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ВЛИЯНИЕ ПОРАЖЕНИЯ ПОЧЕК НА ТЕЧЕНИЕ И ПРОГНОЗ ПРИ ИНФЕКЦИИ COVID-19 ПО ДАННЫМ МЕЖДУНАРОДНОГО РЕГИСТРА «АНАЛИЗ ДИНАМИКИ КОМОРБИДНЫХ ЗАБОЛЕВАНИЙ У ПАЦИЕНТОВ, ПЕРЕНЕСШИХ ИНФИЦИРОВАНИЕ SARS-COV-2»

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Impact of Kidney Damage on the Course and Prognosis of COVID-19 Infection According to the International Registry «Analysis of Chronic Non-Infectious Diseases Dynamics After Covid-19 Infection in Adult Patients»

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Резюме

Цель. Изучение особенностей течения новой коронавирусной инфекции (НКИ) у пациентов с хронической болезнью почек (ХБП), выявление случаев возникновения острого повреждения почек (ОПП) на фоне инфекции COVID-19 и влияние состояния функции почек на прогноз у таких категорий пациентов в острый и постгоспитальный периоды, спустя 3, 6 и 12 месяцев после выздоровления. **Материалы и методы**. В регистр АКТИВ и АКТИВ 2 были включены мужчины и женщины старше 18 лет с диагнозом COVID-19, выставленным на основании положительного ПЦР-теста на COVID-19 и данных характерной рентгенографической или компьютерно-томографической картины органов грудной клетки. **Результаты**. Всего в анализ было включено 9364 пациента (4404 мужчин, средний возраст 59 [48-69]), из них ХБП встречалась у 716 (7,67 %) пациентов, регистрация скорости клубочковой фильтрации (СКФ) во время госпитализации осуществлялась у 8496 (90,7 %) пациентов, значения были распределены следующим образом: ≥90 мл/мин/1,73м^2 — у 4289 (50,5 %) пациентов, 89-60 мл/мин/1,73м^2 — у 3150 (37,1 %) пациентов, 59-45 мл/мин/1,73м^2 — у 613 (7,22 %), 44-30 мл/мин/1,73м^2 — у 253 (2,98 %), 29-15 мл/мин/1,73м^2 — у 110 (1,29 %), <15 мл/мин/1,73м^2 — у 81 (0,95 %) пациента. В 11,6 % случаев (1068 пациентов) за время нахождения в стационаре развилось ОПП, это осложнение формировалось чаще, чем цитокиновый шторм (в 7,46 % у 687 пациентов, p<0,001) или сепсис (в 0,17 % у 16 пациентов, p=0,620). ХБП повышала риск смерти у пациентов с COVID-19 на госпитальном этапе в 3,94 раза в сравнении с пациентами без ХБП. У пациентов с ОПП летальный исход на госпитальном этапе был в 3,94 раза больше, чем у людей без ОПП. Наличие ХБП влияло на выживаемость и в отдалённом постгоспитальном периоде: в течение 3-х месяцев наблюдения риск смерти при наличии ХБП возрастал в 4,88 раза, в течение 6 месяцев — в 4,24 раза, через 12 месяцев — в 8,36 раза. **Заключение**. Распространенность ХБП в группе пациентов с COVID-19 равнозначна таковой в популяции в целом. ОПП развивалась в 11,6 % случаев при инфекции COVID-19 и чаще наблюдалась у пациентов с избыточным весом и гипергликемией. ХБП и ОПП повышали риск госпитальной летальности у пациентов с COVID-19. В постковидном периоде на протяжении 3, 6 и 12 месяцев после выздоровления отмечалось повышение смертности в группе пациентов с ХБП. У пациентов, перенесших ОПП в период коронавирусной инфекции, высокая смертность в постковидном периоде отмечалась только в первые 3 месяца наблюдения.

Ключевые слова: *COVID-19, хроническая болезнь почек, острое повреждение почек*

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Abstract

Objective. To study the course of the new coronavirus infection in patients with chronic kidney disease (CKD), to identify cases of acute kidney injury (AKI) in the setting of COVID-19 infection, and to access the impact of renal function on prognosis in these categories of patients during the acute phase and after hospitalization, at 3, 6, and 12 months after recovery. **Materials and methods.** The ACTIV and ACTIV 2 registries included men and women older than 18 years with a diagnosis of COVID-19 based on a positive PCR test for COVID-19 and a characteristic chest X-ray or computed tomography chest scan. **Results.** A total of 9364 patients (4404 men, average age59 [48-69]) were included in the analysis. 716 (7.67 %) patients had CKD. 8496 (90,7 %) patients had their glomerular filtration rate (GFR) measured during hospitalization, and the values were distributed as follows: ≥90 ml/min/1.73m^2 — in 4289 (50,5 %) patients, 89-60 ml/min/1.73m^2 — in 3150 (37,1 %) patients, 59-45 ml/min/1.73m^2 — in 613 (7,22 %), 44-30 ml/min/1.73m^2 — in 253 (2,98 %), 29-15 ml/min/1.73m^2 — in 110 (1,29 %), <15 ml/min/1.73m^2 — in 81 (0,95 %) patients. 11.6 % of the subjects (n=1068) developed AKI during hospitalization. This complication was reported more often than cytokine storm (in 7.46 % in 687 patients, p<0,001) or sepsis (in 0.17 % in 16 patients, p=620). CKD increased the risk of death by 3.94-fold in patients with COVID-19 during hospitalization compared with patients without CKD. The mortality of patients with AKI during hospitalization was 3.94 times higher than the mortality of those without AKI. CKD also affected long-term survival after hospitalization: within 3 months of follow-up, the risk of death in patients with CKD increased 4.88-fold, within 6 months — 4.24-fold, after 12 months — 8.36-fold. **Conclusion.** The prevalence of CKD in COVID-19 patients is similar to that in the general population. AKI developed in 11.6 % of cases with COVID-19 infection and was observed more frequently in patients with overweight and hyperglycemia. CKD and AKI increased the risk of hospital mortality in patients with COVID-19. In the group of patients with CKD, mortality increased in the post-COVID period, 3, 6 and 12 months after. The high mortality rate of patients who had AKI during the coronavirus infection was observed only in the first 3 months of follow-up in the post-COVID period.

