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ОСОБЕННОСТИ ОСТРОГО КОРОНАРНОГО СИНДРОМА В СОЧЕТАНИИ С ОНКОЛОГИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ У ПАЦИЕНТОВ ПОЖИЛОГО И СТАРЧЕСКОГО ВОЗРАСТА

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Features of Acute Coronary Syndrome in Combination with Oncological Diseases in Elderly and Senile Patients

Резюме

Актуальность. Наличие онкологического заболевания, высокая полиморбидность у пациентов пожилого и старческого возраста могут приводить к осложненному течению острого коронарного синдрома, в том числе развитию острого повреждения почек и/или хронической болезни почек, что способствует ухудшению ближайшего и отдаленного прогноза и увеличению смертности у данной группы пациентов. **Цель исследования.** Изучить течение, клинические и лабораторно-инструментальные особенности острого коронарного синдрома в зависимости от наличия или отсутствия онкологического заболевания у лиц пожилого и старческого возраста. **Материалы и методы.** В исследование было включено 200 пациентов (122 (61%) мужчины, 78 (39%) женщины, медиана (Me) возраста — 69 (65;77) лет). Больных распределили на две группы: 1) основная группа — острый коронарный синдром в сочетании с онкологическим заболеванием (n=100) (61 (61%) мужчина, 39 (39%), женщин, Me возраста — 69 (65;77) лет); 2) группа сравнения — острый коронарный синдром без онкологического заболевания (n=100). Группы были сформированы методом копи-пара в соотношении 1:1 по полу и возрасту. У всех пациентов оценивали данные анамнеза, общее количество заболеваний, индекс коморбидности Charlson, основные клинические и лабораторно-инструментальные параметры, а также развитие осложнений. У 40 (40%) пациентов основной группы и 47 (47%) из группы сравнения проводили забор средней порции утренней мочи в первые сутки госпитализации для определения содержания KIM-1 (молекула острого повреждения почек, пг/мл). На вторые сутки стационарного лечения проводили забор суточной мочи для определения уровня K^+, Na^+, Cl^-, мочевой кислоты, альбумина. **Результаты.** У пациентов основной группы, по данным анамнеза, чаще диагностировали стабильную стенокардию (p=0,042), диабетическую болезнь почек (p=0,017), хроническую болезнь почек (p=0,013) и анемию (p=0,008). Кроме того, у этих больных был выше индекс коморбидности Charlson (8 (6;9) и 5 (4;6) баллов; p <0,001) и общее количество заболеваний (6 (5;7) и 4 (3;5); p <0,001). Пациенты с онкологическим заболеванием при развитии острого коронарного синдрома чаще предъявляли жалобы на одышку (p=0,008) и перебои в работе сердца (p=0,004). У пациентов основной группы была диагностирована более низкая фракция выброса левого желудочка (51,0 (44;55) и 54 (48;57) %, p=0,013). Острое повреждение почек чаще диагностировали в основной группе, чем в группе сравнения (p <0,001), в том числе острое повреждение почек по «базальному» креатинину (p=0,005), по динамике креатинина (p=0,047) и на фоне хронической болезни почек (p=0,003). У больных основной группы уровень KIM-1 в моче был выше (921,0 (425,1;1314,8) и 658,0 (345,6;921,4) пг/мл; p=0,011). У пациентов с острым повреждением почек, в отличие от больных без острого повреждением почек, наблюдался более высокий уровень KIM-1 (999,2 (480,8;1314,1) и 663,1 (360,5;905,2) пг/мл; p=0,008). У больных с острым коронарным синдромом и онкологическими заболеваниями в стационаре чаще развивались ургентные осложнения (p=0,005), в том числе летальный исход (p=0,024) и острая сердечная недостаточность (p <0,001). Также у них

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была выше частота развития ранней постинфарктной стенокардии (p=0,018) и анемии (p=0,005) **Выводы.** В ходе нашего исследования установлено, что больные основной группы имели более высокий индекс коморбидности Charlson, большее количество заболеваний, в том числе стабильную стенокардию, диабетическую болезнь почек, хроническую болезнь почек и анемию. Данные пациенты при развитии острого коронарного синдрома чаще предъявляли жалобы на одышку и перебои в работе сердца. У больных онкологическим заболеванием чаще диагностировали острое повреждение почек, в том числе по «базальному» креатинину, по динамике креатинина и на фоне хронической болезни почек. Уровень KIM-1 в моче был выше у данной группы пациентов. У больных основной группы в стационаре чаще развивались ургентные осложнения, в том числе острая сердечная недостаточность и смерть. Также наблюдалась большая частота ранней постинфарктной стенокардии и анемии.

