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# Metastasis suppressor kisspeptin (KISS1) in the blood serum of lung cancer patients

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## ABSTRACT

**Aim.** To conduct a comparative assessment of the content of kisspeptin (KISS1) metastasis suppressor in the blood serum of apparently healthy individuals and patients with lung cancer (LC) and to analyze the associations between the KISS1 level and clinical and pathological characteristics of the disease.

**Materials and methods.** The study included 74 LC patients and 46 apparently healthy individuals. Stage I LC was diagnosed in 8 patients, stage II LC – in 7 patients, stage III LC – in 28 patients, and stage IV LC – in 31 patients. According to the histologic pattern, 32 tumors were characterized as adenocarcinoma, 29 – as squamous-cell carcinoma, 11 – as small-cell LC (SCLC), and 2 – as large-cell lung carcinoma. The pre-treatment KISS1 level in the blood serum was determined using the enzyme-linked immunosorbent assay kit (KISS1, Cloud-Clone Corp., USA).

**Results.** The median serum KISS1 level in LC patients was 213 (range 7.8–716) pg / ml and was significantly higher than in the control group – 83.4 (0–180) pg / ml ($p < 0.0001$). The ROC analysis of the diagnostic value of serum KISS1 level demonstrated that the sensitivity of the test in relation to the healthy controls was 70% at a cut-off value of 152 pg / ml, and the specificity was 85% (AUC – 0.817; $p < 0.0001$). In stage I–II LC, the sensitivity did not exceed 50%. The level of KISS1 in the blood serum did not depend on the histologic type of the tumor. No significant differences in the serum KISS1 levels were observed both between non-small cell lung cancer (NSCLC) on the whole and neuroendocrine SCLC and between the main histologic types of NSCLC. The level of KISS1 increased with the disease stage ($p < 0.05$). However, none of the TNM staging system indices significantly influenced the level of the marker. No differences were found between serum KISS1 levels in patients with central or peripheral localization of the tumor.

**Conclusion.** The KISS1 level was elevated in LC patients compared to healthy controls and was a stage-dependent marker. It has high diagnostic specificity but insufficient sensitivity, especially at early stages of the disease. Based on the results of this study and literature data on the role of KISS1in NSCLC, we conclude that clinical implications of KISS1 in this disease require further research.

**Keywords:** lung cancer, KISS1, blood serum

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**Conformity with the principles of ethics.** All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at N.N. Blokhin National Medical Research Center of Oncology (Protocol No. 6 of 06.06.2023).

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# Супрессор метастазирования кисспептин (KISS1) в сыворотке крови больных раком легкого

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**РЕЗЮМЕ**

**Цель** – сравнительная оценка содержания супрессора метастазирования кисспептина (KISS1) в сыворотке крови практически здоровых людей и больных раком легкого (РЛ), анализ взаимосвязи уровня KISS1 с основными клинико-морфологическими особенностями заболевания.

**Материалы и методы.** Обследованы 74 больных РЛ и 46 здоровых доноров. У 8 пациентов диагностирована I стадия, у 7 – II, у 28 – III, у 31 – IV стадия. По гистологическому строению 32 опухоли представляли собой аденокарциному, 29 – плоскоклеточный, 11 – мелкоклеточный и две – крупноклеточный рак. Содержание KISS1 в сыворотке крови определяли до лечения наборами реактивов для иммуноферментного анализа (Kisspeptin 1 – KISS1, Cloud-Clone Corp., США).

**Результаты.** Медиана содержания KISS1 в крови больных РЛ составила 213 (пределы колебаний 7,8–716) пг/мл и была значимо выше, чем в контрольной группе: 83,4 (0–180) пг/мл ($p < 0,0001$). ROC-анализ диагностической значимости сывороточного уровня KISS1 показал, что чувствительность данного теста относительно здорового контроля при пороговом уровне 152 пг/мл составляет 70%, специфичность – 85% (AUC – 0,817; $p < 0,0001$). При I–II стадии заболевания чувствительность не превышает 50%. Содержание KISS1 в сыворотке крови не зависит от гистологического типа опухоли. Значимых различий уровней KISS1 как между НМРЛ в целом и нейроэндокринным МРЛ, так и между основными гистологическими типами НМРЛ не наблюдается. Уровень KISS1 возрастает с увеличением стадии заболевания ($p < 0,05$), однако ни один из индексов системы TNM значимо не влияет на уровень маркера. Не обнаружено различий между сывороточными уровнями KISS1 у пациентов с центральной или периферической локализацией опухоли.

