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ORIGINAL ARTICLE

INDICES OF INSULIN-LIKE GROWTH FACTORS FAMILY IN THE LUNG TISSUE OF PATIENTS WITH NON-SMALL CELL LUNG CANCER AFTER COVID-19 OF VARIOUS SEVERITY

O. I. Kit, E. M. Frantsiyants, D. A. Kharagezov, V. A. Bandovkina✉, N. D. Cheryarina, Yu. A. Pogorelova, Yu. N. Lazutin, A. G. Milakin, I. A. Leyman, O. N. Stateshny

National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation
✉ valerryana@yandex.ru

ABSTRACT

Purpose of the study. An analysis of levels of IGF and their carrying proteins in lung tissues of cancer patients depending on the severity of the previous COVID-19 infection.

Patients and methods. The study included 60 patients with histologically verified non-small cell lung cancer (NSCLC) $T_{1-3}N_xM_0$ receiving treatment at the Thoracic Department, National Medical Research Centre for Oncology, in 2020–2021. The control group included 30 NSCLC patients after asymptomatic or mild COVID-19 disease (15 males and 15 females); the main group included 30 (15 men and 15 women) patients after severe or moderate to severe COVID-19 infection. The mean age of patients was 59.11 ± 2.89 years; no significant differences were noted between the control and main groups. All participants gave their informed consent prior to the study approved by the Ethics Committee of National Medical Research Centre for Oncology. Qualitative assessment of IGF-I, IGF-II and IGFBP-1,2,3 levels in the tissues of the tumor, peritumoral area and resection line were measured by ELISA (Mediagnost, Germany). The statistical analysis was performed in the Statistica 10 program, the differences were considered statistically significant at $p < 0.05$.

Results. Regardless of the gender, levels of IGF-I and IGF-II in tumor and resection line samples in patients of the main group were higher than in the control group on average by 1.5–2.2 times, and IGFBP-1 in the tumor was lower by 1.3 times in men and by 5 times in women. The ratio of IGF and IGFBP-1-3 in patients of the control group in perifocal tissues changed towards the parameters in the tumor tissue. IGF/IGFBP-1-3 in men of the main group were lower or did not differ from the indices in the intact tissue, while in women they increased, similarly to the tumor tissue.

Conclusion. An increase in the ratio of IGF and carrier proteins in the tumor tissue of patients in the main group indicated an excessive accumulation of IGF in it, which may contribute to more aggressive growth of malignant tumors. The most pronounced disorders in the system of insulin-like growth factors were found in the tissues of the tumor and intact lung of patients with previous severe and moderate to severe COVID-19.

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

For correspondence:
Valeriya A. Bandovkina – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation.
Address: 63 14 line str., Rostov-on-Don 344037, Russian Federation
E-mail: valerryana@yandex.ru
ORCID: http://orcid.org/0000-0002-2302-8271
SPIN: 8806-2641, AuthorID: 696989

The work followed the ethical principles set forth by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, ed. 2013). The study was approved by the Ethics Committee of the National Medical Research Centre for Oncology (Protocol No. 6 of 02/17/2022). Informed consent was obtained from all participants of the study.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ПОКАЗАТЕЛИ СЕМЕЙСТВА ИНСУЛИНОПОДОБНЫХ ФАКТОРОВ РОСТА В ТКАНИ ЛЕГКОГО БОЛЬНЫХ НЕМЕЛКОКЛЕТОЧНЫМ РАКОМ ЛЕГКОГО, ПЕРЕНЕСШИХ COVID-19 РАЗЛИЧНОЙ СТЕПЕНИ ТЯЖЕСТИ

О. И. Кит, Е. М. Франциянц, Д. А. Харагезов, В. А. Бандовкина✉, Н. Д. Черярина, Ю. А. Погорелова, Ю. Н. Лазутин, А. Г. Милакин, И. А. Лейман, О. Н. Статешный

НМИЦ онкологии, г. Ростов-на-Дону, Российская Федерация
✉ valerryana@yandex.ru

РЕЗЮМЕ

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

Пациенты и методы. В исследование включены 60 больных с гистологически подтвержденным НМРЛ стадии $T_{1-3Nx}M_0$, 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, значимых отличий между контрольной и основной группами не отмечали. Перед началом исследования от участников было получено письменное информированное согласие, одобренное советом по этике ФГБУ «НМИЦ онкологии» Минздрава России. Количественную оценку содержания в ткани опухоли, перифокальной зоне и линии резекции IGF-I, IGF-II и IGFBP-1,2,3 выполняли методом иммуноферментного анализа (ИФА методом (Mediagnost, Германия)). Статистический анализ проводили с использованием программы Statistica 10, значение $p < 0,05$ рассматривалось как показатель статистической значимости.

