

ORIGINAL ARTICLE

## MARKERS OF STRUCTURAL AND CELLULAR RENAL DAMAGE IN LOCALIZED RENAL CELL CARCINOMA BEFORE TREATMENT

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### ABSTRACT

**Purpose of the study.** The purpose of the study was to analyze parameters of molecular markers of structural and cellular renal damage in localized renal cell carcinoma (RCC) with determining the nature of the initial abnormalities in the kidney functional state before the treatment.

**Patients and methods.** The study included 46 patients receiving elective surgical treatment for localized renal cancer in the Department of Oncology, National Medical Research Centre for Oncology. The comparison group included the clinical and laboratory data of 13 healthy people comparable with the RCC patients in terms of age and gender. Cystatin C, IL-18, KIM-1, L-FABP, NGAL were determined in blood and urine in all patients.

**Results.** Evaluation of the kidney functional state of RCC patients showed that the initial values of serum creatinine and the glomerular filtration rate were similar to the reference levels in healthy people, but statistically significant differences were found in the ratios of cystatin C concentrations in the blood and urine in all patients, compared with normal values. Determination of L-FABP indices in RCC patients showed that their levels were 2.5 times higher than normal values, and the urine concentration of IL-18 was 1.7 times higher than normal values ( $p < 0.05$ ). Blood and urine levels of NGAL and KIM-1 did not differ significantly from the comparison group.

**Conclusions.** The development of localized RCC is accompanied by the formation of tubulointerstitial dysfunction with impaired renal filtration capacity. All RCC patients showed elevated endogenous markers of structural and cellular renal damage – cystatin C, L-FABP, and IL-18.

### Keywords:

localized renal cell carcinoma, acute renal injury, cystatin C, interleukin-18, NGAL, L-FABP

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## МАРКЕРЫ СТРУКТУРНОГО И КЛЕТОЧНОГО ПОЧЕЧНОГО ПОВРЕЖДЕНИЯ ПРИ ЛОКАЛИЗОВАННОМ ПОЧЕЧНО-КЛЕТОЧНОМ РАКЕ ДО НАЧАЛА ЛЕЧЕНИЯ

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### РЕЗЮМЕ

**Цель исследования.** Провести анализ показателей молекулярных маркеров структурного и клеточного почечного повреждения при локализованном почечно-клеточном раке (ПКР) с определением характера исходного уровня нарушений функционального состояния почек до начала лечения.

**Пациенты и методы.** В исследование включено 46 больных, находившихся на плановом хирургическом лечении по поводу локализованного рака почки в онкоурологическом отделении ФГБУ «НМИЦ онкологии» Минздрава России. В качестве группы сравнения использовали клинично-лабораторные данные 13 относительно здоровых людей, сопоставимых с группой больных ПКР по возрасту и полу. Изучали: цистатин С, ИЛ-18 (интерлейкин-18), КИМ-1 (молекула-1 повреждения почек (Kidney Injury Molecule-1)), L-FABP (жировой кислотный связывающий белок печени (Fatty Acid Binding Protein)), NGAL (нейтрофильный желатиназо-ассоциированный липокалин-2 (Neutrophil Gelatinase Associated Lipocalin)) в крови и моче.

**Результаты.** Оценка функционального состояния почек больных ПКР показала, что при исходных значениях креатинина сыворотки крови и скорости клубочковой фильтрации соответствующих референтным показателям здоровых людей имели место статистически значимые отличия в соотношении концентрации цистатина С в крови и моче у всех больных по сравнению с нормальными показателями. Исследование показателей L-FABP у больных ПКР в сравнении с группой здоровых людей показало, что концентрация данного показателя плазмы крови была в 2,5 раза выше нормальных значений, а концентрация ИЛ-18 в моче превышала нормальные значения в 1,7 раза ( $p < 0,05$ ). Показатели концентрации NGAL и КИМ-1 в крови и моче не имели значимых различий с группой сравнения.

**Заключение.** Развитие локализованного ПКР сопровождается формированием тубулоинтерстициальной дисфункции с нарушением фильтрационной способности почек. У всех больных ПКР были выявлены повышенные показатели эндогенных маркеров структурного и клеточного почечного повреждения – цистатина С, L-FABP и ИЛ-18.