Key words: *COVID-19, chronic kidney disease, acute kidney damage*

Conflict of interests

The authors declare no conflict of interests

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AH — arterial hypertension, ARB II — angiotensin II receptor blocker, BA — bronchial asthma, BB -beta-blocker, CCB — calcium channel-blocking agent, GC — glucocorticosteroid, ACE inhibitors — angiotensin converting enzyme inhibitors, IHD — ischemic heart disease, BMI — body mass index, CRF — case report form, CT — computer tomography, nCoV — novel coronavirus infection, NSAID — nonsteroidal anti-inflammatory drug, ACE — acute cerebrovascular event, AKI — acute kidney injury, OR — odd ratio, DM — diabetes mellitus, GFR — glomerular filtration rate, AHG — antihyperglycemic drug, AF — atrial fibrillation, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, CHF — chronic heart failure, RR — respiratory rate

Introduction

Management of patients with chronic kidney disease (CKD) and acute kidney injury (AKI) during coronavirus infection and post-COVID rehabilitation is a burning issue of the contemporary therapeutics and is widely discussed by Eurasian and national medical communities [1-4]. On the one hand, it is caused by the features of coronavirus infection in patients with impaired renal function and, on the other hand, by the need in medical support of this patient category, which can be associated with the need in renal replacement therapy [5, 6].

The need in information related to the features of coronavirus infection, in particular in patients with impaired renal function, was satisfied with the help of the following registers: Dynamics Analysis of Comorbidities in SARS-CoV-2 Survivors (AKTIV) and Analysis of Hospitalizations of Comorbid Patients with SARS-CoV-2 (AKTIV 2) [7-9].

Materials and Methods

The AKTIV and AKTIV 2 registers were initiated by the Eurasian Association of Therapists (EAT). The AKTIV and AKTIV 2 registers were approved by the Ethics Committee at the Federal State Autonomous Educational Institution of Higher Education N. I. Pirogov Russian National Research Medical University of the Ministry of Health of the Russian Federation and registered in ClinicalTrials.gov (NCT 04492384, NCT 04709120). For information on the registers, please refer to the web site of the Eurasian Association of Therapists, or go to https://activ.euat.ru and https://activ2.euat.ru. AKTIV and AKTIV 2 registers are multicenter non-interventional retrospective registers of real-life clinical experience. AKTIV had two non-overlapping threads (outpatient thread and inpatient thread). Both threads provided for 6 visits: baseline visit, Day 7–12 visit, final visit (dismissal/hospitalization/death, etc.), and three visits — 3, 6, and 12 months after discharge from the hospital. AKTIV 2 register included information on hospitalised patients only and provided for 3 visits: baseline visit, Day 7–12 visit, final visit (dismissal/hospitalization/death, etc.).

Both registers included men and women over 18 years old with COVID-19 confirmed with a nasopharynx and oropharynx swab, SARS-CoV-2 antibody titer and/or typical computer tomography (CT) findings during the first (for AKTIV) and second (for AKTIV 2) coronavirus waves.

A primary document was the clinical record, which was used to fill out case report forms (CRF) with the following laboratory parameters: RBC, Hb, WBC, lymphocytes, platelets, highly sensitive cardiac troponin T or I, C-reactive protein, procalcitonin, arterial blood gases (pCO_2, pO_2), aspartate aminotransferase, alanine aminotransferase, bilirubin, glucose, albumin, creatinine for eGFR calculation, serum potassium, D-dimer, lactate dehydrogenase, international normalised ratio, fibrinogen, blood oxygen (SpO_2)), chest CT findings, information on drugs, comorbidities, clinical progression, and disease outcome. Glomerular filtration rate was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (Chronic Kidney Disease Epidemiology Collaboration Formula, CKD-EPI, version 2009, taking into account the time of active enrollment and register data processing) integrated with the automated calculator function in case report forms.

A nosologic diagnosis was made on the basis of ICD 10 criteria. More specifically, taking into account the register design, CKD was diagnosed with GFR of no less than 60 mL/min/1.73 m^2

The database was analysed using IBM SPSS Statistics 26. Continuous sampling method was used to select 9364 patients from AKTIV and AKTIV 2. For descriptive statistics calculations, quantitative variables were checked for normal distribution with the help of Shapiro-Wilk's test and Kolmogorov-Smirnov test. If the difference from normal distribution was not statistically significant, the central trend and measure of scatter were described using a mean sample value and standard deviation (M±σ); where the difference from normal distribution was statistically significant, the median and quartiles (Me [Q1; Q3]) were used. Quantitative data from two independent groups were analysed using Mann-Whitney test for independent samples with non-normal distribution (a normality test showed a distribution that was different from normal distribution); quantitative data from three and more groups were analysed with the help of Kruskall-Wallis test with subsequent pair-wise comparison. Qualitative parameters were evaluated using Pearson's chi-squared test or Fisher's exact test, depending on the expected minimal value. For features with statistically significant differences (level of significance < 0.05),

odds and certain relations between nominal characteristics were evaluated with 95 % CI.