Результаты. У больных основной группы, по сравнению с контрольной группой, вне зависимости от пола, в образцах опухоли и линии резекции уровень IGF-I и IGF-II был выше в среднем в 1,5–2,2 раза, а IGFBP-1 в опухоли был ниже в 1,3 раза у мужчин и в 5 раз у женщин. Соотношение IGF и IGFBP-1-3 у больных контрольной группы в ткани перифокальной зоны изменялись в сторону показателей ткани опухоли. В основной группе у мужчин IGF/IGFBP-1-3 оказались ниже или не отличались от условно интактной ткани, а у женщин повышались, как и в ткани опухоли.

Заключение. Повышение соотношения IGF и белков-переносчиков в ткани опухоли больных основной группы свидетельствовало об избыточном накоплении в ней IGF, что может способствовать более агрессивному росту злокачественной опухоли. Наиболее выраженные нарушения в системе инсулиноподобных факторов роста мы обнаружили в ткани опухоли и интактного легкого больных, перенесших COVID-19 в тяжелой и среднетяжелой форме.

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

Для корреспонденции:
Бандовкина Валерия Ахтямовна – д.б.н., старший научный сотрудник лаборатории изучения патогенеза злокачественных опухолей, ФГБУ «НМИЦ онкологии» Минздрава России, г. Ростов-на-Дону, Российская Федерация.
Адрес: 344037, Российская Федерация, г. Ростов-на-Дону, ул. 14-я линия, д. 63
E-mail: valerryana@yandex.ru
ORCID: http://orcid.org/0000-0002-2302-8271
SPIN: 8806-2641, AuthorID: 696989

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INTRODUCTION

At the end of 2019, a new coronavirus infection (COVID-19) spread rapidly around the world, causing more than 105 million cases of the disease and more than 2.3 million deaths [1]. The destruction of lung cells caused by COVID-19 infection triggers a local immune response, recruiting macrophages and monocytes, releasing chemokines and pro-inflammatory cytokines, thereby triggering adaptive immune responses of T- and B-lymphocytes [2]. In most patients with COVID-19, the recruited cells clear the lungs of infection, then the immune response decreases, and patients carry the disease asymptomatically or in a mild form that does not require hospitalization. On the other side, some patients have a severe course of the disease and even die. At the same time, the deterioration of the condition is often associated with unbridled inflammatory damage caused by a cytokine storm, an uncontrolled immune response leading to acute respiratory distress syndrome (ARDS) [3; 4]. In addition, there is evidence that patients who have undergone COVID-19 with a severe course have a significant transcriptional shift, including the genes of the G protein-linked receptor family, *DNAJB1*, *IGF*, *EGFR* and *HDGF*, which can lead to tissue remodeling, mitochondrial dysfunction, and serious systemic disorders [1; 2].

Among all types of cancer during the pandemic, lung cancer patients are of particular interest, since the lungs are the organs most involved in the initial focus of infection, with a high risk of pneumonia and, in severe cases of ARDS, often with irreversible scarring of lung tissue and respiratory problems that persist largely after recovery [2; 4]. In fact, lung cancer is one of the most common types of cancer among COVID-19 patients, due to a local violation of immunity [5; 6].

It is known that the neuroendocrine system plays an important role in the regulation of immune responses [7]. Steroid and peptide hormones, growth factors, including insulin-like factors are synthesized and secreted by various immune cells, and are able to modulate the humoral and cellular immune response by stimulating and proliferating immunocompetent cells [8].

Determination of the important role of the components of the insulin-like growth factor (IGF) family in the carcinogenesis of a number of tumors, including lung cancer, is based on numerous epidemiological and preclinical studies, *in vivo* and *in vitro* experiments and attempts to use drugs that affect the IGF axis [9; 10]. It is known that in lung cancer, the copyicity of genes responsible for the regulation of apoptosis, proliferation, DNA repair, as well as the expression of a number of growth factors changes [11].

Previous studies have confirmed IGF activity in lung tissue. In other words, IGF signaling plays an essential role in lung pathology. Dysregulation of the IGF axis has been demonstrated at all stages of lung carcinogenesis, ranging from dysplastic lesions of the bronchial epithelium to advanced forms of cancer. In addition, IGF-I has been shown to be involved in various diseases, including metabolic disorders, congenital disorders, inflammation, fibrosis, cancer, acute lung injury and ARDS. Additional studies have shown that high IGF-I and IGF-II expression, as well as IGFBP-3 aberrations, are associated with poor prognosis, metastases and progression of malignant diseases [11; 12]. IGF-I is a biomarker in patients with hyperoxia-induced lung damage. IGF-I levels are elevated in lung biopsy samples in ARDS compared to those in healthy people [11]. Serum levels of IGF-I and growth factor-3 binding protein (IGFBP-3) were found to be elevated in patients with early respiratory distress syndrome when epithelial cells are damaged and die. However, their level was low in the late stages of ARDS [13]. In a prospective case-control study, it was shown that the initial plasma levels of IGF-I and IGFBP-3 were significantly lower in cases of ARDS than in the control [14]. Among ARDS cases, IGF-I and IGFBP-3 levels were lower in patients who did not survive than in survivors, and both groups were negatively associated with the risk of 60-day mortality [14].