### Ключевые слова:

локализованный рак почки, острое почечное повреждение, цистатин С, интерлейкин 18, NGAL, L-FABP

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## RELEVANCE

According to world statistics, kidney cancer (RP) is registered annually in 403.3 thousand people, which corresponds to the 15th place among the standardized indicators of the incidence rate. In the Russian Federation, a similar trend is observed, renal cell carcinoma (RCC) is diagnosed in 4 % of patients of both sexes, and among men it is detected in 4.7 %, ranking 3rd among tumors of the genitourinary system with an increase in incidence to 6.9 % among men of socially active age 30–59 years [1; 2]. The growth of malignant kidney diseases dictates the need for a more detailed approach to the study of the pathogenesis of the disease with the possibility of early diagnosis and the necessary correction of the resulting disorders.

Modern targeted drugs and current immunotherapy regimens, as well as new oncosurgery technologies, serve as a guarantee of successful treatment of RCC patients. The standard of surgical treatment of this category of patients is the performance of organ-preserving operations with radical removal of the tumor, which definitely helps to reduce the risk of cardiovascular complications and chronic kidney disease. According to a number of clinical studies, overall survival is comparable in patients after radical nephrectomy and kidney resection. At the same time, it should be noted that the frequency of acute renal injury (AKI) in the postoperative period is 30 % [3; 4]. This is due to factors related to changes in the patient population, the widespread use of potentially nephrotoxic drugs, contrast research methods and an increase in combined surgical interventions. Acute renal dysfunction leads to the formation of nephrosclerosis with the subsequent development and progression of chronic kidney disease (CKD), which has a clear tendency to increase morbidity rates [5]. As is known, AKI is characterized by a complex, morphofunctional state, which is formed both as a result of external factors and due to a number of reasons that cause primary organ damage. In case of a tumor lesion, the formation of renal dysfunction is due to a combination of several pathological processes: firstly, mechanical invasion of the tumor with an anatomical defect in the structure of the renal tissue and destruction of nephrons; secondly, a change in the functional state of the organ due to the influence of biologically active components secreted by the

tumor [6; 7]. In other words, the manifestation of AKI in RCC patients may be due not only to a decrease in the number of normally functioning nephrons after organ-preserving operations and surgical trauma, but also be directly related to concomitant somatic diseases and the presence of initial kidney dysfunctions due to the development of a tumor process in the organ [8].

Of course, the detection of AKI triggers in the perioperative period in patients with localized RP during organ-preserving surgical interventions dictates the need for a more detailed approach to the study of the pathogenesis of the disease with the possibility of timely correction of functional disorders [9].

It would seem that the modern capabilities of computed tomography, renoscintigraphy and excretory urography make it possible to register violations of the structural and functional state of the kidney as much as possible, however, the standard approach in diagnosis does not always form a complete picture of the nature of the disease and the reserve capabilities of the body in the conditions of the development of the tumor process. In order to determine the choice of the optimal volume of surgical intervention, the criteria of the nephrometric diagnostic system R.E.N.A.L. are used. (Radius, Exophytic/endophytic, Proximity, Anterior/posterior, Location), which is based on the analysis of the complex morphometric characteristics of the tumor process with the determination of the level of complexity of the planned operation. The evaluation of the parameters takes into account the endophytic or exophytic growth of the tumor, the diameter of the tumor node with the determination of the anatomical features of the tumor and its location relative to the collecting system of the kidney [10].

The generally recognized use of this scale orients the surgeon in choosing the volume of the planned operation, but does not allow to fully assess the functional state of the renal parenchyma with the determination of the prognosis of renal failure in the postoperative period. According to Kidney Disease Improving Global Outcomes – "Initiative to Improve Global Outcomes of Kidney Diseases" (KDIGO) [11], AKI is diagnosed with a persistent, for 48 hours or more, maximum change in serum creatinine level and/or its increase by 1.5 times within 7 days compared to the baseline level. In this regard, it should be noted that at the present stage of RCC therapy, the assessment of the dynamics of indicators of

markers of functional-structural and cellular renal damage in the process of antitumor treatment is of particular relevance. Thus, the identification of preclinical signs of metabolic dysfunction of the kidney, as a result, may be an important predictor in the development of acute renal failure during radical surgical treatment [5; 12]. Early diagnosis of the imbalance of molecular markers determines the final effect of therapy and the course of the disease in patients with RCC.