Ключевые слова: *острый коронарный синдром, онкологические заболевания, коморбидность, острое повреждение почек, хроническая болезнь почек, молекула почечного повреждения KIM-1*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Relevance. The presence of oncological diseases, high polymorbidity in elderly and senile patients can lead to a complicated course of acute coronary syndrome, including the development of acute kidney injury and/or chronic kidney disease, which contributes to a deterioration of the immediate and long-term prognosis and an increase in mortality. **The research purposes**. To study the course of acute coronary syndrome depending on the presence or absence of oncological diseases in elderly and senile people and to identify clinical and laboratory-instrumental features. **Materials and methods.** The study included 200 patients (men — n=122 (61%), women — n=78 (39%), Me age — 69 (65;77) years). The patients were divided into two groups: 1) the main group — acute coronary syndrome in combination with oncological diseases (n=100) (men — n=61 (61%), women — n=39 (39%), Me age — 69 (65;77) years); 2) the comparison group — acute coronary syndrome without oncological diseases (n=100). The groups were formed by the copy-pair method in a ratio of 1:1 by gender and age. All patients were evaluated for anamnesis parameters, the total number of diseases, the Charlson comorbidity index, the main clinical and laboratory-instrumental parameters and the development of complications. We collected an average portion of morning urine on the first day of hospitalization to determine the content of KIM-1 (pg/ml) in 40 patients of the main group and 47 from the comparison group. We collected daily urine on the 2nd day of hospital treatment to determine the level of K^+, Na^+, Cl^-, uric acid and albumin. **The results.** Patients of the main group, according to the anamnesis, were more often diagnosed with stable angina (p = 0.042), diabetic kidney disease (p = 0.017), chronic kidney disease (p = 0.013) and anemia (p = 0.008). In addition, these patients had a higher Charleson comorbidity index [8 (6; 9) and 5 (4; 6) points; p <0.001] and a total number of diseases [6 (5; 7) and 4 (3; 5); p <0.001]. Patients with oncological diseases with the development of acute coronary syndrome more often complained of shortness of breath (p=0.008) and heart rhythm disturbance (p=0.004). In patients of the main group a lower left ventricular ejection fraction was diagnosed [51.0 (44; 55) and 54 (48; 57), p=0.013]. Acute kidney injury was more frequently diagnosed in the study group than in the comparison group (p <0.001), including acute kidney injury by "basal" creatinine (p=0.005), acute kidney injury by creatinine dynamics (p=0.047), and acute kidney injury by chronic kidney disease (p=0.003). The KIM-1 leel in patients of the main group was higher [921.0 (425.1; 1314.8) and 658.0 (345.6; 921.4) pg/ml; p=0.011]. In patients with acute kidney injury, in contrast to patients without acute kidney injury, a higher level of KIM-1 was detected [999.2 (480.8;1314.1) and 663.1 (360.5;905.2) pg/ml; p=0.008]. Patients with acute coronary syndrome and oncological diseases in the hospital were more likely to develop urgent complications (p=0.005), including death (p=0.024) and acute heart failure (p <0.001). They also had a higher incidence of early post-infarction angina (p=0.018) and anemia (p=0.005). **Conclusions.** Our study found that patients in the main group had a higher Charlson comorbidity index, a greater number of diseases, including stable angina, diabetic kidney disease, chronic kidney disease, and anemia. These patients with the development of acute coronary syndrome more often complained of shortness of breath and heart rhythm disturbance. Patients with oncological diseases were more often diagnosed with acute kidney damage, including «basal» creatinine, creatinine dynamics, and chronic kidney disease. The level of KIM-1 in the urine was higher in this group of patients. Patients of the main group in the hospital were more likely to develop urgent complications, including acute heart failure and death. There was also a high incidence of early post-infarction angina and anemia.

Key words: *acute coronary syndrome, oncological diseases, polymorbidity, acute kidney injury, chronic kidney disease, KIM-1 kidney injury molecule*

Conflict of interests

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ACS — acute coronary syndrome, AKI — acute kidney injury, CKD — chronic kidney disease, KIM-1 — kidney injury molecule 1, OD — oncology disease, SC — serum creatinine

At different times from being diagnosed with oncology disease, 1.9–4.2% of patients develop acute coronary syndrome (ACS). OD significantly increases the risk of a complicated course of ACS, including recurrent myocardial infarction (MI) and death [1].

ACS is often accompanied by a renal pathology (acute cardiorenal syndrome) [2], leading to the deterioration of the immediate and long-term prognosis for the underlying disease [2, 3].

Patients with OD may suffer kidney damage (acute kidney injury (AKI) and/or acute kidney disease (AKD) and/or chronic kidney disease (CKD)) as a result of both the mechanical effect of malignant neoplasm, tumor infiltration, paraneoplastic processes, and nephrotoxic effect of the ongoing anticancer therapy [4, 5].

According to the literature, elderly and senile age and high comorbidity are independent risk factors for ACS and its complications, and a worsening prognosis [6, 7].

Available literature has a few studies describing the clinical features of the ACS course depending on the presence or absence of OD, including those in elderly and senile patients, which once again confirms the relevance of studying this issue [1, 8, 9].

One of the high-potential biomarkers for kidney injury is KIM-1 (kidney injury molecule). Clinical trials showed that KIM-1 is a sensitive and specific biomarker for the diagnosis of AKI induced by anticancer therapy, radiocontrast agents (CA) [contrast-induced AKI (CI-AKI]), as well as after cardiac surgery [2, 10, 11] There is evidence that KIM-1 increases in patients with CKD and is one of the markers of renal cell carcinoma [12]. At the moment, there are not enough data for the widespread practical use of KIM-1; therefore, further research is required on the possible use of this biomarker, including in cases of ACS combined with OD.

Objective of the study: to investigate the course, clinical, laboratory and diagnostic test features of ACS depending on the presence or absence of OD in elderly and senile patients.

Materials and methods

The study (prospective, open-label, observational) was carried out from January 2019 to August 2020 at the State Budgetary Healthcare Institution N. A. Semashko Nizhny Novgorod Regional Clinical Hospital (Nizhny Novgorod).

The study enrolled 200 patients (122 (61%) males, 78 (39%) females, median (Me) age — 69 (65; 77) years). Female patients were older than male patients: 70 (68; 79) and 67 (63; 72) years; p = 0.005.

Patients were divided into two groups: group 1 (trial) — ACS in combination with OD (ACS+OD; n = 100 (61 (61%) males, 39 (39%) females, Me age — 69 (65; 77) years); group 2 (control) — ACS without OD (ACS-OD; n = 100). Groups were formed using a copy-pair method in a 1:1 ratio by gender and age.

Inclusion criteria: ST-segment elevation acute coronary syndrome (STE-ACS), non-ST-segment elevation acute coronary syndrome (NSTE-ACS); for patients of the ACS+OD group — confirmed OD (active and/or with a history of no more than 10 years).

Exclusion criteria: pregnancy and lactation; age > 90 years; severe hepatic or respiratory failure; cancerous cachexia; mental disorders; patient refusal to be included in the study (refusal to sign voluntary informed consent).

