCLC patients after asymptomatic or mild COVID-19 disease (15 men and 15 women); the main group included 30 (15 men and 15 women) patients after severe or moderate to severe COVID-19. The mean age of patients was 59.11 ± 2.89 years. Blood counts of donors of the same age were used as the norm.

Results. The levels of IGF-I, IGF-II, IGFBP2 and IGFBP3 in the blood serum of patients with NSCLC of the main and control groups were higher than those of donors by an average of 2.5, 2.1, 1.7 and 2.7 times, respectively ($p < 0.05$). The concentration of IGFBP1 was higher in the control group compared to the main group, and decreased in relation to donors: in the control in men and women by 1.4 and 1.9 times, and in the main group by 3.0 and 6.4 times, respectively ($p < 0.05$). The ratios of IGF and IGFBP1 increased in both groups: IGF-I/IGFBP1 – in the control group from 3.8 to 4.2 times, and in the main group from 7.9 to 14.4 times; IGF-II/IGFBP1 – in the control from 2.4 to 4.5 times, and in the main group from 6.6 to 12.7 times in men and women, respectively ($p < 0.05$).

Conclusions. The level of ligands and almost all of the studied carrier proteins, except for IGFBP1, increases in the blood of patients with NSCLC of both sexes, regardless of the severity of COVID-19. The ratio of IGF-I/IGFBP1 and IGF-II/IGFBP1 in the blood increases in both groups, most significantly in the group with severe and moderate COVID-19, which indicates excessive accumulation of IGF levels and may contribute to a more aggressive course of the malignant process.

Keywords: non-small cell lung cancer, COVID-19, IGF-I, IGF-II, IGFBP

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013, were observed in the study. The study was approved by the Biomedical Ethics Committee at the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 7/111 dated 02/26/2021). Informed consent was received from all participants of the study.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ВЛИЯНИЕ COVID-19 РАЗЛИЧНОЙ СТЕПЕНИ ТЯЖЕСТИ НА ПОКАЗАТЕЛИ СЕМЕЙСТВА ИНСУЛИНОПОДОБНЫХ ФАКТОРОВ РОСТА В КРОВИ БОЛЬНЫХ НЕМЕЛКОКЛЕТОЧНЫМ РАКОМ ЛЕГКОГО

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РЕЗЮМЕ

Цель исследования. Изучить в сыворотке крови больных немелкоклеточным раком легкого (НМРЛ) содержание IGF и их белков-переносчиков в зависимости от степени тяжести перенесенного COVID-19.

Материалы и методы. В исследование включены 60 больных с гистологически подтвержденным НМРЛ стадии $T_{2-3}N_xM_0$, проходивших лечение в торакальном отделении ФГБУ «НМИЦ онкологии» Минздрава России с 2020 по 2021 гг. В контрольную группу вошли 30 больных раком легкого с бессимптомными или легкими случаями COVID-19 (15 мужчин и 15 женщин), в основную группу – 30 больных (15 мужчин и 15 женщин), перенесших болезнь в тяжелой или среднетяжелой форме. Средний возраст больных составил 59,11 ± 2,89 года. В качестве нормы использовали показатели в крови доноров того же возраста.

Результаты. В сыворотке крови больных НМРЛ основной и контрольной групп уровни IGF-I, IGF-II, IGFBP2 и IGFBP3 были выше значений доноров в среднем в 2,5, в 2,1, в 1,7 и в 2,7 раза соответственно ($p < 0,05$). Концентрация IGFBP1 была выше в контроле по сравнению с основной группой, а по отношению к донорам снижалась: в контрольной группе – у мужчин и женщин в 1,4 и 1,9 раза, а в основной – в 3,0 и 6,4 раза соответственно ($p < 0,05$). Коэффициенты соотношения повышались в обеих группах: IGF-I/IGFBP1 – в контрольной группе от 3,8 до 4,2 раза, а в основной от – 7,9 до 14,4 раза; IGF-II/IGFBP1 – в контрольной от 2,4 до 4,5 раза, а в основной группе – от 6,6 до 12,7 раза у мужчин и женщин соответственно ($p < 0,05$).