In this regard, in order to predict the development and early diagnosis of AKI, our attention was drawn to the use of markers of damage to the structure of the kidneys. Specific markers cystatin C, interleukin-18 (IL-18), fatty Acid Binding protein of the liver/Fatty Acid Binding Protein (L-FABP), neutrophil gelatinase-associated lipocalin-2/Neutrophil Gelatinase Associated Lipocalin (NGAL), Kidney Injury Molecule-1/Kidney Injury Molecule-1 (KIM-1) are of great practical importance, determining the tactics of treatment of patients with impaired function kidneys. It should be noted that cystatin C is the main and most accurate marker in the diagnosis of renal damage and assessment of glomerular filtration rate (GFR) [9]. Interleukin-18 refers to proinflammatory cytokines. This marker is secreted in the distal tubules of the kidneys when exposed to various nephrotoxic factors on the human body, as well as after an episode of ischemia. The active form of IL-18 enters the urine during the development of AKI. However, it should be borne in mind that an increased level of plasma IL-18 is characteristic not only for AKI, but also for autoimmune and inflammatory diseases, including sepsis [5]. Neutrophilic lipocalin-2 (NGAL) is one of the most studied markers of structural kidney damage. This protein is secreted by various tissues of the body, including epithelial cells of the proximal tubules of the kidneys as a result of organ damage. It is a proven fact that an increase in the concentration of NGAL in urine and blood is recorded in cases of renal dysfunction and the development of CKD [13; 14]. Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein with a molecular weight of 90 kDa. Normally, with unchanged kidney tissues, KIM-1 molecules are not detected in blood and urine. High protein expression is detected in cells of regenerating proximal renal tubules after toxic or ischemic damage and is not specific to other damaging agents [14–16]. Detection of L-FABP

in the patient's blood and urine is recorded in response to damage to renal structures. An increase in the excretion of L-FABP in the urine indicates the progression of kidney damage [14]. Taking into account the problem of AKI formation in the early postoperative period in patients with RCC, the study of markers of structural and cellular renal damage before treatment will optimize early diagnosis, determine the timing and tactics of nephroprotective therapy.

**The purpose of the study:** to analyze the indicators of molecular markers of structural and cellular renal damage in localized renal cell carcinoma with determination of the nature of the initial level of violations of the functional state of the kidneys before the start of treatment.

## MATERIALS AND METHODS

This study was conducted at the National Medical Research Centre for Oncology with the approval of the Ethical Committee of the institution and voluntary consent to the participation and processing of personal data in accordance with the standards of the Helsinki Declaration (1964) as amended in 2013. 59 patients were examined. Inclusion criteria: age over 18 years, documented consent of the patient to conduct the study, normal blood creatinine levels. Exclusion criteria: age less than 18 years, refusal of the patient to participate in the study, elevated blood creatinine levels. In all patients, the following parameters were studied in this study: cystatin C, interleukin-18 (IL-18), Kidney Injury Molecule-1 (KIM-1), fatty Acid binding protein of the liver/Fatty Acid Binding Protein (L-FABP), neutrophil gelatinase-associated lipocalin-2/Neutrophil Gelatinase Associated Lipocalin (NGAL) in blood plasma and urine.

The main group included 46 patients with RCC who were treated in the oncurological department. The age criteria of patients with RP at the time of the study were presented: men 30–44 years – 2 patients (6.6 %), 45–59 years – 6 patients (20.3 %), 60–74 years – 15 patients (49.7 %), 75 years and older – 7 patients (23.4 %); women 30–44 years – 1 patient (6.2 %), 45–59 years – 5 patients (31.3 %), 60–74 years – 9 patients (55.8 %), 75 years and older – 1 patient (6.2 %). The median age was 58 (29–76) years. It should be noted that males prevailed in the cohort of patients – 30 out of 46 people (65.3 %). Our data

are consistent with literature data indicating that the incidence of RCC among men is 1.5–2 times higher than in women [17]. According to the preoperative examination, the distribution by stages of the oncological process is represented by T1aN0M0 in 25 patients (54.3 %), T1bN0M0 in 21 patients (45.7 %). Morphological characteristics of the tumor are presented: RCC light-cell variant of the structure in 19 of 46 (41.3 %), papillary in 16 (34.8 %) chromophobic in 11 (23.9 %) patients, with the prevalence of highly differentiated processes in 23 patients (50.0 %). Concomitant diseases in patients with RCC are presented in the Table 1.