Odds ratio (OR) and its 95 % CI were calculated using a one-factor binary logit regression method. The stage 1 mathematical model was generated using a multi-factor binary logit regression method, with variables selected by the authors taking into account study objectives and tasks. For the final model used to select the most significant estimate predictors, a stepwise downward variable selectin algorithm was implemented,

Table 1. *Characteristics of patients included in the АКТИВ and АКТИВ 2 registries with different baseline GFR values*

Characteristic	Total cohort n=9364	GFR ≥90 (n=4289)	GFR 89-60 (n=3150)	GFR 59-45 (n=613)	GFR 44-30 (n=253)	GFR 29-15 (n=110)	GFR <15 (n=81)	p
Age	59,0 [48,0; 68,0]	55,0 (43,0–63,0)	66,0 (57,0–73,0)	73,0 (66,0–81,0)	74,0 (66,0–83,0)	72,0 (61,0–81,0)	62,5 (54,5–71,0)	<0,001* $p_{1\,5}$<0,001* $p_{1\,2}$<0,001* $p_{1\,4}$<0,001* $p_{1\,3А}$<0,001* $p_{1\,3Б}$<0,001* $p_{5\,2}$=1,0 $p_{5\,4}$=0,007* $p_{5\,3А}$<0,001* $p_{5\,3Б}$<0,001* $p_{2\,4}$=0,019* $p_{2\,3А}$<0,001* $p_{2\,3Б}$<0,001* $p_{4\,3А}$=0,302 $p_{4\,3Б}$=0,295 $p_{3А\,3Б}$=1,0
Women	4960 (53 %)	1995 (46,5 %)	1799 (57,4 %)	388 (64,2 %)	1613 (64,7 %)	61 (55,5 %)	49 (61,3 %)	<0,001*
Lethal outcomes	545 (5,8 %)	100 (2,4 %)	184 (5,9 %)	86 (14,6 %)	80 (32,1 %)	42 (40,0 %)	15 (19,5 %)	<0,001*
Overweight	2934 (37,7 %)	1383 (37,9 %)	994 (38,0 %)	174 (35,1 %)	62 (30,4 %)	34 (37,4 %)	29 (39,7 %)	<0,001*
Obesity, degree 1	1701 (21,8 %)	771 %)	642 (24,5 %)	123 (24,8 %)	53 (26,0 %)	16 (17,6 %)	11 (15,1 %)	
Obesity, degree 2	669 (8,5 %)	311 (8,5 %)	248 (9,5 %)	42 (8,5 %)	25 (12,3 %)	12 (13,2 %)	4 (5,5 %)	
Obesity, degree 3	240 (3,08 %)	133 (3,6 %)	96 (3,7 %)	38 (7,7 %)	13 (6,4 %)	5 (5,5 %)	3 (4,1 %)	
CT 1	3136 (41,9 %)	1565 (44,2 %)	1126 (41,8 %)	167 (34,2 %)	64 (30,3 %)	20 (21,7 %)	25 (37,9 %)	<0,001*
CT 2	2563 (34,2 %)	1170 (33,1 %)	973 (36,1 %)	178 (36,5 %)	79 (37,4 %)	35 (38,0 %)	21 (31,8 %)	
CT 3	1005 (13,4 %)	455 (12,9 %)	363 (13,5 %)	87 (17,8 %)	42 (19,9 %)	16 (17,4 %)	12 (18,2 %)	
CT 4	231 (3,1 %)	92 (2,6 %)	73 (2,7 %)	25 (5,1 %)	13 (6,2 %)	13 (14,1 %)	3 (4,5 %)	
SpO_2 75-94 %	2166 (23,1 %)	856 (31,1 %)	810 (38,6 %)	209 (49,4 %)	94 (55,0 %)	42 (54,5 %)	21 (41,2 %)	<0,001*
SpO_2 less than 75 %	55 (0,6 %)	15 (0,5 %)	20 (1,0 %)	9 (2,1 %)	1 (0,6 %)	6 (7,8 %)	0	
Breathing rate 22-29	2314 (25,0 %)	1038 (24,3 %)	810 (25,9 %)	201 (33,5 %)	97 (39,0 %)	42 (38,5 %)	18 (22,5 %)	<0,001*
Breathing rate more than 30	178 (1,9 %)	52 (1,2 %)	66 (2,1 %)	25 (4,2 %)	14 (5,6 %)	9 (8,3 %)	4 (5,0 %)	
Temperature over 38.6-39.0	1634 (17,7 %)	780 (18,4 %)	583 (18,8 %)	115 (19,3 %)	48 (19,2 %)	20 (18,5 %)	11 (14,1 %)	<0,001*
Temperature over 39.0	640 (6,9 %)	354 (8,3 %)	210 (6,8 %)	36 (6,0 %)	11 (4,4 %)	7 (6,5 %)	4 (5,1 %)	
Hypertension	5289 (56,6 %)	1929 (45,1 %)	2196 (70,1 %)	506 (83,8 %)	211 (83,7 %)	85 (77,3 %)	62 (77,5 %)	<0,001*
Smoking	475 (5,09 %)	245 (5,7 %)	123 (3,9 %)	17 (2,8 %)	7 (2,8 %)	4 (3,6 %)	8 (10,8 %)	<0,001*
AF	672 (7,2 %)	157 (3,7 %)	284 (9,1 %)	113 (18,7 %)	65 (25,8 %)	23 (20,9 %)	6 (7,5 %)	<0,001*
IHD	2144 (23 %)	534 (12,5 %)	938 (29,9 %)	289 (47,8 %)	127 (50,4 %)	51 (46,4 %)	26 (32,5 %)	<0,001*
CHF	1595 (17,1 %)	413 (9,7 %)	685 (21,9 %)	241 (39,9 %)	111 (44,0 %)	52 (47,3 %)	24 (30,0 %)	<0,001*
CVA	401 (4,29 %)	95 (2,2 %)	183 (5,8 %)	49 (8,1 %)	35 (13,9 %)	13 (11,8 %)	6 (7,5 %)	<0,001*
DM type 2	1611 (17,3 %)	592 (13,8 %)	602 (19,2 %)	191 (31,6 %)	86 (34,1 %)	32 (29,1 %)	21 (26,3 %)	<0,001*
COPD	408 (4,3 %)	151 (3,5 %)	150 (4,8 %)	44 (7,3 %)	28 (11,1 %)	7 (6,4 %)	8 (10,0 %)	<0,001*
BA	321 (3,44 %)	138 (3,2 %)	122 (3,9 %)	23 (3,8 %)	6 (2,4 %)	2 (1,8 %)	3 (3,8 %)	0,487
Cancer	536 (5,74 %)	195 (4,6 %)	212 (6,8 %)	48 (7,9 %)	25 (9,9 %)	12 (10,9 %)	5 (6,3 %)	<0,001*
Anemia	1976 (22,7 %)	809 (19,3 %)	636 (20,8 %)	188 (31,9 %)	110 (44,7 %)	61 (56,0 %)	56 (70,0 %)	<0,001*