Заключение. У больных НМРЛ обоего пола в крови вне зависимости от тяжести перенесенного COVID-19, повышается уровень лигандов и почти всех исследованных белков-переносчиков, кроме IGFBP1. Соотношение IGF-I/IGFBP1 и IGF-II/IGFBP1 крови повышается в обеих группах, наиболее значимо в группе перенесших COVID-19 в тяжелой и среднетяжелой форме, что свидетельствует об избыточном накоплении уровня IGF в крови.

Ключевые слова: немелкоклеточный рак легкого, COVID-19, IGF-I, IGF-II, IGFBP

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «НМИЦ онкологии» Минздрава России (выписка из протокола заседания № 7/111 от 26.02.2021 г.). Информированное согласие получено от всех участников исследования.

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INTRODUCTION

The COVID-19 pandemic, caused by the appearance of severe acute respiratory syndrome 2 (SARS-CoV-2), has led to millions of cases and hundreds of thousands of deaths worldwide [1–3]. The biological sex of a person played a fundamental role in the heterogeneous outcomes of COVID-19 [4–6].

Among all types of cancer, lung cancer patients are of particular interest in the conditions of the COVID-19 pandemic, since the main primary focus of infection with the virus, the respiratory tract, is already at risk due to the presence of a tumor [7]. Previous outbreaks of respiratory viruses have shown that lung cancer patients are more vulnerable than other cancer patients because their pathological respiratory epithelium is probably more prone to rapid penetration of the virus into the lungs [8]. In fact, lung cancer is one of the most common types of cancer among cancer patients with COVID-19 [9; 10]. It is assumed that patients with lung cancer are at a higher risk of this severe form of COVID-19 [9; 11]. Recent studies have shown that the mortality rate of lung cancer patients is higher than that of the general population when infected with COVID-19 [12; 13]. However, comprehensive global data on the impact of the new coronavirus infection on the course of malignant disease in patients with lung cancer have not yet been presented.

Studies have shown that severe consequences in patients with COVID-19 do not develop directly due to the replication of SARS-CoV-2 itself, but are relatively associated with destructive inflammatory reactions caused by a huge activation of immune cells [14]. Therefore, an adjusted immune response is necessary to control and eliminate SARS-CoV-2 infection. On the other hand, uncorrected immune reactions and the production of a large number of inflammatory mediators and cytokines can have adverse and sometimes fatal consequences [15–17].

Insulin-like factor IGF-I and carrier protein IGFBP3 are most often associated with malignant lung tumors [18]. It is known that most of the circulating IGF-I is bound to the soluble plasma protein IGFBP3, while a very small percentage of IGF-I remains in an unbound, biologically active and accessible form. IGF-I can be "neutralized" after binding to IGFBP3, thereby suppressing its mitogenic and anti-apoptotic properties [19]. Thus, the IGF-I/IGFBP3 ratio is considered an indicator of IGF-I bioavailability. High serum IGF-I levels correlate with an increased risk of lung cancer, while high IGFBP3 levels are associated with a reduced risk of disease [20]. Moreover, in vitro studies have shown that IGF-1 promotes the growth and invasion of lung cells, which indicates the role of the IGF-I pathway in the oncogenic growth of non-small cell lung cancer (NSCLC) [21].

However, the significance of IGF-I and IGF-II as prognostic biomarkers has not yet been established. Based on these considerations, we sought to evaluate the serum levels of IGF-I, IGF-II and IGFBP1-3 in patients with NSCLC who had suffered COVID-19 of varying severity.

Purpose of the study: to elaborate the indicators of the system of insulin-like growth factors in the blood serum of patients with NSCLC who have suffered a coronovirus infection of varying severity.

MATERIALS AND METHODS

Prior to participation in the study, all patients received written informed consent. This study was approved by the Ethics Commission of the National Medical Research Centre for Oncology.