**Заключение.** Уровень KISS1 в сыворотке крови больных РЛ повышен по сравнению с контролем и является стадия-зависимым маркером. Он обладает высокой диагностической специфичностью, но недостаточной чувствительностью, в особенности на ранних стадиях заболевания. Основываясь на собственных результатах и данных литературы о роли KISS1 при НМРЛ, полагаем, что клиническое значение кисспептина при данном заболевании заслуживает дальнейшего более углубленного изучения.

**Ключевые слова:** рак легкого, KISS1, сыворотка крови

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## INTRODUCTION

Kisspeptin, or metastatin, a product of the *KISS1* gene, is now considered to be a metastasis suppressor for different tumors. The *KISS1* gene, which encodes a protein composed of 145 amino acid residues (kisspeptin-145) that subsequently cleaves into minor functionally active proteins, was discovered in 1996 as a melanoma metastasis suppressor gene [1, 2]. Metastasis suppression after the restoration of KISS1 expression was also demonstrated in several other cell lines characterized by high metastatic potential [3–5]. Under normal conditions, the physiological role of kisspeptin includes the invasion of placental trophoblasts as well as the regulation of gonadotropin secretion [6]. The mechanisms mediating the ability of this protein to suppress metastasis formation are still insufficiently explored. However, it is known that it exerts its effects through the GPR54 receptor associated with G-proteins from the Gq/11 subfamily [7, 8].

The largest expression of the *KISS1* and *GPR54* genes is observed in the placenta and various brain structures, including the hypothalamus and basal nucleus [9], while low expression is found in the pancreas, kidneys, lungs, prostate, and small intestine [7]. The expression level of *KISS1* has ambiguous prognostic value in different malignant tumors. Particularly, it correlates with the invasiveness of some human tumors, including renal cell cancer, melanoma, esophageal cancer, bladder cancer, breast cancer, ovarian cancer, and prostate cancer [10]. The study of metastasis suppressor genes and their products not only increases the understanding of the mechanisms of tumor progression, but also has practical value for the diagnosis, prognosis, and the establishment of new molecular targets for antitumor therapy [11]. In terms of noninvasive and possibly early diagnosis of tumors, the most interesting approach consists not in the study of gene and protein expression in tumor tissue, but rather in the identification of their soluble forms circulating in the peripheral blood. Quite a few works devoted to the study of circulating kisspeptin in patients with pancreatic [12], colorectal [13], and gastric cancer [14] have been published. The data on the role of the *KISS1* gene and its product, kisspeptin, in lung cancer (LC) are scarce and rather ambiguous [15–18].

The aim of this study was to conduct a comparative assessment of KISS1 content in the blood serum of apparently healthy persons and patients with lung cancer and to analyze the associations between the marker level and the clinical and pathologic characteristics of the disease.

## MATERIALS AND METHODS

The study included 74 LC patients (54 males and 20 females) aged 31–85 years (median – 74 years) undergoing examination and treatment at the N.N. Blokhin National Medical Research Center of Oncology, and 46 apparently healthy persons (22 males and 24 females) aged 29–76 years (median – 45 years). The clinical diagnosis was confirmed in all patients by the results of the morphologic assessment of the tumor according to the 2021 WHO Classification of Lung Tumors (WHO, 2021). Stage I LC was diagnosed in 8 patients, stage II – in 7 patients, stage III – in 28 individuals, and stage IV – in 31 patients. By the histologic pattern, 32 tumors were characterized as adenocarcinoma (AC), 29 – as squamous-cell carcinoma, 11 – as small-cell LC (SCLC), and 2 – as large-cell lung carcinoma.

All procedures performed in the study involving patients and healthy controls comply with the standards of the Ethics Committee of the Research Center and the Declaration of Helsinki (1964) and its further amendments, or equivalent ethical norms. All participants included in the study signed an informed voluntary consent. The study was approved by the local Ethics Committee at N.N. Blokhin National Medical Research Center of Oncology (Protocol No. 6 of 06.06.2023).

KISS1 content in the blood serum obtained by a standard procedure before the initiation of a specific treatment was measured with the help of the reagent kit for direct enzyme-linked immunosorbent assay Kisspeptin 1 – KISS1 (Cloud-Clone Corp., USA) according to the manufacturer's instructions. The registration of the results was performed using the automatic immune enzymatic analyzer BEP 2000 Advance (Siemens Healthcare Diagnostics, Germany). The content of the marker was expressed in picograms (pg) per 1 ml of blood serum.

The data obtained were processed using the GraphPad Prism 9.0 program package. The nonparametric Mann – Whitney and Kruskal – Wallis tests, the median test (*Me (25–75%)),* and the Spearman's rank correlation coefficient were used to compare the parameters and analyze their relationships. The analysis of the diagnostic value of the test based on the assessment of its sensitivity and specificity was performed by constructing ROC curves and calculating the area under the curve (AUC). Differences and correlations were considered statistically significant at $p < 0.05$.