Note: BA — bronchial asthma, IHD — ischemic heart disease, CT — computed tomography, CVA — acute cerebrovascular accident, DM — diabetes mellitus, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CHF — chronic heart failure;
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis.

which was followed by AIC (Akaike information criterion) evaluation. Once the final model had been generated using the ROC analysis, the area under curve (AUC) was evaluated, while the model sensitivity and specificity were evaluated in Youden point. The survival time was analysed using Kaplan-Meier's survival curves; statistical significance of the differences in evaluation of the survival time was evaluated using the log-rank test. The cuttoff threshold for the level of significance in statistical hypotheses testing was $p < 0.05$. Predictors with the level of significance of $p \geq 0.05$ could be used in the final model, provided that their exclusion would result in a marked increase in AIC (features interaction effect). The design, justification and statistical analysis of the studies are detailed in the article [10].

All in all, 9364 patients were included in the analysis (4404 (47 %) men, mean age: 59 years old [48–69]). Glomerular filtration rate (GFR) upon admission which was calculated automatically when blood plasma creatinine was entered upon admission on day 1, was recorded in 8496 (90.7 %) patients, with the following distribution of results: ≥ 90 mL/min/1.73 m^2 — 4289 (50.5 %) patients; 89–60 mL/min/1.73 m^2 — 3150 (37.1 %) patients, 59–45 mL/min/1.73 m^2 — 613 (7.22 %) patients, 44–30 mL/min/1.73 m^2 — 253 (2.98 %) patients, 29–15 mL/min/1.73 m^2 — 110 (1.29 %) patients, < 15 mL/min/1.73 m^2 — 81 (0.95 %) patients.

Mean age of patients which were added to the register was 59.0 years old [48.0; 68.0]. The maximum age was observed in the cohort with GFR of 44–30 mL/min/1.73 m^2 — 74.0 years old [66.0–83.0], the minimal age — in patients with GFR of over 90 mL/min/1.73 m^2 — 55.0 years old [43.0–63.0]. 4960 (53 %) patients were females. In the groups with various GFR values, the distribution of deaths was as follows: GFR of over 90 mL/min/1.73 m^2 — 100 (19.7 %) patients, 89–60 mL/min/1.73 m^2 — 184 (36.3 %) patients, 59–45 mL/min/1.73 m^2 — 86 (16.8 %) patients, 44–30 mL/min/1.73 m^2 — 80 (15.8 %) patients, 29–15 mL/min/1.73 m^2 — 42 (8.3 %) patients, GFR of less that 15 mL/min/1.73 m^2 — 15 (2.8 %) patients; p overall < 0.001.

Patients with GFR of 59–15 mL/min/1.73 m^2 vs. patients with GFR of over 60 mL/min/1.73 m^2 tended to more frequently have severe changes in their lungs (CT 3–4, p <0.001), impaired saturation (75–94 % and below 75 %, p <0.001), increased RR (over 22 respirations per minute, p <0.001), fever (over 38.6°C).

Both the general cohort and patients with GFR below 60 mL/min/1.73 m^2 had the following most common comorbidities: arterial hypertension (AH) (p <0.001), ischemic heart disease (IHD) (p <0.001), chronic heart failure (CHF) (p < 0.001), anemia (p <0.001), type 2 diabetes mellitus (DM2) (p <0.001).

ANALYSIS RESULTS

Incidence of Renal Diseases (CKD, AKI) in Patients with COVID-19

It should be noted that the AKTIV register included 716 (7.67 %) SARS-CoV-2 patients with pre-existing CKD; this number corresponds to the information on CKD incidence in the general population in the Russian Federation [11]. A proportion of CKD patients was higher in the group of patients over 60 years old (11.9 % of patients over 60 years old) and lower in patients below 60 years old (3.53 % of the total number of patients below 60 years old). CKD distribution taking into account GFR in the groups of patients below 60 years old and over 60 years old was not calculated.