Forty-one (41%) patients had active OD, 26 (26%) had a history of disease of 1 to 5 years, and 33 (33%) had a history of disease of 5 to 10 years. The most frequent localizations of oncological process in patients of the study group were the following: lungs, prostate gland, mammary glands, which totaled 48% (n = 48). Lymph node involvement was diagnosed in 32 (32%) patients, distant metastases were found in 16 (16%) patients. Three (3%) patients were diagnosed with multiple primary metachronous tumors (interval between diagnosed tumors was at least 1 year and at least 6 months for cancer in situ). Fifty-seven (57%) patients had malignant neoplasms at early (T1-2) stages and 27 (27%) — at late (T3-4) stages according to TNM classification. Eighty-five (85%) patients received treatment for OD (Fig. 1). Twenty-two (22%) patients underwent radiotherapy (in 54.5% of cases — above the diaphragm, 45.5% — below the diaphragm). All patients who underwent surgical treatment underwent radical surgery (77; 77%).

When assessing the severity of the condition of cancer patients according to the ECOG (Eastern Cooperative Oncology Group) scale, 88 (88%) patients scored 0–1 points, 12 (12%) scored 3–4 points.

All patients were evaluated for the number of chronic non-communicable diseases (1–2, 3–5, >5 diseases) and the Charlson comorbidity index.

Patients with STE-ACS/ NSTE-ACS were diagnosed and treated according to the current clinical guidelines [6, 7].

All patients were assessed for the frequency and structure of urgent (in-hospital mortality, recurrent myocardial infarction (MI), stent thrombosis, acute heart failure (AHF), ventricular tachycardia, ventricular fibrillation, acute left ventricular aneurysm, grade III atrioventricular blockade, acute cerebrovascular event, thromboembolism of pulmonary artery) and non-urgent (early postinfarction angina (EPA), ventricular extrasystole

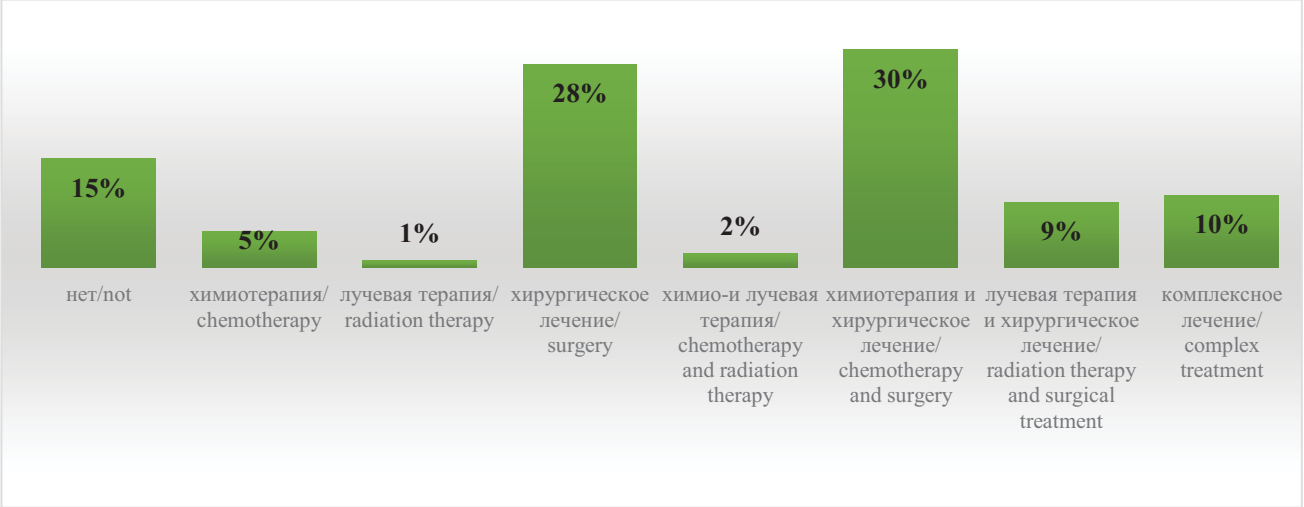

Figure 1. *Type of treatment for cancer patients*

of high grades according to the Lown scale (class 3–5), atrial fibrillation, paroxysms of supraventricular tachycardia, sinus node dysfunction) complications.

AKI was diagnosed according to the following criteria of clinical guidelines: an increase in serum creatinine (SC) ≥ 26.5 μmol/l over 48 hours or an increase in SC ≥ 1.5 times from basal (AKI by basal creatinine), or an increase in baseline SC (AKI by changes over time) over seven days; taking into consideration: basal SC as SC corresponding to the estimated glomerular filtration rate (eGFR) 75 ml/min/1.73 m^2; baseline SC as SC at the time of patient hospitalization, followed by its assessment over time after 1–7 days. AKI with underlying CKD was diagnosed if the patient had CKD. In patients with AKI, transient AKI, persistent AKI and acute kidney disease (AKD) were confirmed by creatinine changes over time. Transient AKI was diagnosed if AKI was resolved within two days, and persistent AKI — if resolved in 2–7 days. AKD was established when signs of kidney damage persisted for 7–90 days after an AKI episode in the hospital.

Oligouric/ anuric AKI was diagnosed in cases of urine output rate of < 0.5 ml/kg/h for six hours or more. Twelve (12%) patients with OD and 6 (6%) patients without OD had indications for bladder catheterization. Therefore, hourly urine output as a criterion for AKI was considered only for these patients [2].

CKD diagnosis was confirmed according to the current clinical guidelines in the presence of medical history data with morphological and/or laboratory confirmation of persistent kidney damage for more than three months [3]. Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula (2011).

Forty (40%) patients of the study group (ACS+OD) and 47 (47%) patients of the control group (ACS-OD) underwent special additional tests that were carried out at the AVK-Med Central Laboratory (Nizhny Novgorod). 10 ml of midstream morning urine was sampled into BD Vacutainer tubes (n = 87) on the first day of hospitalization to determine the amount of KIM-1 (pg/ml) using the ENZoLife Scientific KIM-1 ELISA test system (USA). On the second day of inpatient treatment, 10 ml of daily urine were taken to determine the levels of K^+, Na^+, Cl^-, uric acid, and albumin. Albumin and uric acid were determined by a colorimetric method; K^+, Na^+, Cl^- — by indirect potentiometry using the cobas c 501+ISE analyzer (Roche Diagnostics, Switzerland).