## RESULTS

At the first stage of the research, KISS1 content in the blood serum of LC patients was compared to that of healthy controls to evaluate the possible diagnostic value of this marker. Median serum KISS1 concentration in LC patients was 213 (range 7.8–716) pg / ml and was significantly higher than in the control group – 83.4 (range 0–180) pg / ml (Fig. 1, *a*; $p < 0.0001$).

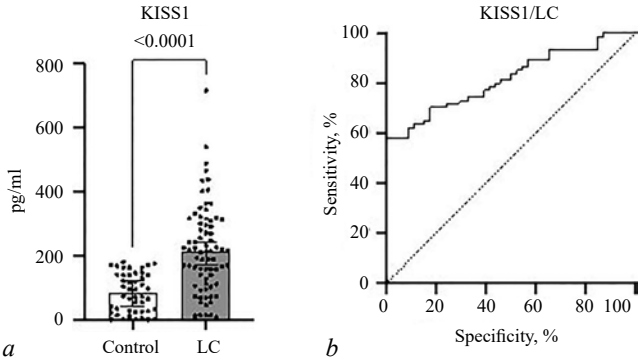


Fig. 1. Comparative analysis of KISS1 content in the blood serum of LC patients and the control group (a), ROC analysis of KISS1 in LC patients (b): area under the curve (AUC) is 0.829 ($p < 0.0001$)

The ROC analysis of the diagnostic value of the KISS1 level in the serum of LC patients demonstrated (Fig. 1, *b*) that the sensitivity of this test in relation to healthy controls was 70% at an optimal cut-off value of 152 pg / ml, and the specificity was 85% (AUC was 0.817 with a 95% confidence interval (CI) of 0.759–0.899; $p < 0.0001$). The analysis of the marker level depending on the disease stage (Table 1) indicates that at early (I–II) clinical stages, the sensitivity did not exceed 50%.

The serum KISS1 level in male patients was significantly higher than in female patients (*Me* 221 and 162 pg / ml, respectively; $p < 0.05$). Similar significant differences were also observed in the control group. A weak but statistically significant positive correlation was found between serum KISS1 level and the age of LC patients ($r_s = 0.31$; $p = 0.007$). Meanwhile, in the control group, the KISS1 – age correlation was negative: $r_s = -0.29$; $p = 0.048$.

Next, we assessed serum KISS1 content in relation to the histologic type of LC. The comparison was made both between the groups of SCLC and non-SCLC (NSCLC) as a whole and between various types of NSCLC (Figure 2).

It was established that serum KISS1 content did not depend on the histologic type of the tumor, since no significant differences were found either between the combined NSCLC and neuroendocrine SCLC patient groups or between patients with various NSCLC variants. However, in all histologic types of LC, the KISS1 level was significantly higher than in the control group.

Based on the observation above, further analysis of associations of serum KISS1 levels with the indices of tumor advancement and localization was performed for the LC group as a whole, without considering the histologic pattern of the tumor (Table).

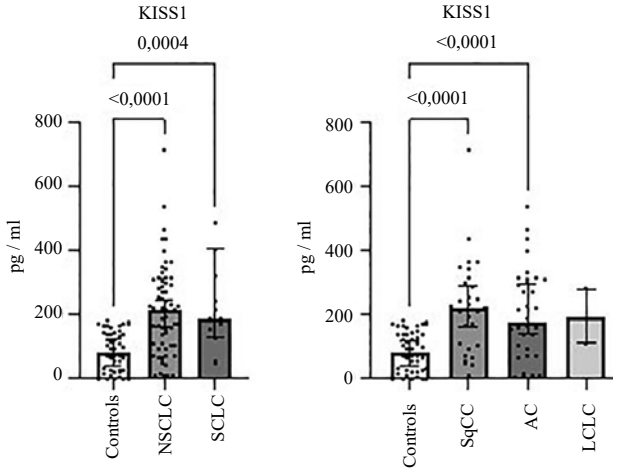


Fig. 2. KISS1 content in the blood serum of LC patients depending on the histologic type of the tumor

Table

**KISS1 content in the blood serum of LC patients in relation to clinical and pathological characteristics**

| Parameter | KISS1, pg / ml | | |
|---|---|---|---|
| | *Me* | 25–75% | *p* |
| Gender | | | |
| – male ($n = 54$); | 221 | 149.8–316 | 0.042 |
| – female ($n = 20$) | 162 | 77.7–230 | |
| Stage: | | | |
| I ($n = 8$); | 188 | 69.9–275 | |
| II ($n = 7$); | 148 | 45.1–193 | 0.042 |
| III ($n = 28$); | 241 | 157–351 | |
| IV ($n = 31$) | 216 | 139–296 | |
| Tumor size (T): | | | |
| – T1–T2; | 187.6 | 111.0–271.0 | 0.179 |
| – T3–T4 | 224.8 | 128.0–317.1 | |
| Nodal status (N): | | | |
| – N0; | 210.4 | 88.8–293.9 | 0.569 |
| – N+ | 215.8 | 119.5–314.2 | |
| Distant metastasis (M): | | | |
| – M0; | 201.6 | 88.4–303.5 | 0.405 |
| – M+ | 218.5 | 159.1–311.8 | |
| Localization: | | | |
| – central; | 224.8 | 106.9–316.6 | 0.248 |
| – peripheral | 178.1 | 109.9-255.2 | |