Although the role of IGF-I in COVID-19 has not been fully determined, it is known that it modulates influenza A-mediated lung damage in rats [15]. Elevated concentrations of inflammatory cytokines, such as IL-6, TNF-α, are considered as one of the main causes of ARDS in patients infected with COVID-19. Therefore, effective suppression of the cytokine storm is important to prevent deterioration and reduce mortality from COVID-19 [3]. It is assumed that patients with lung cancer are at a higher risk of this severe form of COVID-19 [5; 6]. 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 [16].

The accuracy of treatment prescriptions in patients with non-small cell lung cancer depends on the exact histological classification of the tumor, analysis of specific markers and genetic mutations, which allows choosing the most effective individual method of therapy, excluding the use of empirical treatment and the associated risk of side effects [11; 12].

Given the role of the IGF system in lung development and its involvement in immune responses, the assessment of IGF levels and their binding proteins may further shed light on the mechanisms underlying the pathogenesis of lung cancer against the background of COVID-19.

The purpose of the study: to examine the system of insulin-like growth factors and their carrier proteins in the lung tissues of patients with NSCLC, depending on the severity of COVID-19.

PATIENTS AND METHODS

Before the start of the study, oral and written informed consent was received from the participants, approved by the Ethics Council of the National Medical Research Centre for Oncology. The study included men and women (60 people in total) with histologically or cytologically confirmed stage $T_{1-3}N_xM_0$ NSCLC, ECOG(PS) ≤ 2 working status, adequate organ function based on standard laboratory tests, including a general blood test, serum biochemistry and coagulogram. The main exclusion criteria were previous treatment of NSCLC, type II diabetes mellitus, as 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 with lung cancer with asymptomatic or mild cases of COVID-19 (15 men and 15 women), the main group included 30 patients (15 men and 15 women) who had the disease in severe or moderate form. The average age of the patients was 59.11 ± 2.89 years, no significant differences between the control and main groups were noted.

According to the recommendations, a PCR smear from the nasopharynx for COVID-19 was obtained in all patients. The selection criteria included patients of both sexes, over the age of 18, and the absence of drug or alcohol dependence. In addition, patients with a known prior inflammatory condition were excluded. There were no significant differences between the groups by gender.

Quantitative assessment of IGF-I, IGF-II and IGFBP-1,2,3 content was performed by the ELISA method (Mediagnost Germany).

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

Initially, it was of interest to study the lung tissue not affected by the malignant process – conditionally intact tissue (resection line). The results are presented in table 1. In the control group, there were differences in the content of some IGF system factors in intact lung tissue between men and women. Thus, men had 2.6 times higher IGF-I level, 2 times higher IGFBP-1 level, and women had 1.4 times higher IGF-II level. There was no difference in the content of IGFBP-2 and IGFBP-3.

In the intact lung tissue of patients of the main group, a statistically significant increase was found relative to the indicators in the control group of IGF-I and IGF-II levels: in men – 1.6 times and 1.8 times, respectively, in women – 2.2 times and 1.8 times, respectively. At the same time, the higher content of IGF-I in men and IGF–II in women remained. Of the studied carrier proteins, the difference between the control and the main groups was found only for IGFBP-2: an increase of 1.3 times in men and 1.9 times in women.

Next, the tumor tissue was studied. It was found that in the tumor tissue of the control group of men and women, the level of IGF-I was 1.5 times and 1.9 times higher than in the corresponding conditionally intact tissue, respectively, and IGF-II – 1.5 times and 2.1 times, respectively. The level of carrier proteins was reduced: IGFBP-1 by 1.75 times in men, IGFBP-2 by 1.4 times in men and 2.2 times in women, and IGFBP-3 by 1.6 times in men and 6.4 times in women.

In the tumor tissue of the main group, an increase in the level of IGF-I in men and women relative to the corresponding intact tissue was also found by 1.6 times and 1.3 times, respectively, IGF-II – by 1.6 times and 2 times, respectively. The level of IGFBP-1 in men was 2 times lower relative to the corresponding intact tissue, in women – 6 times. The level of IGFBP-2 was 3.3 times lower only in women, and IGFBP-3 was 1.7 times lower in both men and 4.4 times lower in women. At the same time, the higher content of IGF-I in men and IGF–II in women also remained.

It turned out that in the tumor samples in men of the main group, the level of IGF-I and IGF-II was 1.7 times and 2 times higher than in the control group, respectively, against the background of 2.1 times increased IGFBP-2 and the absence of significant changes in the levels of other binding proteins, whereas in women of the main group in the samples Compared with the control tumor, the level of IGF-I and IGF-II was increased by 1.5 times and 1.7 times, respectively, but IGFBP-1 was reduced by 5 times.