It should be noted that according to general clinical and anamnestic examinations, the vast majority of patients – 91.3 % had concomitant diseases, which are classified as modifiable risk factors for the development and progression of chronic kidney disease [11].

As a comparison group, clinical and laboratory data of 13 relatively healthy people, comparable to the group of patients with RCC by age and gender, were used.

Indicators of markers of renal damage were carried out before treatment and determined by enzyme immunoassay using standard test kits: cystatin C

(BioVendor, Czech Republic), IL-18 (Bender Medsystems, USA), NGAL (BCM Diagnostics, USA), KIM-1 (BCM Diagnostics, USA), L-FABP (Hycultbiotech, Netherlands).

Statistical support was carried out using a package of certified application programs Statistica 6.0. (StatSoft, USA). The significance of the differences in the average values of the indicator was carried out according to the Student-Fisher t-criterion for independent samples with reliable indicators at a significance level of  $p < 0.05$ .

## RESEARCH RESULTS AND DISCUSSION

A comprehensive assessment of the functional state of the kidneys of patients with RCC showed that the initial values of serum creatinine corresponded to the reference values of healthy people – from 50 to 110 mmol/l and amounted to  $63.9 \pm 26.8$  mmol/l ( $41.1–101.8$ ) ( $p < 0.05$ ). The calculation of the initial GFR was performed according to the formula Modification of Diet in Renal Disease study with classification according to the National Kidney Foundation/ Kidney Disease Outcomes Quality Initiative classification National Kidney Foundation [18]. The median GFR was 73 (55–103) ml/min/1.73 m<sup>2</sup>. These indicators, at first

Table 1. Concomitant diseases in the group of patients with RCC

| Concomitant disease                         | RCC patients (n = 46) |      |
|---|-----------------------|------|
|   | Abs. n.               | %    |
| Not detected                                | 4                     | 5.3  |
| Diseases, that don't impact the RCC flow    |                       |      |
| COPD  | 3                     | 3.9  |
| Bronchial Asthma                            | 1                     | 1.3  |
| Hepatobiliary system chronic diseases       | 7                     | 9.2  |
| Lower limb veins varices                    | 14                    | 19.4 |
| Peptic ulcer of the stomach and duodenum 12 | 2                     | 2.6  |
| Diseases, that impact the RCC flow          |                       |      |
| Diabetes mellitus                           | 7                     | 9.2  |
| Arterial hypertension                       | 13                    | 17.6 |
| Cardiovascular diseases                     | 9                     | 11.8 |
| Kidney stones                               | 3                     | 3.9  |
| Chronic urinary tract infections            | 2                     | 2.6  |
| Obesity/metabolic syndrome                  | 5                     | 6.6  |



glance, create an idea of the normal functioning of the organ during the development of a malignant tumor in a patient. However, according to the modern concept of AKI development, the concentration of creatinine and GFR in blood plasma during the development of renal dysfunction are not sufficiently informative criteria. Thus, the variability of creatinine concentration depends on many factors such as gender, weight, age, composition of the diet, body mass index, etc. [19–21].

The most accurate and promising endogenous marker in the assessment of renal damage is cystatin C, which is produced by the body's nuclear cells and enters the bloodstream evenly, maintaining a constant level of concentration in blood plasma. Cystatin C is an inhibitor of lysosomal proteinases, the main function of which is aimed at protecting the body from uncontrolled activation of proteolysis of its own proteins. Low affinity to other serum proteins and small molecular weight allows cystatin C to be freely excreted in the renal glomeruli. Due to megalin-kubulin-mediated endocytosis, cystatin C is able to be maximally metabolized in the epithelial cells of the proximal tubules of the kidneys [22]. An increase in the excretion of cystatin C and an increase in its concentration in urine indicates a violation of reabsorption in the proximal tubules and the formation of tubular dysfunction [23].