A statistically significant increase in the serum KISS1 concentration was observed along with progression of the disease stage ($p < 0.05$ according to the median test), but none of the TNM system criteria (the size of the primary tumor T, the presence of both regional N and distant metastases M) significantly affected the level of the marker. No differences were found between serum KISS1 levels in patients with central or peripheral localization of LC.

## DISCUSSION

We found that the level of KISS1 protein, the product of corresponding metastasis suppressor gene, in the blood serum of LC patients is significantly elevated compared to healthy controls and increases with progression of the disease. The study group included both patients with classical NSCLC, and those with neuroendocrine SCLC. However, no fundamental differences in serum KISS1 levels were found between these two LC types. No differences were found in different histologic variants of NSCLC. The analysis of the diagnostic value of serum KISS1 in LC demonstrated rather high (85%) specificity of this test in relation to healthy controls, but its sensitivity was only 70% for all participants and did not exceed 50% at early stages of LC.

The increase in the level of the soluble form of the metastasis suppressor KISS1 in the blood serum of LC patients as a whole, and particularly at advanced stages of the disease, is somewhat paradoxical from a fundamental point of view, but is consistent with the data of some publications devoted to the study of circulating KISS1 (in the blood serum or plasma) [12–14; 16]. All these studies demonstrated an increase in the level of this protein in patients with various tumors (pancreatic, colorectal, and gastric cancer) compared to healthy controls. Though in the most detailed of these publications [12], neither significant associations between KISS1 levels and the clinical and pathological characteristics of pancreatic cancer nor any effects of this marker on the overall and relapse-free survival of patients were found.

The study by S. Zheng et al. [19] demonstrated that *KISS1* expression at the mRNA level in NSCLC patients was significantly lower at advanced disease stages and was inversely correlated with regional metastasis. The authors also found that *KISS1* expression was higher in primary tumors than in the secondary metastatic focus, which indirectly confirms the functional role of KISS1 as a metastasis suppressor. Similar results were obtained by Y.B. Sun et al. [15]; according to their data, not only was KISS1 and KISS1R expression lower at stage IV NSCLC compared to stage IIIB LC, but also soluble KISS1 levels in the blood serum at the advanced stage were decreased. At the same time, the survival of patients with high tumor KISS1 and KISS1R expression was better than that of patients with tumors not expressing these proteins. At the same time, E.M. Karapanagiotou et al. [17] did not find any differences in plasma KISS1 levels between NSCLC patients and healthy controls, as well as between patients with locally advanced and metastatic cancer.

The results of our study, which indicate that KISS1 content in the blood serum increases with the progression of lung tumors, are consistent with the results of L. Gatti et al. [16], who demonstrated elevation of its level in NSCLC patients as compared to controls and a decrease in its level after surgery or chemotherapy.

## CONCLUSION

Currently, studying possible clinical implications of genes and proteins that function as metastasis suppressors in various cancers is becoming of particular interest. They are considered primarily as potential targets of new types of molecular-targeted therapy and as possible prognostic or diagnostic markers.

The present study demonstrates that the level of one of such proteins, KISS1 or kisspeptin, significantly increases in the blood serum of LC patients as compared to healthy controls regardless of the histologic type of the tumor and is a stage-dependent marker in this disease. It has sufficiently high diagnostic specificity (85%), but is not sensitive enough, especially at early stages of the disease. Based on our results and rather controversial literature data on the role of KISS1 in NSCLC, we conclude that the clinical significance of kisspeptin in LC deserves further in-depth study.

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## Authors' contribution

Gershtein E.S. – analysis of literature data, drafting of the manuscript. Kovaleva O.V. – analysis of literature data, statistical processing of research results. Kuzmin Yu.B., Alferov A.A. – acquisition of experimental data. Rogozhin D.V. – morphological examination of tumors. Stilidi I.S., Yanushevich O.O. – academic editing of the manuscript. Kushlinskii N.E. – conception and design, general management, academic editing of the manuscript. All authors have read and approved the final version of the manuscript before publication, agree to be responsible for all aspects of the work and ensure that they have properly considered and resolved issues related to the accuracy and integrity of all parts of the work.

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