The perifocal zone of the tumor is a kind of buffer area between the tumor and conditionally unaffected lung tissue. It seems that the individual absolute values of the family of insulin-like growth factors and their carrier proteins in the tissues of the perifocal zone in patients of both sexes of the control and main groups are more close to the values in the tumor tissue than in the resection line. Thus, in patients of both sexes of the control group, the level of IGF-I and IGF-II in the perifocal zone was 1.3–1.7 times higher on average, compared with conditionally intact tissue; compared with the indicators in the tumor, there were no significant differences in men, and in women IGF-II was 1.4 times lower. The content of carrier proteins in the perifocal zone in men of the control group was 1.6 times lower on average than in the resection line, in women IGFBP-2 and IGFBP-3 were 1.4 times and 6.9 times lower, respectively, but all indicators of carrier proteins did not significantly differ from the tumor and only IGFBP-2 in women were 1.5 times higher. In patients of the main group, the situation was different: in men in the n/a zone, the level of IGF-II and IGFBP-1 was higher than in the resection line, but lower IGF-II and higher IGFBP-1 than in the tumor, while the indicators of IGF-I and other carrier proteins in men of the main group did not differ from the resection line. In the women of the main group, the content of IGF-II in the n/a was lower than in the resection line and the tumor, all the carrier proteins were in greater numbers in the resection line, and IGF-I had no significant differences from the indicators in the conditionally intact tissue and in the tumor.

Of particular interest was the ratio of IGF to carrier proteins, on the one hand demonstrating the bioavailability of the studied growth factors, and on the other hand indicating the possible prevailing biological effects of IGFBP (Table 2).

When studying the ratio of insulin-like growth factors and carrier proteins in the intact tissue of all lung cancer patients, sexual differences were found. Thus, the indicators of IGF-I/IGFBP-2 and IGF-I/IGFBP-3 in women were 2.3 times and 4 times lower than in men in the control group, respectively, and in the main group, on average 2.3 times, IGF-II/IGFBP-1 and IGF-II/IGFBP-2, on the contrary, is higher: in the control group 2.7 times and 1.6 times, respectively, in the main group IGF-II/IGFBP-1 is 1.8 times higher; whereas IGF-I/IGFBP-1 and IGF-II/IGFBP-3 had no significant differences in the control group and IGF-I/IGFBP-1, IGF-II/IGFBP-2 and IGF-II/IGFBP-3 – in the main group.

At the same time, most of the calculated coefficients in intact tissue, with the exception of IGF-I/IGFBP-2 and IGF-II/IGFBP-2, were higher in patients of the main group, compared with the control group. Thus, in the intact tissue of men of the main group, the level of IGF-I/IGFBP-1, IGF-I/IGFBP-3, IGF-II/IGFBP-1 and IGF-II/IGFBP-3 was on average 1.9 times higher than in the corresponding control group. In intact tissue of women, the level of IGF-I/IGFBP-1, IGF-I/IGFBP-3, IGF-II/IGFBP-1 and IGF-II/IGFBP-3 was 1.7–3.3 times higher than in the corresponding control group.

It is obvious that there was also a dissonance between the level of IGF and carrier proteins in the tumor tissue, since the content of growth factors increased in tumor samples, and proteins, with rare exceptions (IGFBP-2 in men of the main group and IGFBP-1 in women of the control group), on the contrary, decreased. Moreover, this concerned the tumor tissue of patients of both groups. In the tumor tissue of male and female patients of the control group, all the studied coefficients significantly exceeded similar values in the corresponding intact tissues. In men, the level of IGF-I/IGFBP-1, IGF-I/IGFBP-2, IGF-I/IGFBP-3, IGF-II/IGFBP-1, IGF-II/IGFBP-2 and IGF-II/IGFBP-3 was

Table 1. Levels of insulin-like growth factors and their carrier proteins in lung tissues of cancer patients, depending on the severity of COVID-19