Patients of both groups were comparable in the terms of the type and number of drugs prescribed in hospital. Patients with OD were more often prescribed inotropic stimulation (16 (16%) and 6 (6%); p = 0.024) during the acute period of myocardial infarction.

Selective coronary angiography (SCA) was less frequently performed in patients with ACS and OD (74 (74%) and 91 (91%); p = 0.002). Patients with OD were also less likely to receive re-perfusion treatment (58 (58%) and 76 (76%); p = 0.007), in particular, primary percutaneous coronary intervention (PCI) (46 (46%) and 64 (64%); p = 0.011). Four patients of the study group underwent thrombolytic therapy without PCI. A pharmaco-invasive approach was used in 8 (8%) patients in the ACS+OD group and in 12 (12%) patients in the ACS-OD group (p = 0.346).

The following were considered as study limitations: different localization of the oncological process, different activity, severity and duration of OD, determining the KIM-1 level in several patients in the study sample.

Statistical analysis of the obtained results was carried out using the IBM SPSS Statistics 23 special-purpose software. The correct distribution of a quantitative feature was assessed using the Kolmogorov — Smirnov (n > 50) and Shapiro — Wilk (n < 50) tests. In the case of a normal distribution, quantitative data were presented as the mean and standard deviation (M±SD); with a distribution other than normal, the obtained data were presented as a median (Me) and interquartile range (Q_{25}; Q_{75}). In the case of a normal distribution, two groups

were compared on a quantitative basis with Student's t-test for independent samples; with a distribution other than normal, Mann — Whitney U-test was used. Chi-square test (χ^2) was used to compare qualitative features. If the expected values were less than 5, Fisher's exact test (two-tailed test) was used. If the expected values were in the range from 5 to 10, χ^2 test with Yates's correction for continuity was used. Spearman's rank correlation coefficient (R) was used to assess the strength of the relationship between features. Multivariate regression modeling (logistic regression) was used to analyze independent predictors. Differences were considered statistically significant at $p < 0.05$ [13].

The study was performed in accordance with the standards of Good Clinical Practice and principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee. Written informed consent was obtained from all patients prior to enrollment in the study.

Results and discussion

We carried out a comparative analysis of patients with ACS depending on the presence or absence of OD according to medical history data (Table 1). Patients of both groups were comparable by gender (p = 1.0) and age (1.0)

Patients of the study group were more often diagnosed with stable angina, diabetic kidney disease and anemia. Patients with ACS and OD also had a higher Charlson comorbidity index and a higher total number of diseases. Patients of the study group more often had CKD (S3a-S5), severe albuminuria/ proteinuria (A3-A4). Two patients of the ACS+OD and ACS-OD groups with C5 stage CKD were on RRT (long-term hemodialysis) before hospitalization. Two patients of the study group with C4 stage of CKD were in the process of preparing for RRT (forming arteriovenous fistula).

Patients with OD more often complained of dyspnea (44 (44%) and 26 (26%); p = 0,008) and irregular

Table 1. *Comparative characteristics of patients with ACS, depending on the presence or absence of cancer according to anamnesis [n (%); Me (Q25; Q75)]*

Options	ACS+Cancer (n=100)	ACS-Cancer (n=100)	p
Postinfarction cardiosclerosis	34 (34%)	33 (33%)	0,881
Stable angina	78 (78%)	65 (65%)	0,042
I FC	2 (2,6%)	2 (3,1%)	1,0
II FC	32 (41,0%)	23 (35,4%)	0,490
III Fc	39 (50,0%)	37 (56,9%)	0,409
IV FC	5 (6,4%)	3 (4,6%)	0,728
Arterial hypertension	100 (100%)	100 (100%)	1,0
Chronic heart failure	85 (85%)	76 (76%)	0,108
I FC	11 (12,9%)	15 (19,7%)	0,243
II FC	48 (56,5%)	37 (48,7%)	0,324
III Fc	25 (29,4%)	24 (31,6%)	0,766
IV FC	1 (1,2%)	-	-
Diabetes mellitus	39 (39%)	32 (32%)	0,301
Diabetic kidney disease	21 (21%)	9 (9%)	0,017
Glomerulonephritis	1 (1%)	-	-
Urolithiasis disease	12 (12%)	7 (7%)	0,335
Kidney cysts	32 (32%)	29 (29%)	0,645
Kidney cancer with nephrectomy	6 (6%)	-	-
Chronic kidney disease, (C3A-C5 stage)	44 (44%)	27 (27%)	0,013
C3A	26 (59,1%)	21 (77,8%)	0,175
C3B	15 (34,1%)	5 (18,5%)	0,149
C4	2 (4,5%)	-	-
C5	1 (2,3%)	1 (3,7%)	1,0
A0	13 (29,5%)	10 (37,0%)	0,515
A1	5 (11,4%)	7 (25,9%)	0,190
A2	8 (18,2%)	7 (25,9%)	0,634
A3	17 (38,6%)	3 (11,2%)	0,026
A4	1 (2,3%)	-	-
Anemia	32 (32%)	16 (16%)	0,008
Body mass index	27,9 (25,0;32,7)	28,6 (26,4;32,0)	0,217
Charlson comorbidity index, points	8 (6;9)	5 (4;6)	<0,001
Number of diseases	6 (5;7)	4 (3;5)	<0,001

Note: FC — functional class

heartbeat (18 (18%) and 5 (5%); p = 0.004) during ACS development, which may be a consequence of heart failure and/or cardiotoxicity of previous chemotherapy and/or radiation therapy. [1].

Patients were comparable in terms of hemodynamic level at admission, duration of hospital stay and ACS type (STE-ACS and NSTE-ACS) (Table 2).