The study included men and women (60 people in total) with histologically or cytologically confirmed stage $T_{2-3}N_xM_0$ NSCLC, ECOG (PS) ≤ 2 working status, adequate organ function based on standard laboratory tests, including a complete blood count, serum biochemistry and coagulogram. The main exclusion criteria were previous treatment of NSCLC, type II diabetes mellitus, since it could affect IGF levels, and other concomitant neoplasms over the past five years, with the exception of non-melanoma skin carcinomas. The stage was determined according to the TNM classification. The step-by-step examination included computed tomography (CT) of the chest, abdominal cavity and brain. Bone scans were performed based on symptoms. All patients were examined before the start of treatment.

The control group included 30 patients (15 men and 15 women) with lung cancer with asymptomatic or mild cases of COVID-19, the main group included 30 patients (15 men and 15 women) those who have suffered COVID-19 in severe or moderate form. The age of the patients was: the control group of men 59.8 ± 1.67 (52–74); the control group of women 56.3 ± 3.98

(35–75); the main group of men 61.13 ± 1.82 (52–74); the main group of women 58.4 ± 3.73 (35–74).

According to the recommendations, a smear from the nasopharynx for COVID-19 PCR was obtained in all patients.

Collection of blood samples. Serum levels of IGF-I, IGF-II and IGFBP1,2,3 in peripheral blood were evaluated at the beginning of treatment. Blood samples were centrifuged at 5000 rpm for 10 minutes, then blood serum was collected and stored at –80 °C. Quantitative assessment of circulating levels of IGF-I, IGF-II and IGFBP1,2,3 was performed by enzyme immunoassay (Mediagnost, Germany). According to the recommendations available in the instructions for standard ELISA kits, each laboratory itself must determine the parameters of the norm characteristic of the examined population. The blood levels of IGF-I, IGF-II and IGFBP1,2,3 in conditionally healthy donors (20 men and 20 women) aged 40 to 75 years were taken as the norm. Since the donor studies were conducted in 2019, this contingent did not suffer from COVID-19 infection.

Statistical analysis. Statistical analysis was carried out using the Statistica 10 program. Normality was assessed using Kolmogorov-Smirnov methods, differences between groups were determined using the Student's t-test or the Mann-Whitney U-test, depending on the normality of the distribution. The value of $p < 0.05$ was considered as an indicator of statistical significance.

RESEARCH RESULTS

It was found that most of the indicators were higher in control group patients' blood serum than the values donors: in men, the level of IGF-I, IGF-II, IGFBP2 and IGFBP3 was increased by 2.7 times, 1.7 times, 2.1 times and 2.6 times, respectively, in women – by 2.2 times, 2.3 times, 1.4 times and 2.8 times, respectively (Table 1).

Only IGFBP1 in men and women of the control group was lower than the values in healthy donors by 1.4 times and 1.9 times, respectively. At the same time, the level of IGFBP1 was 1.4 times higher in the blood serum of men than in women and IGFBP2 was 1.5 times higher, and the level of IGF-II was 1.3 times higher in women than in men.

In the blood serum of patients of the main group, most of the indicators, as well as in patients of the

Table 1. Insulin-like growth factors and their carrier proteins in the blood of patients with lung cancer, depending on the severity of COVID-19

Groups	Sex	IGF-I ng/ml	IGF-II ng/ml	IGFBP1 ng/ml	IGFBP2 ng/ml	IGFBP3 ng/ml
Control	M	286.7 ± 19.7 $p^1 = 0.0000$	624.9 ± 51 $p^1 = 0.0020$ $p^2 = 0.0255$	8.56 ± 0.78 $p^1 = 0.0291$ $p^2 = 0.0479$	844.5 ± 63.2 $p^1 = 0.0000$ $p^2 = 0.0031$	3908.4 ± 277 $p^1 = 0.0000$
	F	230.1 ± 15.8 $p^1 = 0.0000$	839.8 ± 75.6 $p^1 = 0.0000$	6.22 ± 0.67 $p^1 = 0.0004$	551.4 ± 46 $p^1 = 0.0319$	4259.2 ± 415.4 $p^1 = 0.0000$
Main	M	274.9 ± 27.4 $p^1 = 0.0000$	775.7 ± 60 $p^1 = 0.0000$	3.96 ± 0.24 $p^1 = 0.0000$ $p^2 = 0.0000$ $p^3 = 0.0000$	638.6 ± 76.8 $p^1 = 0.0142$	3811.9 ± 563.6 $p^1 = 0.0003$
	F	240.7 ± 45.3 $p^1 = 0.0079$	720.7 ± 65.3 $p^1 = 0.0003$	1.9 ± 0.16 $p^1 = 0.0000$ $p^3 = 0.0000$	601.7 ± 66.1 $p^1 = 0.0208$	4196.6 ± 421.6 $p^1 = 0.0000$
Normal values		106.2 ± 12.5	360.6 ± 58.6	12.1 ± 1.3	405 ± 45.7	1502.4 ± 59.8