Groups	Sex	IGF-I ng/g t	IGF-II ng/g t	IGFBP-1 ng/g t	IGFBP-2 ng/g t	IGFBP-3 ng/g t
Resection line tissue						
Control	Males	9.6 ± 0.75 p^1 = 0.0000	6.7 ± 0.57 p^1 = 0.0000	0.35 ± 0.04 p^1 = 0.0000	22.8 ± 1.28	226.9 ± 14.8
	Females	3.7 ± 0.31	9.4 ± 0.83	0.18 ± 0.02	20.3 ± 1.78	296.7 ± 21.3
Main	Males	14.9 ± 1.18 p^1 = 0.0000 p^2 = 0.0000	11.8 ± 1.1 p^1 = 0.0000 p^2 = 0.0000	0.3 ± 0.02 p^1 = 0.0000	30.4 ± 2.3 p^1 = 0.0000 p^2 = 0.0000	204.4 ± 15.8 p^1 = 0.0000
	Females	8.3 ± 0.64 p^2 = 0.0000	16.7 ± 1.3 p^2 = 0.0000	0.24 ± 0.02	39.3 ± 2.5 p^2 = 0.0000	255.8 ± 19.4
Tumor tissue						
Control	Males	14.1 ± 1.8 p^1 = 0.0000 p^3 = 0.0000	9.8 ± 1.9 p^1 = 0.0000 p^3 = 0.0000	0.2 ± 0.03 p^3 = 0.0000	16.1 ± 1.5 p^1 = 0.0000 p^3 = 0.0000	142.2 ± 30.7 p^1 = 0.0000 p^3 = 0.0000
	Females	7.1 ± 1.3 p^3 = 0.0000	19.7 ± 1.4 p^3 = 0.0000 p^4 = 0.0000	0.2 ± 0.03	9.3 ± 2.6 p^3 = 0.0000 p^4 = 0.0000	46.2 ± 2.5 p^3 = 0.0000
Main	Males	24.4 ± 3.4 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	19.3 ± 2.4 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000	0.15 ± 0.01 p^1 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	33.1 ± 2.6 p^1 = 0.0000 p^2 = 0.0000	123.4 ± 9.2 p^1 = 0.0000 p^3 = 0.0000 p^4 = 0.0000
	Females	10.7 ± 1.6 p^3 = 0.0000	33.3 ± 2.5 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	0.04 ± 0.01 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	11.8 ± 1.5 p^3 = 0.0000	58.7 ± 5.0 p^3 = 0.0000 p^4 = 0.0000
Perifocal zone tissue						
Control	Males	12.0 ± 0.94 p^1 = 0.0000 p^3 = 0.0000	8.6 ± 0.65 p^1 = 0.0000 p^3 = 0.0000	0.2 ± 0.03 p^3 = 0.0000	16.6 ± 1.2 p^3 = 0.0000	135.3 ± 10.0 p^1 = 0.0000 p^3 = 0.0000
	Females	6.3 ± 0.65 p^3 = 0.0000	14.6 ± 1.1 p^3 = 0.0000	0.17 ± 0.02	14.2 ± 1.2 p^3 = 0.0000	43.3 ± 3.5 p^3 = 0.0000
Main	Males	12.3 ± 1.0	16.8 ± 1.3 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000	0.41 ± 0.03 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000	34.5 ± 2.7 p^1 = 0.0000 p^2 = 0.0000	261.3 ± 21.0 p^1 = 0.0000 p^2 = 0.0000
	Females	10.3 ± 0.88 p^2 = 0.0000	11.5 ± 1.0 p^2 = 0.0000 p^3 = 0.0000	0.08 ± 0.009 p^2 = 0.0000 p^3 = 0.0000	14.2 ± 1.2 p^3 = 0.0000	77.9 ± 5.9 p^2 = 0.0000 p^3 = 0.0000

Note: statistically significant in relation to: [1] – to the indicator for women in the corresponding group; [2] – to the corresponding indicator in the control group; [3] – ro the corresponding indicator in tumor tissue; [4] – to the corresponding indicator in the perifocal zone tissue;
"g t" stands "gram of tissue".