According to the literature, patients with OD are more often diagnosed with NSTE-ACS. Coronary catastrophe often develops with the progression of OD or during its active management due to endothelial dysfunction caused by anticancer therapy, spasm of coronary arteries, tumor embolism, a discrepancy between blood flow and increased myocardial requirements due to anemia, and also rupture of an atherosclerotic plaque with subsequent atherothrombosis [1]. In our study, patients with OD were comparable in ACS type (STE-ACS/ NSTE-ACS).

Echocardiography was performed in 94 (94%) patients of the study group and 99 (99%) patients in the control group (Table 3). Other patients were not examined due to death on the first day of hospitalization. Patients of the study group demonstrated lower ejection fraction (EF) of the left ventricle (LV) and a lower rate of heart failure (HF) with preserved EF, which could be a consequence of early antitumor therapy, as well as acute heart failure (AHF) in ACS.

There were more patients with urgent complications in the study group (39 (39%) and 21 (21%); p = 0.005) (Table 4), including in-hospital mortality and AHF (Killip classes II–IV), which is consistent with literature data [1]. The majority of patients (16; 72.7%) died in the

Table 2. *The parameters of the hospital period in patients with ACS, depending on the presence or absence of cancer [n (%); Me (Q25; Q75)]*

Options	ACS+Cancer (n=100)	ACS-Cancer (n=100)	p
Systolic blood pressure, mm Hg st	140 (124;150)	140 (125;148)	0,754
Diastolic blood pressure, mm Hg st	83 (75;90)	80 (79;90)	0,817
Heart rate, beats per minute	80 (72;86)	76 (70;86)	0,168
Length of hospital stay, bed-day	9 (7;11)	9 (8;11)	0,483
ST-elevation ACS NSTE ACS	49 (49%) 51 (51%)	44 (44%) 56 (56%)	0,395

Note: NSTE-ACS — Non-ST-segment elevation acute coronary syndrome

Table 3*. Analysis of patients with ACS depending on the presence or absence of cancer by echocardiography parameters [Me (Q25; Q75; n (%)]*

Indicators	ACS+Cancer (n=94)	ACS-Cancer (n=99)	p
Left ventricular EF, %	51,0 (44;55)	54 (48;57)	0,013
Heart failure with preserved EF	53 (56,4%)	69 (69,7%)	0,037
Heart failure with intermediate EF	26 (27,7%)	23 (23,2%)	0,480
Heart failure with low EF	15 (16,0%)	7 (7,1%)	0,053

Note: EF — ejection fraction

Table 4*. The frequency and structure of urgent complications of the hospital period in patients with ACS, depending on the presence or absence of cancer*

Options	ACS+Cancer (n=100)	ACS-Cancer (n=100)	p
Intrahospital mortality	16 (16%)	6 (6%)	0,024
Recurrent myocardial infarction	3 (3%)	3 (3%)	1,0
Stent thrombosis	2 (2%)	3 (3%)	1,0
Killip (II-IV class)	28 (28%)	7 (7%)	<0,001
Acute left ventricular aneurysm	5 (5%)	3 (3%)	0,489
Ventricular tachycardia	3 (3%)	4 (4%)	1,0
Ventricular fibrillation	2 (2%)	5 (5%)	0,445
AV-block III degree	3 (3%)	1 (1%)	0,621
Acute cerebral circulation failure	2 (2%)	1 (1%)	1,0
Pulmonary thromboembolism	1 (1%)	2 (2%)	1,0

Note: AV — atrioventricular

first three days of hospitalization. The following were the main causes of death: MI (13; 59.1%, MI in combination with OD (study group) (8; 36.4%), MI in combination with ACE (control group) (1; 4.5%).

Patients of both groups were comparable in the frequency and type of non-urgent complications during hospitalization (44 (44%) and 41 (41%); p = 0.668). At the same time, the frequency of RPS in the ACS+OD group was higher (15 (15%) and 5 (5%); p = 0.018), which could be associated with a lower frequency of reperfusion treatment, a greater tendency to hypercoagulation and thrombus formation, vasospasm and instability of atherosclerotic plaques caused by endothelial dysfunction in cancer patients [1, 6, 7].

Patients of the study group were more often diagnosed with anemia (38 (38%) and 20 (20%); p = 0.005) during hospital stay; this may be due to: chronic inflammation, a history of cytotoxic anticancer therapy, more frequent bleeding, and CKD [14].

AKI was more often found in patients of the study group (49 (49%) and 25 (25%), p < 0.0001). AKI by "basal" creatinine was confirmed in 32 (32%) and 15 (15%) patients respectively (p = 0.005); including AKI by creatinine changes over time — in 13 (13%) and 8 (8%) patients, respectively (p = 0.616). AKI only by creatinine changes over time was established in 17 (17%) patients in the ACS+OD group and in 10 (10%) patients in the ACS-OD group (p = 0.148). AKI with underlying CKD was registered in 36 (36%) and 17 (17%) patients, respectively (p = 0.002).

Among all patients with AKI, based on the creatinine changes over time (30 (30%) and 18 (10%), p = 0.047), transient AKI was diagnosed in 6 (20%) and 4 (22%) patients, respectively (p = 0.855); persistent AKI — in 9 (30%) and 6 (33%) patients, respectively (p = 0.936); ACD — in 15 (50%) and 8 (45%) patients, respectively (p = 0.941).

Oligouric/anuric AKI was found in 7 (7%) and 4 (4%) patients, respectively (p = 0.535). Stage 1 AKI was established primarily by creatinine level, and stages 2–3 — by oligouric/anuric type of AKI (by diuresis rate). At the time of discharge from the hospital, patients with AKD required no change of the CKD stage that existed before hospitalization. In connection with AKI that developed during hospitalization, four (4%) patients of the study group underwent renal replacement therapy (RRT) via veno-venous hemodiafiltration.

In our opinion, the high incidence of AKI in patients with OD could be associated with higher comorbidity, CKD, and AHF.

Twenty-two (11%) patients died in hospital. The deceased patients were diagnosed with AKI 3 times more often than the survivors (21 (95.5%) and 53 (29.8%), p < 0.0001).