In our study, the determination of the concentration of cystatin C before the start of treatment showed that in 21 patients (45.7 %) in blood plasma, this indicator varied within normal values, in 25 patients (54.3 %) the content of cystatin C exceeded 1000 ng/ml. Subsequently, all patients of the main group were divided into 2 subgroups: 1st – cystatin with 1000 ng/ml and below, 2nd – cystatin With above 1000 ng/ml. The results of the study of cystatin C in the blood showed that in all patients with normal values of cystatin C, the glomerular filtration rate corresponded to physiological values, with an increased concentration of cystatin C, GFR was almost 1.5 times lower compared to healthy people ( $p < 0.05$ ) (Table 2).

When evaluating the data, it was determined that statistically significant differences occurred in the ratio of the concentration of cystatin C in the blood and urine of all patients compared with normal indicators. So, in subgroup 1, the concentration of cystatin C in the blood was 1.8 times lower, and in subgroup 2 – 1.4 times higher ( $p < 0.05$ ) compared to healthy. The content of cystatin C in urine in subgroup 1, with normal GFR and serum creatinine values was increased almost 2 times ( $p < 0.05$ ) In subgroup 2, with elevated plasma cystatin C with reduced GFR, indicators within normal values were recorded. The

Таблица 2. Показатели маркеров почечного повреждения в плазме крови у больных ПКР до начала лечения и здоровых пациентов ( $M \pm m$ )

| Indicator                   | Study group                    |                                     |                                      |
|-----------------------------|--------------------------------|-------------------------------------|--------------------------------------|
|                             | Healthy people<br>( $n = 13$ ) | RCC patients                        |                                      |
|                             |                                | 1st subgroup ( $n = 21$ )           | 2nd subgroup ( $n = 25$ )            |
| Cystatin C in blood (ng/mg) | $877.1 \pm 81.9$               | $787.4 \pm 110.3$ (638.9–919.3)     | $1284.0 \pm 113.7^1$ (1196.8–1335.7) |
| Cystatin C in urine (ng/mg) | $1068.7 \pm 83.4$              | $2154.1 \pm 223.6^1$ (194.8–4086.4) | $1088.2 \pm 86.4$ (510.5–2035)       |
| Blood L-FABP (ng/ml)        | $0.42 \pm 0.03$                | $0.37 \pm 0.07$ (0.21–0.6)          | $0.92 \pm 0.09^1$ (0.7–0.33)         |
| Urine L-FABP (ng/ml)        | $0.34 \pm 0.21$                | $0.28 \pm 0.03$ (0.15–0.49)         | $0.69 \pm 0.05^1$ (2.04–0.018)       |
| Blood IL-18 (pg/ml)         | $33.7 \pm 2.7$                 | $20.0 \pm 1.8$ (8.7–44.4)           | $90.7 \pm 8.6^1$ (18.7–259)          |
| Urine IL-18 (pg/ml)         | $19.8 \pm 2.2$                 | $18.0 \pm 2.4$ (6.3–32.2)           | $28.6 \pm 2.4^1$ (3.4–56.3)          |
| Blood NGAL (ng/ml)          | $3.06 \pm 0.30$                | $2.65 \pm 1.00$ (1.7–4.1)           | $3.57 \pm 0.80$ (2.2–6.3)            |
| Urine NGAL (ng/ml)          | $1.11 \pm 0.21$                | $0.23 \pm 0.05$ (0.06–0.17)         | $0.31 \pm 0.05$ (0.02–0.46)          |
| Blood KIM-1 (ng/ml)         | $0.21 \pm 0.01$                | $0.18 \pm 0.02$ (0.07–0.36)         | $0.14 \pm 0.01$ (0.06–0.27)          |
| Urine KIM-1 (ng/ml)         | $0.55 \pm 0.21$                | $1.30 \pm 0.10$ (0.09–2.6)          | $1.50 \pm 0.20$ (0.4–2.8)            |

Note: <sup>1</sup> – the significance of differences in comparison with healthy ( $p < 0.05$ ). IL-18 – interleukin-18; L-FABP – fatty acid binding protein of the liver; KIM-1 – kidney damage molecule-1; NGAL – neutrophil lipocalin-2.

results obtained indicate the diagnostic value of determining the concentration of cystatin C as the most accurate and early indicator of the development of renal damage at the preclinical stage. The nature of these changes in the concentration of cystatin C can be associated with the presence of renal dysfunction caused by a tumor lesion of the kidney [23].