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

Groups	Sex	IGF-I/ IGFBP-1	IGF-I/ IGFBP-2	IGF-I/ IGFBP-3	IGF-II/ IGFBP-1	IGF-II/ IGFBP-2	IGF-II/ IGFBP-3
Resection line tissue							
Control	Males	28.0 ± 5.4	0.42 ± 0.02 p^1 = 0.0000	0.04 ± 0.006 p^1 = 0.0000	19.6 ± 4.0 p^1 = 0.0000	0.29 ± 0.02 p^1 = 0.0000	0.03 ± 0.004
	Females	20.7 ± 1.4	0.18 ± 0.009	0.01 ± 0.0007	52.5 ± 3.7	0.46 ± 0.04	0.03 ± 0.001
Main	Males	49.9 ± 5.7 p^2 = 0.0000	0.49 ± 0.07 p^1 = 0.0000	0.07 ± 0.01 p^1 = 0.0000 p^2 = 0.0000	39.7 ± 6.1 p^1 = 0.0000 p^2 = 0.0000	0.39 ± 0.05	0.06 ± 0.009 p^2 = 0.0000
	Females	35.0 ± 5.5 p^2 = 0.0000	0.21 ± 0.03	0.03 ± 0.001 p^2 = 0.0000	69.7 ± 3.4 p^2 = 0.0000	0.43 ± 0.03	0.07 ± 0.01 p^2 = 0.0000
Tumor tissue							
Control	Main	70.6 ± 11.4 p^1 = 0.0000 p^3 = 0.0000	0.88 ± 0.16 p^3 = 0.0000	0.11 ± 0.04 p^1 = 0.0003 p^3 = 0.0000	49.4 ± 8.5 p^1 = 0.0000 p^3 = 0.0000	0.61 ± 0.1 p^1 = 0.0000 p^3 = 0.0000	0.07 ± 0.02 p^1 = 0.0000 p^3 = 0.0000
	Females	36.4 ± 9.4 p^3 = 0.0000	0.82 ± 0.28 p^3 = 0.0000 p^4 = 0.0000	0.15 ± 0.03 p^3 = 0.0000	100.0 ± 13.9 p^3 = 0.0000	2.3 ± 0.7 p^3 = 0.0000 p^4 = 0.0000	0.43 ± 0.04 p^3 = 0.0000 p^4 = 0.0000
Main	Males	165.8 ± 38.0 p^1 = 0.0006 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	0.74 ± 0.07 p^3 = 0.0000 p^4 = 0.0000	0.2 ± 0.03 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	128.7 ± 9.6 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	0.58 ± 0.1 p^1 = 0.0000 p^3 = 0.0000 p^4 = 0.0062	0.16 ± 0.02 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000
	Females	267.5 ± 34.8 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	0.91 ± 0.11 p^3 = 0.0000	0.18 ± 0.04 p^3 = 0.0000 p^4 = 0.0000	832.5 ± 94.1 p^2 = 0.0000 p^3 = 0.0000 p^4 = 0.0000	2.9 ± 0.6 p^3 = 0.0000 p^4 = 0.0000	0.57 ± 0.02 p^3 = 0.0000 p^4 = 0.0000
Perifocal zone tissue							
Control	Males	61.4 ± 11.9 p^1 = 0.0000 p^3 = 0.0000	0.73 ± 0.11 p^1 = 0.0000 p^3 = 0.0000	0.09 ± 0.004 p^1 = 0.0000 p^3 = 0.0000	43.9 ± 7.9 p^1 = 0.0000 p^3 = 0.0000	0.52 ± 0.07 p^1 = 0.0000 p^3 = 0.0000	0.06 ± 0.004 p^1 = 0.0000 p^3 = 0.0000
	Females	37.8 ± 7.1 p^3 = 0.0000	0.45 ± 0.08 p^3 = 0.0000	0.15 ± 0.02 p^3 = 0.0000	87.1 ± 13.2 p^3 = 0.0000	1.03 ± 0.08 p^3 = 0.0000	0.34 ± 0.05 p^3 = 0.0000
Main	Males	30.6 ± 4.4 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000	0.36 ± 0.01 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000	0.05 ± 0.003 p^1 = 0.0000 p^2 = 0.0000 p^3 = 0.0000	41.4 ± 1.8 p^1 = 0.0000	0.49 ± 0.08 p^1 = 0.0000	0.07 ± 0.01 p^1 = 0.0000
	Females	130.5 ± 19.3 p^2 = 0.0000 p^3 = 0.0000	0.73 ± 0.12 p^2 = 0.0000 p^3 = 0.0000	0.13 ± 0.009 p^3 = 0.0000	145.4 ± 19.7 p^2 = 0.0000 p^3 = 0.0000	0.82 ± 0.13 p^2 = 0.0000 p^3 = 0.0000	0.15 ± 0.01 p^2 = 0.0000 p^3 = 0.0000

Note: statistically significant in relation to: [1] – to the indicator for women in the corresponding group; [2] – to the corresponding indicator in the control group; [3] – to the corresponding indicator in tumor tissue; [4] – to the corresponding indicator in the perifocal zone tissue; "g t" stands "gram of tissue".

higher by more than 2 times, in women – 1.8 times, 4.6 times, 15 times, 1.9 times, 5 times and 14.3 times, respectively. At the same time, in the tumor tissue of women in the control group, almost all indicators exceeded similar values in the tissue of men.

The same pattern was observed in the tumor tissue of men and women of the main group. In men, the level of IGF-I/IGFBP-1, IGF-I/IGFBP-2, IGF-I/IGFBP-3, IGF-II/IGFBP-1, IGF-II/IGFBP-2 and IGF-II/IGFBP-3 was 1.5–3.3 times higher on average; in women, the values and the spread were wider: 7.6 times, 4.3 times, 6 times, 12 times, 6.7 times and 8.1 times, respectively. At the same time, in the tumor tissue of the women of the main group, almost all indicators (with the exception of IGF-I/IGFBP-3) exceeded similar values in the tissue of men.

In the tissue of the perifocal zone, the balance between growth factors and their carrier proteins also changed. In men and women of the control group, all the coefficients of the ratio of growth factors to carrier proteins were higher than in the resection line by an average of 1.7–2.5 times, only IGF-I/IGFBP-3 and IGF-II/IGFBP-3 in women by 15 times and 11.3 times, respectively, but in men all coefficients had no significant differences from those in the tumor, whereas in women with the exception of IGF-I/IGFBP-2 and IGF-II/IGFBP-2.