Note: statistically significant in relation to: [1] – to the indicator in donors; [2] – to the indicator in women in the corresponding group; [3] – to the corresponding indicator in the control group.

control group, were higher than the values of conditionally healthy donors. In the blood serum of men of the main group, the level of IGF-I, IGF-II, IGFBP2 and IGFBP3 was increased 2.6 times, 2.2 times, 1.6 times and 2.5 times, respectively, in women – 2.3 times, 2 times, 1.5 times and 2.8 times, respectively. Also, as in patients of the control group, in the main group, the level of IGFBP1 was lower in donors: in men by 3.1 times, in women by 6.4 times. And only by this indicator there were differences between the control and the main groups: the level of the carrier protein in men of the control group was 2.2 times higher than in the blood serum of men of the main group, in women – by 3.3 times (Table 1).

According to some indicators, we found no fundamental differences in the blood of patients of the control and main groups groups, although all the studied indicators had significant differences from the values in healthy donors.

Further, it was of interest to investigate the ratios of IGF and carrier proteins, since it is known that most of the circulating IGF is associated with soluble plasma IGFBP proteins, while a small percentage of IGF remains in an unbound and biologically active form. The results are presented in table 2.

It was found that the ratio of IGF-I/IGFBP1 and IGF-II/IGFBP1 in the blood serum of male patients of the control group was 3.8 times and 2.4 times higher than in healthy donors, respectively, and in the blood of women – 4.2 times and 4.5 times, respectively. Even more pronounced changes were found in the blood serum received from the main group: the ratio of IGF-I/IGFBP1 and IGF-II/IGFBP1 was higher than in healthy donors by 7.9 times and 6.6 times, respectively, and in women – by 14.4 times and 12.7 times, respectively. I.e. the ratio of IGF-I/IGFBP1 and IGF-II/IGFBP1 in the blood was significantly higher in patients who underwent Covid-19 in severe and moderate form: in men – 2.1 times and 2.7 times, respectively, in women – 3.4 times and 2.8 times, respectively, compared with patients of the control group (Table 2).

Thus, in the blood serum of lung cancer patients of both sexes, regardless of the severity of COVID-19, there is an increase in the level of ligands and almost all of the studied carrier proteins, except IGFBP1, a family of insulin-like growth factors with an increase in the ratio of IGF-I/IGFBP1 and IGF-II/IGFBP1. The transmitted infection of COVID-19 in severe and moderate form further aggravates the level of the IGF-I/

Table 2. Ratios of insulin-like growth factors to carrier proteins in the blood of patients with lung cancer, depending on the severity of COVID-19