Table 5. *Laboratory indicators in patients with ACS, depending on the presence or absence of OZ [M±SD, Me (Q25; Q75)]*

Indicators	ACS+Cancer, n=100	ACS-Cancer, n=100	p
Hemoglobin, g/l	126,9±26,7	135,6±19,6	0,009
Hematocrit	0,407±0,084	0,435±0,060	0,006
Creatinine upon admission, μmol/l	97,0 (82,2;125,8)	89,8 (78,2;103,2)	0,005
Creatinine upon discharge, μmol/l	107,2 (92,2;135,8)	95,1 (82,0;110,7)	<0,001
Estimated $GFR_{CKD-EPI}$ upon discharge discharge, ml/min/1,73m^2	56,3 (40,5;68,2)	63,8 (53,3;75,3)	0,002
Urea upon admission, mmol/l	6,4 (5,0;9,1)	5,4 (4,6;6,8)	0,001
Urea upon discharge, mmol/l	7,6 (5,5;10,9)	6,0 (5,0;7,7)	<0,001
Na^+, upon discharge, mmol/l	136,6 (134,0;139,1)	138,0 (136,1;143,0)	0,006
Glucose, mmol/l	6,20 (5,30;8,00)	5,64 (4,83;6,86)	0,049
Total protein, g/l	68,7 (64,6;71,9)	71,7 (66,4;74,9)	0,014
Total bilirubin, μmol/l	15,0 (10,3;20,3)	10,7 (8,1;15,8)	<0,001
High density lipoproteins, mmol/l	1,06 (0,88;1,31)	1,22 (1,00;1,47)	0,012

Note: GFR — glomerular filtration rate

Table 6. *Indicators of daily urine in patients with ACS, depending on the presence or absence of cancer [M±SD, Me (Q25; Q75)]*

Indicators	ACS+Cancer n=40	ACS-Cancer n=47	p
Uric acid, μmol / day	3582 (2311;4830)	2771 (2230;3941)	0,303
K^+, mmol / day	44,2 (27,9;56,3)	49,1 (35,1;86,5)	0,031
Na^+, mmol/day	160,2±79,7	166,8±80,2	0,721
Cl^-, mmol/day	108,2 (73,1;140,3)	127,7 (79,2;184,4)	0,237
Albumin, mg/day	26,0 (5,7;92,7)	10,2 (3,8;51,2)	0,092

Laboratory blood parameters were analyzed (Table 5).

Daily urine parameters were also evaluated in patients with OD and without OD (table 6). In patients of both groups, parameters of daily excretion of all markers under investigation were within the reference range. A lower level of daily potassium excretion was revealed in the ACS+OD group in comparison with patients without OD. According to O'Donnell M. et al. (2019), decreased potassium excretion may be associated with the progression of CKD. It may also lead to an increased risk of cardiovascular events and death [15].

Urinary syndrome including, hematuria (37 (37%) and 12 (12%); $p < 0.001$), was found more often (62 (62%) and 42 (42%), $p = 0.005$) in patients with ACS and OD. Also, proteinuria level was higher in patients with ACS and OD than in patients without OD (0.1 (0; 0.32) and 0 (0; 0.1) g/l; $p = 0.001$).

There are currently no generally accepted reference values of KIM-1 levels in urine. Depending on the reagent manufacturer and the method of determination, reference values of KIM-1 level in urine can range from 147 to 2,120 pg/ml [10, 11].

In our study, median KIM-1 in urine in all patients with ACS (n = 87) was 725.6 (420.0; 1,087.5) pg/ml.

In patients of the ACS+OD group, KIM-1 level was higher in comparison with patients without OD [921.0 (425.1; 1,314.8) and 658.0 (345.6; 921.4) pg/ml; $p = 0.011$] (Fig. 2). In our opinion, this may be due to the more frequent development of AKI in patients with OD. It was also found that KIM-1 in kidney tissue plays a dual role. On the one hand, its increased production can contribute to uncontrolled proliferation and angiogenesis, acting as a factor of carcinogenesis and metastasing of renal cell carcinoma. Moreover, according to several experimental studies, the expression of the KIM-1 gene can increase in cases of other malignant neoplasms. On the other hand, KIM-1 may be involved in the regeneration of renal tubules after AKI (nephroprotection) [12].

Comorbidity was higher in the study group, which could also have an effect on the development of kidney pathology and, as a consequence, on the increase in KIM-1 level.

No correlations of KIM-1 level with creatinine and eGFR were revealed in our study, which is consistent with the results of a retrospective study conducted by Wajda J. et al. (2020) [16]. This may probably be due to the fact that KIM-1 is a marker that mainly indicates damage to the proximal tubules [2].

In contrast to patients without AKI (n = 58), patients with AKI (n = 29) demonstrated a higher level of KIM-1 (999.2 (480.8; 1,314.1) and 663.1 (360.5; 905.2) pg/ml; $p = 0.008$) which is consistent with literature data [2, 10, 16]. They also had higher albuminuria (62.0 (11.4; 221.0) and 9.7 (4.6; 28.1) mg/day; $p = 0.002$). There were no statistically significant differences in KIM-1 level in patients with different stages of AKI.

Patients with AKD had higher KIM-1 level in urine than patients without AKD (1,238.4 (444.6; 1,397.3) and 704.0 (401.7; 996.3) pg/ml; $p = 0.025$), as well as a higher albuminuria level (79.5 (19.3; 303.0) and 10.6 (5.0; 56.2) mg/day; $p = 0.013$).

Patients with CKD had a higher albuminuria level compared to patients without CKD (26.0 (6.8; 119.5) and 4.8 (2.5; 9.4) mg/day; $p = 0.017$). There were no statistically significant differences in KIM-1 level in patients with different stages of CKD.

Patients with active OD and history of OD had no statistically significant differences in the levels of KIM-1, K^+, Na^+, Cl^-, uric acid, albumin in urine.