CKD with AH, DM2 and obesity increased the need in anti-cytokine therapy in COVID-19 patients, and this is an indirect reason for more severe course of coronavirus infection in patients with CKD (Table 2).

According to Table 2, COVID-19 patients who did not require targeted therapy included patients with CKD; however, the group of patients who required anti-cytokine therapy included a significant number of patients with CKD. Apparently, CKD comorbidities have a role to play. A more severe infection was recorded in patients with CKD and comorbidities, rather than in CKD alone. This trend was observed also in evaluation of odds ratio (OR): OR was indeed higher in patients with CKD.

AKI symptoms were recorded in 9206 (98.3 %) questionnaires. During hospitalisation, AKI developed in 11.6 % (1068 patients out of 9206 patients), i.e., in every 8–9th patient. When the AKI data from the register were analysed, either physician's notes from medical records or the difference in creatinine levels of ≥ 30 μmol/L [12] during hospitalisation, which were measured twice, were taken into account. It is worth mentioning that AKI developed more frequently than cytokine storm (7.46 %, 687 patients out of 9209 patients) or sepsis (0.17 %, 16 patients out of 9411 patients) (p < 0.001). In identified AKI cases, changes in creatinine levels corresponded to stage 1 (because of the study design, diuresis was not assessed).

When analysing the register database, the authors attempted to single out risk factors affecting development of AKI and a number of other complications in patients with COVID-19. After a follow-up examination (assessment of creatinine level changes, CRP, CT stage, previous target therapy), the sample group was divided into two groups depending on the presence or absence of the following signs: AKI, cytokine storm, C-reactive protein (CRP) level of over 100 mg/L. Then, the body mass index (BMI) was assessed for each group (Table 3).

Mean BMI values for patients with or without AKI corresponded to overweight. BMI in patients with AKI was statistically higher than the BMI of patients without AKI (p = 0.018). In the AKI group, BMI was 29.6 mg/m^2

Table 2. *Comparison of study groups of patients with COVID-19 according to the frequency of targeted therapy depending on the comorbidities*

Factor	Did not receive targeted therapy	Received targeted therapy	p	V	OR; 95 % CI
		Hypertension			
	n=9047	n=292			
No	3951 (43,7 %)	99 (33,9 %)	0,001	0,034	1,51; 1,18–1,93
Yes	5096 (56,7 %)	193 (66,1 %)			
		DM type 2			
	n=9047	n=292			
No	7525 (83,2 %)	203 (65,9 %)	<0,001	0,063	2,17; 1,68–2,80
Yes	1522 (16,8 %)	89 (30,5 %)			
		CKD			
	n=9047	n=292			
No	8377 (92,6 %)	246 (84,2 %)	<0,001	0,055	2,34; 1,69–3,23
Yes	670 (7,4 %)	46 (15,8 %)			
		Obesity			
	n=8990	n=291			
No	6645 (73,9 %)	186 (63,9 %)	<0,001	0,040	1,6; 1,25–2,04
Yes	2345 (26,1 %)	105 (36,1 %)			

Note: DM — diabetes mellitus, CKD — chronic kidney disease.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis. Only 9281 (99,1 %) patient questionnaires our of 9364 contained information on the use or non-use of targeted therapy together with the obesity status. The targeted therapy was defined as Salirumab, Olokizumab and Levilimab.

Table 3. *The influence of BMI on various factors (Mann-Whitney test)*

Characteristic	Characteristic absent Me (Q1 — Q3)	Characteristic present Me (Q1 — Q3)	p
AKI	27,8 (24,8–31,6)	29,6 (25,1–33,5)	0,018
Cytokine storm	27,5 (24,4–31,2)	28,7 (25,6–32,8)	<0,001
CRP level more than 100 мг/л	27,7 (24,7–31,7)	28,7 (25,5–32,7)	<0,001
Mortality rate	5,7 (5,0–7,0)	6,9 (5,6–9,18)	<0,001

Note: BMI — body mass index, AKI — acute kidney injury, CRP — C-reactive protein

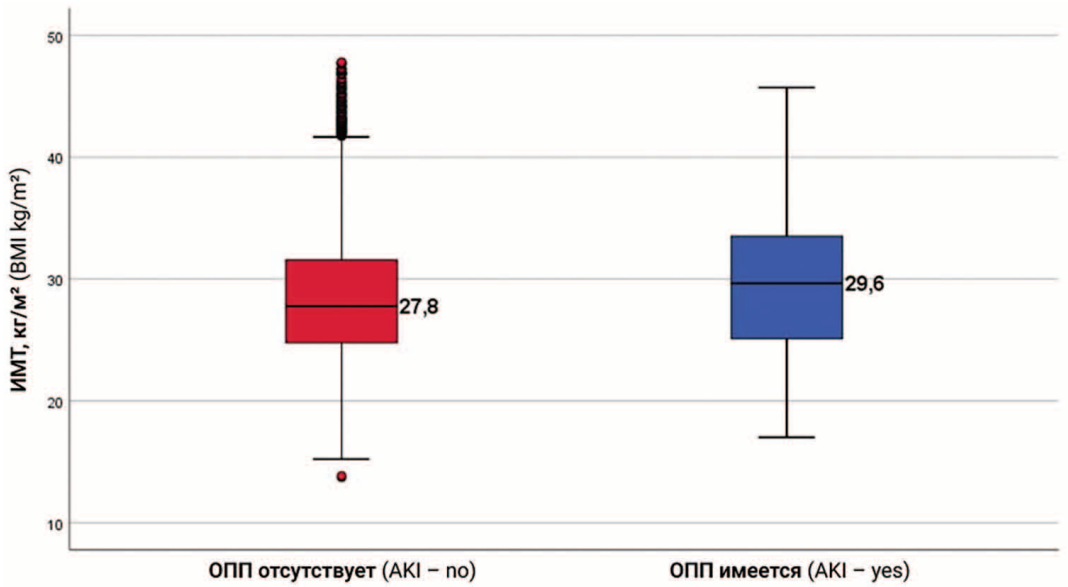

Figure 1. *Relationship between the presence and absence of AKI and BMI*
Note: BMI — body mass index, AKI — acute kidney injury

(Q1 = 25.1; Q3 = 33.5), whereas patients without AKI had BMI of 27.8 kg/m^2 (Q1 = 24.8; Q3 = 31.6) (Figure 1).