In order to predict the development of AKI in patients who were scheduled for surgical treatment in the volume of kidney resection, a more detailed study of the levels of markers was conducted: L-FABP, IL-18. The data is given in Table 2.

When studying the concentrations of L-FABP and proinflammatory cytokine IL-18 in blood plasma and urine in patients with RCC before the start of surgical treatment, significant differences were revealed compared with healthy people (Table 2). L-FABP is a fatty acid binding protein of the liver, which belongs to the markers of the cytoplasmic protein family with a molecular weight of 15 kDa and participates in intracellular transport of long-chain fatty acid with expression by liver cells in response to the damaging factor. It is known that L-FABP is also expressed in the straight and convoluted parts of the renal tubules in acute interstitial tissue damage and is not detected in urine in healthy people. A number of researchers have noted the important role of L-FABP in the development of oxidative stress as an effective cytoprotector [24]. Analysis of clinical data showed that in the preoperative period, L-FABP plasma values were 1.9 times higher than those in the comparison group ( $p < 0.05$ ). The concentration of L-FABP in urine was increased 2.3-fold ( $p < 0.05$ ) only in patients of subgroup 2, who previously had an increased concentration of cystatin C and a decrease in GFR with a diagnosed preclinical stage of CKD. Probably, this increase in the level of L-FABP in patients with RCC compared to a group of healthy individuals indicates functional disorders with damage to the epithelium of the proximal tubules of the kidneys, which can be regarded as a preclinical change in the functional and structural components of the kidneys. The results obtained can be compared with the studies conducted by Kamiyo-Ikemori A. in patients at an early stage of nondiabetic CKD, in which the level of L-FABP concentration in urine was significantly higher than the reference values [18; 21]. When assessing the IL-18 indicators, it was revealed that in comparison with the group of healthy patients in patients with RCC, the concentration of this indicator of blood plasma

was 2.5 times higher than normal values, and the concentration of IL-18 in urine exceeded normal values by 1.7 times ( $p < 0.05$ ). According to the literature, an increase in the concentration of IL-18 and L-FABP in urine is observed with the development of renal insufficiency [24–26]. The simultaneous increase of IL-18 and L-FABP markers in the blood of patients with RCC before treatment was regarded by us as a sign associated with the development of a malignant process in the kidney. Additionally, in order to assess the full picture of changes in the structural and functional state of the kidneys during the malignant process, we studied and analyzed NGAL and KIM-1 markers. As can be seen from Table 2, the concentration of NGAL and KIM-1 in blood and urine had no significant differences with the comparison group. Accordingly, these markers are not advisable to use in order to determine renal dysfunction in the early stages of the disease. However, at the present stage of development of oncology, the dynamics of indicators of molecular markers of renal damage KIM-1 and NGAL should be considered as a predictor of effective antitumor treatment of patients with RCC.

## CONCLUSION

As a result of this study, it was found that the development of localized kidney cancer is accompanied by the formation of tubulointerstitial dysfunction with impaired filtration capacity of the kidneys. Thus, elevated indicators of endogenous markers of structural and cellular renal damage – cystatin C, L-FABP and IL-18 were detected in all patients with RCC. At the same time, there were no clinical manifestations of renal dysfunction in these patients, and the initial values of GFR and creatinine were within the reference values. Thus, routine determination of creatinine and glomerular filtration rate cannot guarantee the normal functioning of the kidneys. Probably, the severity of changes in the markers of cellular renal damage of cystatin C, L-FABP and IL-18 is the most prognostically significant in determining the degree of damage to the renal tubules and the risk of acute renal damage before surgical treatment. It should be borne in mind that early diagnosis of initial functional disorders is a necessary condition in choosing a rational tactics of nephroprotective therapy with the predestination of the development of undesirable complications, including acute renal injury at the stage of surgical treatment.

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 Ushakova N. D. – writing the text of the manuscript, received data analysis;  
 Rozenko D. A. – consultation;  
 Popova N. N. – direct conduction of the study;  
 Rozenko A. D. – processing and analysis of results;  
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