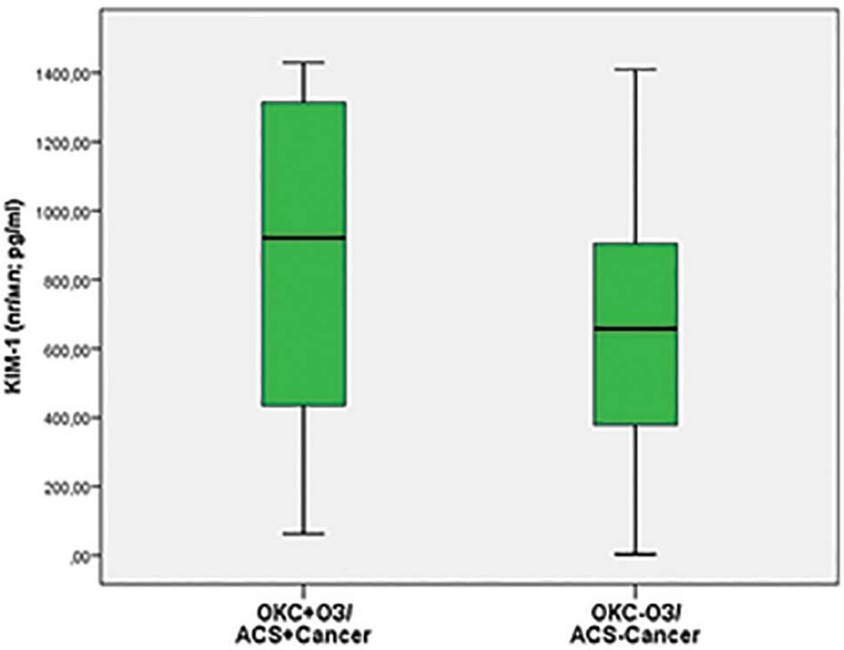

Figure 2. *Levels of KIM-1 [Me (Q25; Q75) pg/ml] in patients with ACS, depending on the presence or absence of cancer*

Fifty-five (27.5%) patients demonstrated a complicated course of ACS (urgent and non-urgent complications), seven of them (8%) with a fatal outcome. A higher albuminuria level was observed in patients with a complicated ACS course (24.7 (7.0; 129.1) and 6.4 (2.6; 14.1) mg/day; p = 0.001) including urgent complications (80.8 (22.8; 145.4) and 8.8 (3.6; 18.7) mg/day; p < 0.001), including AHF (139.5 (43.9; 325.8) and 9.9 (4.5; 39.9) mg/day; p < 0.001), and a fatal outcome (122.0 (27.4; 419.9) and 10.6 (5.1; 62.0) mg/day; p = 0.028).

Albuminuria is known to be an independent risk factor for a complicated ACS course [3]. In our study, according to logistic regression data, a change in albuminuria level by 1 mg/day increased the risk of urgent complications by 6% [OR 1.006 (95% CI 1.001–1.010); p = 0.019], including a fatal outcome — by 5% [OR 1.005 (95% CI 1.001–1.010); p = 0.026], and AHF — by 8% [OR 1.005 (95% CI 1.003–1.013); p = 0.003].

According to the literature, hyperuricemia and, as a consequence, hyperuricuria can develop during the progression of OD, chemotherapy and/or radiation therapy [4, 5]. Our study revealed no differences in this parameter in patients with and without OD, which may be associated with a small number of patients with T4 stage according to the TNM classification (7; 7%) and distant metastases (16; 16%). At the same time, patients with AHF (1,830.2 (552.4; 3,181.8) and 3,215.5 (2,519.7; 4,283.3) mmol/day; p = 0.007) and deceased patients (1,244.3 (361.3; 2,783.0) and 3,100.2 (2,378.0; 4,199.3) μmol/day; p = 0.006) were diagnosed with a lower daily excretion of uric acid in comparison with patients without AHF and the patients who survived. This could be associated with a higher frequency of advanced stages of CKD (S3b-S5) in patients with AHF (p < 0.001) and deceased patients (p <0.001), as well as with more frequent detection of oligouria/anuria (p = 0.012 and p <0.001, respectively).

Conclusion

Our study revealed that elderly and senile patients with OD (active and/or in history) have some special features of the ACS course. According to their medical history, they were more likely to be diagnosed with stable angina, diabetic kidney disease, CKD and anemia. They had a higher Charlson Comorbidity Index, more concomitant diseases, and lower LVEF than patients without OD. Patients with OD more often complained of dyspnea and irregular heartbeat during ACS, which may be a consequence of heart failure and/or cardiotoxicity of previous chemotherapy and/or radiation therapy. Patients with OD were more often diagnosed with AKI, including AKI by basal creatinine, AKI by creatinine changes over time and AKI with underlying CKD, which may be associated with higher comorbidity, CKD and AHF. KIM-1 level in urine was higher in patients with a combination of ACS and OD, which may be a consequence of more frequent AKI. Patients with ACS and OD more often developed urgent complications during hospitalization, including AHF and death. There was also a high incidence of early postinfarction angina and anemia. The information obtained suggests that this group of patients with ACS requires more attention in order to optimize diagnostic and therapeutic tactics to reduce the risk of fatal and non-fatal complications and improve the prognosis and quality of life.

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Список литературы / References:

1. Лубоятникова Е.С., Дупляков Д.В. Острый коронарный синдром у пациентов со злокачественными новообразованиями. Российский кардиологический журнал. 2017; (3): 140-144. doi: 10.15829/1560-4071-2017-3-140-144.
Luboyatnikova E.S., Duplyakov D.V. Acute coronary syndrome in malignancy patients. Russian Journal of Cardiology. 2017; (3):140-144. doi: 10.15829/1560-4071-2017-3-140-144. [in Russian].
2. Смирнов А.В., Румянцев А.Ш. Острое повреждение почек. Часть I. Нефрология. 2020; 24(1): 67-95. doi: 10.36485/1561-6274-2020-24-1-67-95.
Smirnov A.V., Rumyantsev A.S. Acute kidney disease. Part I. Nephrology (Saint-Petersburg). 2020; 24(1):67-95. doi: 10.36485/1561-6274-2020-24-1-67-95. [in Russian].
3. Ассоциации нефрологов. Клинические рекомендации. Хроническая болезнь почек. 2019. [Электронный ресурс]. URL: http://nonr.ru/wp-content/uploads/ 2020/01/Cln_guidlines_CKD_24.11_final-3-3.pdf. (дата обращения: 01.11.2020).
Assotsiatsii nefrologov. Klinicheskie rekomendatsii. Khronicheskaya bolezn' pochek. 2019. [Electronic resource]. URL: http://nonr.ru/wp-content/uploads/ 2020/01/Cln_guidlines_CKD_24.11_final-3-3.pdf. (date of the application: 01.11.2020).
[in Russian].