Fasting glucose levels were assessed. In patients with coronavirus infection and AKI, the values were 6.0 (5.2; 8.55) mmol/L, i.e., statistically higher than in patients without AKI (5.8 (5.0; 7.0) mmol/L) (p = 0.011).

Analysis of CKD and AKI Impact on Hospital Mortality and Post-Covid Mortality

Analysis of hospital mortality depending on the presence or absence of CKD is presented in Table 4. It was observed that CKD increased the risk of death in COVID-19 patients by 3.94 times (95 % CI [3.15; 4.89], 0.0001); therefore, CKD can be a factor of adverse hospital outcome in COVID-19 patients. At the same time, the risk of hospital mortality in the presence of CKD was higher in the group of patients below 60 years old (OR = 5.0, CI [2.59; 8.91], p < 0.001) vs. patients over 60 years old (OR = 2.61 CI [2.05; 3.30], p < 0.001).

The risk of hospital mortality was extremely high in the group of patients with GFR of 44–30 mL/min/1.73 m^2 (OR = 19.5, CI [14.0; 27.2]) and 29–15 mL/min/1.73 m^2 (OR = 27.6, CI [17.7; 42.7]), corresponding to CKD stages 3B and 4 with subsequent minor reduction in the risk at CKD stage 5. It is worth mentioning that there were just 78 (0.9 %) stage 5 patients, including 62 (79.5 %) patients who survived and 16 (20.5 %) patients who died, which could potentially affect statistics. According to observations of CKD stage 5 patients (n = 72,734) in Russia, mortality in COVID-19 patients is high (approx. 24.4 %) [13].

The odds of dying during hospitalisation in COVID-19 patients who develop AKI is 3.94 times higher than in patients without AKI (CI [3.24; 4.78], p = 0.0001).

The register database analysis demonstrated that CKD in patients with coronavirus infection also increases the risk of death during the post-COVID period (Table 5). During the first three months of the follow-up period, the risk of death in patients with CKD increased 4.88-fold (CI [2.42; 9.13], p < 0.001); during the six months of the follow-up period, there was a 4.24-fold increase (CI [0.60; 16.3], p = 0.126); and in 12 months the risk increased 8.36-fold (CI [1.73; 29.3], p = 0.012). Thus, even in a distant prospect of a year-long follow-up, when the mortality during the post-COVID period in the general population falls, the impact from CKD on survival rates was even higher.

It is essential to understand whether AKI during COVID affects mortality rates during the post-COVID period (Table 6). The analysis demonstrated that this impact was observed during the first three months only. At the same time, the odds of dying in 3 months after COVID for patients who had AKI during thier disease was 3.59 tims higher vs. patients without AKI (CI [1.87; 6.50], p < 0.001). AKI management during coronavirus infection was associated with high mortality rates over a short period of time (for three months) with gradual evening out (Table 6).

Table 4. *Comparison of the impact of renal factors on in-hospital mortality in patients with COVID-19*

	Survivors N=8662	Lethal outcomes N=545	OR; 95 % CI	p. ratio	p-overall	Total number
CKD — no	8067 (93,3 %)	425 (78,0 %)				
CKD — yes	579 (6,70 %)	120 (22,0 %)	3,94 [3,15; 4,89]	0,0001		
CKD up to 60 years old — no	4428 (96,7 %)	77 (85,6 %)			<0,001	4669
CKD up to 60 years old — yes	151 (3,30 %)	13 (14,4 %)	5,00 [2,59; 8,91]	<0,001		
CKD over 60 years — no	3612 (89,5 %)	348 (76,5 %)			<0,001	4493
CKD over 60 years — yes	426 (10,5 %)	107 (23,5 %)	2,61 [2,05; 3,30]	<0,001		
GFR						8388
≥ 90 ml/min/1.73m^2	4147 (52,6 %)	100 (19,6 %)				
89-60 ml/min/1.73m^2	2926 (37,1 %)	185 (36,3 %)	2,62 [2,05; 3,37]	<0,001		
59-45 ml/min/1.73m^2	511 (6,49 %)	86 (16,9 %)	6,98 [5,15; 9,44]	0,0001		
44-30 ml/min/1.73m^2	170 (2,16 %)	80 (15,7 %)	19,5 [14,0; 27,2]	0,0001		
29-15 ml/min/1.73m^2	63 (0,80 %)	42 (8,25 %)	27,6 [17,7; 42,7]	0,0001		
<15 ml/min/1.73m^2	62 (0,79 %)	16 (3,14 %)	10,8 [5,80; 18,9]	<0,001		
AKI					<0,001	9207
AKI no	7769 (89,7 %)	375 (68,8 %)				
AKI yes	893 (10,3 %)	170 (31,2 %)	3,94 [3,24; 4,78]	0,0001		