Groups	Sex	IGF-I/ IGFBP1	IGF-I/ IGFBP2	IGF-I/ IGFBP3	IGF-II/ IGFBP1	IGF-II/ IGFBP2	IGF-II/ IGFBP3
Control	M	33.5 ± 1.7 p^1 = 0.0000	0.34 ± 0.02	0.07 ± 0.005	73 ± 2.6 p^1 = 0.0000 p^2 = 0.0000	0.74 ± 0.04	0.16 ± 0.008
	F	37 ± 5.6 p^1 = 0.0000	0.42 ± 0.06	0.05 ± 0.009	135 ± 5.2 p^1 = 0.0000	1.32 ± 0.09	0.2 ± 0.01
Main	M	69.4 ± 4.7 p^1 = 0.0000 p^2 = 0.0016 p^3 = 0.0000	0.43 ± 0.05	0.07 ± 0.02	195.9 ± 10.2 p^1 = 0.0000 p^2 = 0.0002 p^3 = 0.0000	1.21 ± 0.11	0.2 ± 0.05
	F	126.7 ± 12.8 p^1 = 0.0000 p^3 = 0.0000	0.4 ± 0.04	0.06 ± 0.02	379.3 ± 49.5 p^1 = 0.0000 p^3 = 0.0000	1.2 ± 0.14	0.17 ± 0.03
Normal values		8.8 ± 1.3	0.36 ± 0.009	0.07 ± 0.006	29.8 ± 3.8	0.9 ± 0.08	0.24 ± 0.03

Note: statistically significant in relation to: [1] – to the indicator in donors; [2] – to the indicator in women in the corresponding group; [3] – to the corresponding indicator in the control group.

IGFBP1 and IGF-II/IGFBP1 ratio, which leads to an increase in free, biologically active IGF.

DISCUSSION

The IGF pathway is a complex, multilevel system of ligands, receptors, carrier proteins and cellular signaling cascades with several levels of regulation. In a broad sense, the IGF family modulates cell behavior through endocrine, paracrine, and autocrine pathways [22]. Binding of IGF complexes to their corresponding receptors induces cellular adaptation, which promotes survival, proliferation and invasion under normal conditions of human physiology and in many types of cancer [23].

Two insulin-like growth factors, i.e. IGF-I and IGF-II, have been identified. Although IGF-II is assumed to regulate differentiation and survival of fetal musculoskeletal cells, understanding of its mechanisms of action is limited. At the same time, its molar ratio with respect to IGF-I in adults is 3:1. Since the unfavorable expression of IGF-II can affect a number of metabolic conditions, it is assumed that IGF-II continues to affect tissues throughout life [24]. Studies have also shown the involvement of IGF-II in phenotypic plasticity, potentially leading to more aggressive and resistant clones in progressive tumors [25]. The study of IGF-II in this context is a very active and developing research topic. On the contrary, information about the function of IGF-I revealed a link between a violation of its regulation and oncogenesis [22].

In this study, we found that in the blood serum of lung cancer patients, regardless of the severity of COVID-19, most indicators of the system of insulin-like growth factors and their carrier proteins were elevated, and regardless of the gender of the patients. The exception was the IGFBP1 protein, the level of which in the blood of patients was reduced, especially in patients of the main group.

Regarding IGF-I, our results confirm studies [20] that have shown that high levels of IGF-I in blood serum correlate with an increased risk of lung cancer. And the study [26] was the first to evaluate serum IGF-I levels in patients with severe COVID-19 compared to healthy people. The results showed that serum IGF-I levels in patients with severe COVID-19 did not differ significantly compared to healthy subjects. Therefore, it is logical to assume that the increase in the level of indicators of the system of insulin-like factors is the result of the presence of NSCLC in patients and is not associated with the infection. It is now well known that subjects in the general population whose serum IGF-I levels are at the upper limit of the normal range are at increased risk of developing several types of cancer [27].

Proteins binding insulin-like growth factor (IGFBPs) 1–6 bind IGF, but not insulin with high affinity. Initially, they were identified as serum carriers and passive inhibitors of IGF action. However, subsequent studies have shown that IGFBPs not only inhibit the actions of IGF, but in many cases they also enhance these actions. IGFBPs are widely expressed in most tissues and are flexible endocrine and autocrine/paracrine regulators of IGF activity, which is necessary for this important physiological system. More recently, it has been established that individual IGFBPs have IGF-independent action [28].

In this study, it was shown that the men of the control group had higher blood serum levels of IGFBP1 and IGFBP2, but not IGFBP3, compared with women, i.e. there were gender differences. In the blood of patients of the main group, gender differences were preserved only for the IGFBP1 protein. At the same time, in patients of both sexes of the main group, a decrease in the level of IGFBP1 was found relative to the indicators in the blood of the control group of patients.