4. Колина И.Б., Бобкова И.Н. Поражение почек при злокачественных образованиях. Клиницист. 2014; 8(2):7-16. doi: 10.17650/1818-8338-2014-2-7-16.
Kolina I.B., Bobkova I.N. Porazhenie pochek pri zlokachestvennykh obrazovaniyakh. Klinitsist. 2014; 8(2): 7-16. doi: 10.17650/1818-8338-2014-2-7-16. [in Russian].
5. Захарова Е.В. Остроумова О.Д. Онконефрология: поражения почек при использовании противоопухолевых препаратов. Обзор литературы — Часть 1. Нефрология и диализ. 2020; 22(3):393-395. doi: 10.28996/2618-9801-2020-3-383-395.
Zakharova E.V. Ostroumova O.D. Onkonefrologiya: porazheniya pochek pri ispol'zovanii protivoopukholevykh preparatov. Obzor literatury — Chast' 1. Nefrologiya i dializ. 2020; 22(3): 393 395. doi: 10.28996/2618-9801-2020-3-383-395. [in Russian].
6. Российское кардиологическое общество. Клинические рекомендации. Острый инфаркт миокарда с подъемом сегмента ST электрокардиограммы. 2020. [Электронный ресурс]. URL: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_OKS_sST.pdf. (дата обращения: 01.11.2020).
Rossiiskoe kardiologicheskoe obshchestvo. Klinicheskie rekomendatsii. Ostryi infarkt miokarda s pod"emom segmenta ST elektrokardiogrammy. 2020. [Electronic resource]. URL: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_OKS_sST.pdf (date of the application: 01.11.2020). [in Russian].
7. Российское кардиологическое общество. Клинические рекомендации. Острый коронарный синдром без подъема сегмента ST электрокардиограммы. 2019. [Электронный ресурс]. URL: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_OKS_bST.pdf. (дата обращения: 01.11.2020).
Rossiiskoe kardiologicheskoe obshchestvo. Klinicheskie rekomendatsii. Ostryi koronarnyi sindrom bez pod"ema segmenta ST elektrokardiogrammy. 2019. [Electronic resource]. URL: https://scardio.ru/content/Guidelines/2020/Clinic_rekom_OKS_bST.pdf. (date of the application: 01.11.2020). [in Russian].
8. Styczkiewicz K., Styczkiewicz M., Myćka M., et al. Clinical presentation and treatment of acute coronary syndrome as well as 1-year survival of patients hospitalized due to cancer: A 7-year experience of a nonacademic center. Medicine (Baltimore). 2020; 99(5): e18972. doi:10.1097/MD.0000000000018972.
9. Iannaccone M., D'Ascenzo F., Vadalà P., et al. Prevalence and outcome of patients with cancer and acute coronary syndrome undergoing percutaneous coronary intervention: a BleeMACS substudy. Eur Heart J Acute Cardiovasc Care. 2018; 7(7): 631-638. doi: 10.1177/2048872617706501.
10. Ahmed S.A., Hamed M.A. Kidney injury molecule-1 as a predicting factor for inflamed kidney, diabetic and diabetic nephropathy Egyptian patients. J Diabetes Metab Disord 2015; 14: 6. [Electronic resource]. URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4347934. (date of the application: 01.11.2020).
11. Ren H., Zhou X., Dai D., et al. Assessment of urinary kidney injury molecule-1 and interleukin-18 in the early post-burn period to predict acute kidney injury for various degrees of burn injury. BMC Nephrol. 2015; 16: 1-10. doi: 10.1186/s12882-015-0140-3.
12. Солохина М.П., Сергеева Н.С., Маршутина Н.В. и др. КИМ как потенциальный серологический/уринологический опухолеассоциированный маркер почечно-клеточного рака и нефротоксичности химиопрепаратов. Онкоурология. 2019; 15(3): 132–42. doi: 10.17650/1726-9776-2019-15-3-132-142.
Solokhina M.P., Sergeeva N.S., Marshutina N.V. i dr. KIM kak potentsial'nyi serologicheskii/urinologicheskii opukholeassotsiirovannyi marker pochechno-kletochnogo raka i nefrotoksichnosti khimiopreparatov. Onkourologiya. 2019; 15(3): 132–42. doi: 10.17650/1726-9776-2019-15-3-132-142. [in Russian].
13. Трухачёва Н.В. Медицинская статистика: учеб. пособие. Ростов-на-Дону: Феникс. 2017; 324 с.
Trukhacheva N.V. Meditsinskaya statistika: ucheb. posobie. Rostov-na-Donu: Feniks. 2017; 324 p. [in Russian].
14. Madeddu C., Gramignano G., Astara G., et al. Pathogenesis and treatment options of cancer related anemia: perspective for a targeted mechanism-based approach. Front Physiol. 2018; 9: 1294. doi: 10.3389/fphys.2018.01294.
15. O'Donnell M., Mente A., Rangarajan S., et al. Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality: prospective cohort study. BMJ. 2019; 364: l772. doi: 10.1136/bmj.l772.
16. Wajda J., Dumnicka P., Kolber W., et al. The Marker of Tubular Injury, Kidney Injury Molecule-1 (KIM-1), in Acute Kidney Injury Complicating Acute Pancreatitis: A Preliminary Study. J Clin Med. 2020;9(5):1463. doi: 10.3390/jcm9051463.