Note: AKI = acute kidney injury, GFR = glomerular filtration rate, CKD = chronic kidney disease
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Table 5. *Analysis of mortality in the post-COVID period depending on CKD at baseline*

Visit		CKD no	CKD yes
Visit 4 (3 months after the discharge)	Survived N=3089	2931 (94,9 %)	158 (5,11 %)
	Died N=58	46 (79,3 %)	12 (20,7 %)
	OR, 95 %CI	Ref.	4,88 [2,42; 9,13]
	p-ratio	Ref.	<0,001
	p overall	<0,001	
Visit 5 (6 months after the discharge)	Survived N=2485	2377 (95,7 %)	108 (4,35 %)
	Died N=13	11 (84,6 %)	2 (15,4 %)
	OR, 95 %CI	Ref.	4,24 [0,60; 16,3]
	p-ratio	Ref.	0,126
	p overall	0,109	
Visit 6 (12 months after the discharge)	Survived N=1774	1704 (96,1 %)	70 (3,95 %)
	Died N=12	9 (75,0 %)	3 (25,0 %)
	OR, 95 %CI	Ref.	8,36 [1,73; 29,3]
	p-ratio	Ref.	0,012
	p overall	0,011	

Note: CKD stands for chronic kidney disease.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Table 6. *Analysis of long-term mortality in patients with COVID-19, depending on the presence/absence of AK*

Visit		AKI no	AKI yes
Visit 4 (3 months after the discharge)	Survived N=3103	2849 (91,8 %)	254 (8,19 %)
	Died N=58	44 (75,9 %)	14 (24,1 %)
	OR, 95 %CI	Ref.	3,59 [1,87; 6,50]
	p-ratio	Ref.	<0,001
	p overall	<0,001	
Visit 5 (6 months after the discharge)	Survived N=2493	2294 (92,0 %)	199 (7,98 %)
	Died N=13	11 (84,6 %)	2 (15,4 %)
	OR, 95 %CI	Ref.	2,22 [0,31; 8,50]
	p-ratio	Ref.	0,360
	p overall	0,280	
Visit 6 (12 months after the discharge)	Survived N=1782	1649 (92,5 %)	133 (7,46 %)
	Died N=12	12 (100,0 %)	0 (0,0 %)
	OR, 95 %CI	Ref.	8,36 [1,73; 29,3]
	p-ratio	Ref.	0,99
	p overall	1,00	

Note: AKI stands for acute kidney injury.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Impact from the Drug Therapy on Mortality Rates in COVID-19 Patients with CKD

It can be interesting to review the data on the impact from various drug therapies on survival rates in COVID-19 patients with CKD (Table 7). The total number of CKD patients was 693, including 120 patients who died (17.3 %) and 573 survivors (82.7 %).

The use of ARB was associated with a decrease in mortality rates in patients with CKD during the infection (OR 0.5, CI [0.3; 0.8], p = 0.004). In patients who died, ARB was administered in 15.8 % of cases (19 patients), while in the survivor group it was administered in 28.4 % of cases (163 patients). There was just an insignificant association between compared parameters (V = 0.047). The odds of death in patients with CKD who were treated with hydroxychloroquine decreased 1.7-fold (95 % CI: 0.4–0.99). There was just an insignificant association between compared parameters (V = 0.077).

At the same time, ACE inhibitors did not have any significant impact over the risk of death (p > 0.05). Statin, BB, and CCB therapy did not have any significant impact on the survival rates in CKD patients (p > 0.05). The use of therapies for making COVID-19 less severe (inhalation or IV steroids, paracetamol, acetylsalicylic acid, antihistamines, bronchodilators, and targeted therapy did not have any impact on mortality rates in patients with CKD (p > 0.05). Nonsteroidal anti-inflammatory drugs (NSAIDs) were associated with a minor, but statistically significant decrease in mortality rates. The odds of dying in patients with CKD who took NSAIDs was 2 times lower (95 % CI: 0.3–0.9, p = 0.030). There was just an insignificant association between compared parameters (V = 0.082). The odds of dying in patients with CKD who took antihyperglycemic (AHG) tablets decreased by 3.3 times (95 % CI: 0.1–0.8, p = 0.011). There was just an insignificant association between compared parameters (V = 0.097).

The use of hydroxychloroquine had a positive effect on survival rates (OR 0.6, CI [0.4; 0.99], p = 0.043. There was just an insignificant association between compared parameters (V = 0.077). The odds of dying in patients with CKD who were treated with interferons increased by 4.2 times (95 % CI: 1.5–11.6, p = 0.007). There was just a minor association between compared parameters (V = 0.142). The odds of dying in patients with CKD who were treated with diuretics increased by 1.7 times (95 % CI: 1.2–2.6, p = 0.007). There was just a minor association between compared parameters (V = 0.102). The odds of death in patients with CKD who were treated with expectorant drugs decreased by 0.6 times (95 % CI: 0.4–0.9, p = 0.009). There was just a minor association between compared parameters (V = 0.1).

Since there were no deaths in patients with AKI in treatment groups, the AKI impact on mortality rates could not be assessed.