In men of the main group in the perifocal zone, only the ratio coefficients of the first insulin-like growth factor to carrier proteins were lower than in the resection line: IGF-I/IGFBP-1, IGF-I/IGFBP-2, IGF-I/IGFBP-3 on average 1.5 times, the ratio of IGF-II to proteins the carriers had no significant differences from the indicators in the resection line. Compared with the tumor in the men of the main group in the perifocal zone, all the ratio coefficients, with the exception of IGF-II/IGFBP-2, were lower: IGF-I/IGFBP-1 by 5.4 times, IGF-I/IGFBP-2 by 2.1 times, IGF-I/IGFBP-3 by 4 times, IGF-II/IGFBP-1 by 3.1 times and IGF-II/IGFBP-3 by 2.3 times. In the women of the main group, all ratio coefficients in the perifocal zone were higher than in the resection line by 1.9–4.3 times, but lower than in the tumor by 1.3–5.8 times.

It turned out that in men in the main group, only the ratio coefficients of the first insulin-like growth factor to carrier proteins were lower than in the control group by an average of 2 times, while the ratio of IGF-II to carrier proteins had no significant differences. In the perifocal zone in women of the main group, compared with the perifocal zone of the control group, IGF-I/IGFBP-1 was 3.5 times higher, IGF-I/IGFBP-2 was 1.6 times higher, and IGF-II/IGFBP-1 was 1.7 times higher, but lower than IGF-II/IGFBP-2 1.3 times and IGF-II/IGFBP-3 2.3 times, only IGF-I/IGFBP-3 had no significant differences.

That is, when considering the ratio of IGF and their carrier proteins in patients of the control group, the indicators in the tissue of the perifocal zone were closer to the values in the tumor tissue. Another trend was noted in the tissue of the perifocal zone of patients of the main group. Thus, the ratio of IFG and carrier proteins in men was closer to the values in the conditionally intact tissue, and in women – to the values in the tumor tissue.

DISCUSSION

Currently, there is no doubt that IGF-axis signaling is crucial for cellular survival, proliferation, antioxidant function and control of cell damage and death in various organs and tissues, including the lungs [17; 18]. The family of insulin-like growth factors includes IGF-I, IGF–II, their receptors – IGF-IR and IGF-IIR, and proteins binding insulin-like growth factors – IGFBP-1–6 [19]. Studies have proven the role of IGF signaling in lung development, as well as in inflammatory diseases, cancer and fibrosis [20; 21]. IGF-I and IGF-II are involved in various physiological and pathophysiological processes, including fetal growth and development, metabolic disorders, congenital disorders, inflammation, fibrosis, cancer, acute lung injury [9]. IGF-II has also been found to be overexpressed in some types of cancer, which contributes to tumor growth and survival. At the tissue level, IGF-I and IGF-II are mainly overexpressed in various types of cancer and can serve as a mitogenic stimulus in a paracrine or autocrine manner, and a violation of the regulation of the IGF axis has been demonstrated at all stages of lung carcinogenesis [22].

In his research, Shin J. with co-authors (2022) deployed that COVID-19 infection disrupts the signaling pathway of insulin-like growth factor in respiratory, metabolic and endocrine cells and tissues [23], resulting in violations of innate immune functions, such as neutrophil chemotaxis, phagocytic cell function and recruitment of inflammatory macrophages in tissues [24].

It turned out that even conditionally intact lung tissue taken on the resection line had differences in the

studied parameters of the IGF axis in patients of the control and main groups, and it was in patients who underwent COVID-19 in severe form in the studied tissue that the level of IGF-I and IGF-II was elevated, and the carrier proteins either decreased, or did not change their concentration, with the exception of IGFBP-2. This fact may indicate that in patients with lung cancer, the tumor microenvironment changes under the influence of a severely suffered COVID-19 disease. In particular, it is known that persistent unregulated inflammation at the site of injury disrupts the regeneration process and ultimately leads to the formation of tissue fibrosis and scarring [25]. And human observational studies conducted by Shin and co-authors (2022) showed that higher basal expression of insulin-like growth factor receptors may be associated with an increase in the age of lung tissue in men, as well as with comorbid diseases such as obesity and type 2 diabetes mellitus, which are well-established risk factors for severity and COVID-19 mortality [23]. It is noteworthy that higher expression of IGF receptors and lower expression of IGF/insulin signaling pathway mediators are largely associated with unfavorable critical outcomes in patients with COVID-19 and worse molecular signs of the disease, such as elevated levels of IL-1 and IL-6, cell damage and death [23].

There are six known types of IGFBP, of which IGFBP-3 is the most studied. One of the well-studied roles of IGFBP involves the delivery of IGF to target cells as its endocrine function. In addition, IGFBP-3 secretion has been reported in various tissues, which indicates its paracrine or autocrine function, in addition to endocrine. The role of IGFBP, depending on the insulin-like growth factor, includes facilitated delivery of IGF to its receptors on the cell surface and activation of the downstream signaling cascade associated with it [26].