Currently, there is interest in IGFBP1, namely its IGF-dependent and independent action from the position of influencing insulin sensitivity [29]. A completely different interest is shown in the IGFBP3 protein, which is the main circulating IGFBP, and also has an IGF-independent effect in response to DNA damage and EGF signaling. It has been found that the expression of recombinant human IGFBP3 (rhIGFBP3) blocks the IGF-dependent action of IGFBP3, and it has been shown that it has anti-cancer activity in vitro and in vivo [30]. However, a recent study of 11 gastric cancer cell lines showed that IGFBP1 expression levels were extremely low in all cell lines [31]. IGFBP1 is also known to block DNA synthesis, cell growth and differentiation, and also enhances the action of IGF-I in combination with certain reagents, such as platelet-depleted plasma, or in certain cell lines [22]. In [32], there was a tendency to reduce the risk of lung cancer with an increase in the concentration of IGFBP1 in serum, but these results did not reach statistical significance.

Insulin is the main regulator of IGFBP1, inhibiting its synthesis in the liver and other tissues, and the observed tendency to reverse the risk of lung cancer with IGFBP1 may be a consequence of higher insulin levels. The physiological relationship between IGFBP1 and insulin is reflected in the authors' data, which showed an inverse correlation of insulin with the concentration of IGFBP1 in the blood. Only one study has linked IGFBP1 to poor overall survival in lung adenocarcinoma [33].

It is known that an increase in the ratio between IGF and IGFBP reflects an increase in free, biologically active IGF, therefore, treatments that reduce this ratio have significant appeal as cancer prevention tools in people without cancer and with cancer relapses [34]. IGFBPs modulate cell proliferation, survival, differentiation, migration, and invasion. The IGFBP family provides an additional, predominantly extracellular mechanism for regulating IGF activity. A distinctive feature of IGFBPs is their binding to IGF-I and IGF-II, but not to insulin with high affinity. In most cases, they inhibit the actions of IGF, preventing binding to IGF receptors, but they can also enhance their action. IGF-independent actions of IGFBP have also been described over the past two decades. More recently, they have also been shown to regulate aging and autophagy, as well as angiogenesis. Due to these cellular effects, IGFBPs are involved in a number of physiological and pathological processes, including processes underlying metabolism, immune regulation, cancer and neurological diseases [28].

We studied the ratio of IGF and IGFBP in the blood serum of patients of the control and main groups. It turned out that only IGF-I/IGFBP1 and IGF-II/IGFBP1 were elevated. Moreover, these ratios had not only some gender differences, but also depended on the severity of Covid-19: if only the IGF-II/IGFBP1 ratio had gender differences in the control group, then in the main group both IGF-I/IGFBP1 and IGF-II/IGFBP1 in women exceeded the values in the blood of men.

In the literature, we have not found similar data in oncopathology. An increase in IGF-I and the binding proteins IGFBP-1 and IGFBP3 was recorded in damage and death of lung epithelial cells, as well as in early acute respiratory distress syndrome (ARDS), while a decrease in IGF-1 and IGFBP3 was reported in the late stages of ARDS [35]. As a rule, IGFBP3 is the most common IGFBP in the blood and acts as a transport workhorse for the IGF protein superfamily [35]. Consequently, its main IGF-dependent function is to control the amount of free IGF in circulation, which provides numerous subsequent effects, including dosing IGF for cell proliferation or enhancing apoptosis.

CONCLUSION

Thus, regardless of the severity of COVID-19, the blood serum levels of ligands and almost all of the studied carrier proteins, increases in NSCLC patients of both sexes, except IGFBP1. The IGF-I/IGFBP1 and IGF-II/IGFBP1 blood ratios increase in both groups, however most significantly in the group of severe and moderate form COVID-19 survivors, which indicates an excessive accumulation of IGF levels in the blood. IGF-system biomarkers may be useful in screening, prognosis and treatment of lung cancer, although their exact application requires further research.

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