Table 7. *Survival of patients with CKD and COVID-19 infection according to the therapeutic intervention*

Class of drugs	Survivors (n=573)	Lethal outcomes (n=120)	p	OR; 95 %CI	Cramer's V
ACE inhibitors					
Not prescribed	373 (65,1 %)	71 (59,2 %)	0,218		0,047
Prescribed	200 (34,9 %)	49 (40,8 %)			
ARA					
Not prescribed	410 (71,6 %)	101 (84,2 %)	0,004*	0,5 (0,3–0,8)	0,108
Prescribed	163 (28,4 %)	19 (15,8 %)			
Statins					
Not prescribed	423 (73,8 %)	84 (70,0 %)	0,390		0,033
Prescribed	150 (26,2 %)	36 (30,0 %)			
BB					
Not prescribed	297 (51,8 %)	66 (55,0 %)	0,528		0,024
Prescribed	276 (48,2 %)	54 (45,0 %)			
CCB					
Not prescribed	428 (74,7 %)	94 (78,3 %)	0,401		0,032
Prescribed	145 (25,3 %)	26 (21,7 %)			
ICS					
Not prescribed	562 (98,1 %)	116 (96,7 %)	0,308		0,037
Prescribed	11 (1,9 %)	4 (3,3 %)			

Таблица 7. *(Окончание)*
Table 7. *(The end)*

Class of drugs	Survivors (n=573)	Lethal outcomes (n=120)	p	OR; 95 %CI	Cramer's V
		Paracetamol			
Not prescribed	320 (55,8 %)	75 (62,5 %)	0,181		0,051
Prescribed	253 (44,2 %)	45 (37,5 %)			
		Aspirin			
Not prescribed	451 (78,7 %)	96 (80,0 %)	0,752		0,012
Prescribed	122 (21,3 %)	24 (20,0 %)			
		NSAIDs			
Not prescribed	475 (82,9 %)	109 (90,8 %)	0,030*	0,5 (0,3–0,9)	0,082
Prescribed	98 (17,1 %)	11 (9,2 %)			
		Antihistamines			
Not prescribed	355 (97,8 %)	92 (100 %)	0,368		0,067
Prescribed	8 (2,2 %)	0			
		Bronchodilators			
Not prescribed	517 (90,2 %)	107 (89,2 %)	0,724		0,013
Prescribed	56 (9,8 %)	13 (10,8)			
		Interferons (SC)			
Not prescribed	355 (97,8 %)	84 (91,3 %)	0,007*	4,2 (1,5–11,6)	0,142
Prescribed	8 (2,2 %)	8 (8,7 %)			
		Hydroxychloroquine			
Not prescribed	428 (74,7 %)	100 (83,3 %)	0,043*	0,6 (0,4–0,99)	0,077
Prescribed	145 (25,3 %)	20 (16,7 %)			
		IV CS			
Not prescribed	333 (63,5 %)	81 (68,6 %)	0,296		0,041
Prescribed	191 (36,5 %)	37 (31,4 %)			
		Short-acting insulins			
Not prescribed	460 (81,1 %)	91 (76,5 %)	0,245		0,044
Prescribed	107 (18,9 %)	28 (23,5 %)			
		Long-acting insulin			
Not prescribed	482 (85,0 %)	108 (90,8 %)	0,1		0,063
Prescribed	85 (15,0 %)	11 (9,2 %)			
		Oral hypoglycemic medications			
Not prescribed	505 (89,1 %)	115 (96,6 %)	0,011*	0,3 (0,1–0,8)	0,097
Prescribed	62 (10,9 %)	4 (3,4 %)			
		Diuretics			
Not prescribed	324 (57,1 %)	52 (43,7 %)	0,007*	1,7 (1,2–2,6)	0,102
Prescribed	243 (42,9 %)	67 (56,3 %)			
		Expectorants			
Not prescribed	259 (45,7 %)	70 (58,8 %)	0,009*	0,6 (0,4–0,9)	0,1
Prescribed	308 (54,3 %)	49 (41,2 %)			
Antiplatelets					
Not prescribed	439 (76,6 %)	94 (78,3 %)	0,684		0,015
Prescribed	134 (23,4 %)	26 (21,7 %)			
		Targeted therapy			
Not prescribed	265 (76,6 %)	70 (75,3 %)	0,790		0,013
Prescribed	81 (23,4 %)	23 (24,7 %)			

Note: The differences were considered statistically significant at p<0.05. ACE — angiotensin-converting enzyme; ARA — angiotensin II receptor antagonists; BB — beta-blockers; CCB — slow calcium channels blockers; CS — corticosteroids; ICS — inhaled corticosteroids; NSAIDs — non-steroidal anti-inflammatory drugs.
* — The difference in the number of covid patients is due to the fact that not all items in the questionnaires were completed, which affected the results of the statistical analysis

Conclusion

Thus, the analysis of the AKTIV and AKTIV 2 databases demonstrated that the incidence of CKD in COVID-19 patients is not higher than in the general population. AKI developed in 11.6 % of COVID-19 cases and was more common in patients with overweight and hyperglycemia. CKD and AKI increased the risk of hospital mortality in COVID-19 patients. It was also noted that, during 3 and 12 months of follow-up during the post-COVID period, mortality in CKD patients increased, and the highest difference in mortality rates was observed in 12 months. Patients who had AKI during coronavirus infection had high mortality rates in post-COVID period during first three months of follow-up. Certain drugs were efficient in reducing mortality rates in COVID-19 patients with CKD; therefore, existing drug regimens can be adjusted for this patient group. Specifically, ARB, NSAIDs, hydroxychloroquine, antihyperglycemic tablets, and mucolytics can be useful. Data analysis was retrospective, and analysis results can be used as a basis for randomised clinical trials in COVID-19 patients with CKD.

According to the authors, the limitations of this study are incorrect CRF filling-out (omissions, lack of information in primary medical records), which affects the data quality. Also, no multi-factor analysis was conducted in this study and it can be conducted at later stages. The study design did not provide for collection of pre-hospital medical information, that is why "CKD" refers to patients with an isolated GFR reduction of less than 60 mL/min/1.73 m^2.

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