It is noteworthy that the tumor tissue in patients with lung cancer of the main group, regardless of gender, contained significantly higher concentrations of IGF-I and IGF-II, but lower levels of IGFBP-1 binding proteins, compared with those in men and women of the control group. This may be due to the greater aggressiveness of the tumor process in patients who have undergone COVID19 in severe form, with lung tissue damage. In addition, there is evidence that lung cancer tissue is characterized by increased local production of IGF-I, IGF-II and IGF-I receptor (IGF-IR), but reduced IGFBP expression. Modulated expression of these molecules is associated with aggressive disease, local lymph node metastases, and poor clinical outcomes [27]. Several IGF-IR inhibitors are under clinical development for the treatment of solid tumors, including lung cancer [22].

CONCLUSIONS

These literature data are consistent with the results obtained by us on an increase in the production of IGF-I, IGF-II in the tumor tissue of men and women of the control group and a decrease in the expression of IGF-binding protein-3. In addition to this, we showed a change in the level of two more carrier proteins, which is of a gender nature: in the tumor tissue of men, the expression of IGFBP-1 and IGFBP-2 was also increased, and in the tumor tissue of women – IGFBP-2. Violations in the system of insulin-like factors were especially clearly reflected in the study of the ratio of IGF and carrier proteins. The increase in the ratio of IGF and carrier proteins in the tumor tissue shown by us in this study may indicate an excessive accumulation of IGF in it, which contributes to the growth and survival of neoplasm. The most pronounced disorders in the system of insulin-like growth factors were found in the tumor tissue and intact lung of patients who underwent COVID-19 in severe and moderate form. Considering that IGF-I is involved in inflammation, fibrosis, cancer, acute lung injury and ARDS, and is also a biomarker in patients with hyperoxia-induced lung damage, the results obtained can be considered as a reaction of patients' lung tissue to the infection and its intensive therapy.

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Information about authors:

Oleg I. Kit – Academician at the Russian Academy of Sciences, Dr. Sci. (Med.), professor, general director, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-3061-6108, SPIN: 1728-0329, AuthorID: 343182, Scopus Author ID: 55994103100, ResearcherID: U-2241-2017

Elena M. Frantsiyants – Dr. Sci. (Biol.), professor, deputy general director for science, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0003-3618-6890, SPIN: 9427-9928, AuthorID: 462868, ResearcherID: Y-1491-2018, Scopus Author ID: 55890047700

Dmitriy A. Kharagezov – Cand. Sci. (Med.), oncologist, surgeon, head of the department of thoracic oncology, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-0640-2994, SPIN: 5120-0561, AuthorID: 733789, ResearcherID: AAZ-3638-2021, Scopus Author ID: 56626499300

Valeriya A. Bandovkina✉ – Dr. Sci. (Biol.), senior researcher of the laboratory for the study of pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2302-8271, SPIN: 8806-2641, AuthorID: 696989

Natalya D. Cheryarina – doctor at the laboratory for the study of the pathogenesis of malignant tumors, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-3711-8155, SPIN: 2189-3404, AuthorID: 558243

Yuliya A. Pogorelova – Cand. Sci. (Biol.), senior researcher at laboratory of malignant tumor pathogenesis study, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: http://orcid.org/0000-0002-2674-9832, SPIN: 2168-8737, AuthorID: 558241

Yuriy N. Lazutin – Cand. Sci. (Med.), associate professor, leading researcher of the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-6655-7632, SPIN: 5098-7887, AuthorID: 364457

Anton G. Milakin – MD, oncologist of the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0002-2589-7606, SPIN: 7737-4737, AuthorID: 794734

Igor A. Leyman – Cand. Sci. (Med.), MD, oncologist of the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-2572-1624, SPIN: 2551-0999, AuthorID: 735699

Oleg N. Stateshniy – MD, oncologist at the department of thoracic surgery, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation. ORCID: https://orcid.org/0000-0003-4513-7548, SPIN: 9917-1975, AuthorID: 1067071

Contribution of the authors:

Kit O. I. – scientific management of the research; final analysis of the research;
Frantsiyants E. M. – scientific guidance, research concept, material analysis, manuscript writing, final conclusions;
Kharagezov D. A. – management of patients, surgical stages of treatment, critical analysis of the material;
Bandovkina V. A. – preparation and editing of the manuscript, verification of critical intellectual content;
Cheryarina N. D. – statistical analysis of the results obtained, editing of the manuscript;
Pogorelova Yu. A. – ELISA tests, data analysis;
Lazutin Yu. N. – analysis of clinical data of patients;
Milakin A. G. – management of patients, review of publications, technical editing of the article;
Leyman I. A. – patient management, critical data analysis;
Stateshny O. N. – patient management, critical data analysis.
All authors have made an equivalent contribution to the preparation of the publication.