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ACUTE KIDNEY INJURY IN SEVERE PNEUMONIA ASSOCIATED WITH COVID-19

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ABSTRACT. The clinical and epidemiological features of acute kidney injury in severe and extremely severe pneumonia associated with coronavirus disease-2019 (COVID-19) are considered. An observational prospective study was conducted with the inclusion of 117 patients, including 75 men and 42 women, suffering from severe and extremely severe pneumonia associated with COVID-19, who were treated in the intensive care unit of the 1586th Military Clinical Hospital in 2020–2022. Acute kidney injury was diagnosed in 21 (17.9%) patients (stage 1 in 10, stage 2 in 4, and stage 3 in 7 patients), kidney dysfunction was recorded in 22 (8.8%) patients (serum creatinine was higher than normal, but does not reach the diagnostic criteria of Kidney Disease Improving Global Outcomes). Four patients underwent renal replacement therapy. The probability of kidney damage increases with age (the average age of the patients with acute kidney damage is 65 (58; 71) years, and those without acute kidney damage was 47.5 (41; 55) years; $p = 0.0001$). Compared with patients without acute kidney injury, patients with acute kidney injury scored higher on the scales NEW ($p = 0.000975$), SMRT-CO ($p = 0.011555$), and Sequential Organ Failure Assessment ($p = 0.000042$). Among those suffering from acute kidney injury, significantly more pronounced manifestations of systemic inflammation were determined (leukocytes, $p = 0.047324$; platelets, $p = 0.001230$; ferritin, $p = 0.048614$; and D-dimer, $p = 0.004496$). In the general cohort, the mortality rate was 22.2%, whereas a significant intergroup difference in mortality was observed, i.e., 52.4% in patients with acute kidney injury and 15.62% in those without acute kidney injury (Chi-squared criterion, 13.468; $p < 0.001$). Invasive artificial lung ventilation was performed in 19.66% of the patients, and a significant intergroup difference was identified, with 66.7% in patients with acute kidney injury and 9.38% in patients without acute kidney injury (Chi-squared criterion, 35.810; $p < 0.001$). The durations of treatment in the intensive care unit in patients with and without acute kidney injury were 9 (7; 14) and 6 (4; 10) days, respectively. After the treatment, all patients with acute kidney injury had fully recovered kidney function upon discharge. In general, acute kidney injury occurs in almost every fifth patient with severe and extremely severe pneumonia associated with COVID-19, aggravates the condition of patients, and increases mortality. The alertness of doctors regarding acute kidney injury and early diagnosis and timely nephroprotective treatment may reduce the possibility of adverse disease outcomes.

Keywords: acute kidney injury; new coronavirus infection; pneumonia; systemic inflammation; invasive artificial lung ventilation; nephroprotective treatment; unfavorable outcome of the disease.

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ОСТРОЕ ПОВРЕЖДЕНИЕ ПОЧЕК ПРИ ТЯЖЕЛОМ ТЕЧЕНИИ ПНЕВМОНИЙ, АССОЦИИРОВАННЫХ С НОВОЙ КОРОНАВИРУСНОЙ ИНФЕКЦИЕЙ (COVID-19)

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Резюме. Рассматриваются клинико-эпидемиологические особенности острого повреждения почек при пневмониях тяжелого и крайне тяжелого течения, ассоциированных с новой коронавирусной инфекцией. Проведено наблюдательное проспективное исследование с включением 117 больных, из них 75 мужчин и 42 женщины, страдающих пневмониями тяжелого и крайне тяжелого течения, ассоциированными с новой коронавирусной инфекцией, находившихся на лечении в отделении реанимации и интенсивной терапии 1586-го Военного клинического госпиталя в 2020–2022 гг. Острое повреждение почек диагностировано у 21 (17,9%) больного (1-я стадия — у 10; 2-я стадия — у 4; 3-я стадия — у 7 больных), у 22 (8,8%) больных зафиксирована дисфункция почек (увеличение суточного креатинина выше нормы, но не достигающей диагностических критериев KDIGO). Четверым больным проводилась заместительная почечная терапия. Установлено, что с возрастом увеличивается вероятность поражения почек (средний возраст больных, страдающих острым повреждением почек, — 65 (58; 71) лет; без острого повреждения почек — 47,5 (41; 55) лет; $p = 0,0001$). Больные, страдающие острым повреждением почек, по сравнению с больными без острого повреждения почек набрали больше баллов по шкалам NEW ($p = 0,000975$); SMRT-CO ($p = 0,011555$); SOFA ($p = 0,000042$). Также среди страдающих острым повреждением почек определялись статистически значимо более выраженные проявления системного воспаления (лейкоциты ($p = 0,047324$), тромбоциты ($p = 0,001230$), ферритин ($p = 0,048614$), D-димер ($p = 0,004496$)). Летальность в общей когорте составила 22,2%, при этом зафиксирована статистически значимая межгрупповая разница по летальности: больные, страдающие острым повреждением почек, — 52,4%, без острого повреждения почек — 15,62% (критерий Хи-квадрат — 13,468; $p < 0,001$). Инвазивная искусственная вентиляция легких проводилась 19,66% больным, статистически значимая межгрупповая разница составила: больные, страдающие острым повреждением почек — 66,7%, больные без острого повреждения почек — 9,38% (критерий Хи-квадрат — 35,810; $p \leq 0,001$). Продолжительность лечения в отделении реанимации и интенсивной терапии у больных, страдающих острым повреждением почек, была больше (9 (7; 14) дней; без острого повреждения почек — 6 (4; 10) дней). После проведенного лечения у всех больных, страдавших острым повреждением почек, к моменту выписки из стационара функция почек восстановилась в полном объеме. В целом острое повреждение почек встречается почти у каждого пятого больного при пневмониях тяжелого и крайне тяжелого течения, ассоциированных с новой коронавирусной инфекцией, утяжеляет состояние больных и увеличивает летальность. Настороженность врачей в отношении острого повреждения почек, ранняя диагностика и своевременное нефропротективное лечение может снижать возможность наступления неблагоприятных исходов заболевания.

Ключевые слова: острое повреждение почек; новая коронавирусная инфекция; пневмония; системное воспаление; инвазивная искусственная вентиляция легких; нефропротективное лечение; неблагоприятный исход заболевания.

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BACKGROUND

The coronavirus disease 2019 (COVID-19) is a novel coronavirus infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a high mortality rate¹. The first cases of SARS-CoV-2 infection were registered at the end of 2019 in the city of Wuhan in China [1]. As of June 10, 2022, more than 532 million cases and approximately 6.3 million deaths from COVID-19 have been reported worldwide according to the World Health Organization². SARS-CoV-2 enters the human body through the epithelium of the upper respiratory tract, stomach, and intestines [2]. Extremely severe COVID-19 is registered in 5% of the patients, severe form in 14%, and mild form in 81% [3]. Approximately 10.2% of patients with severe COVID-19 are transferred to intensive care units (ICUs) for treatment [4].

The main indication for transferring patients to the ICU is an acute respiratory failure (60%–70%) [5]. The need for mechanical ventilation varies and, according to different publications, ranges from 29.3% (China) [6], 59% (UK) [7], to 89.9% (USA) [8]. The mortality rate of patients with severe and extremely severe COVID-19 and receiving therapy in the ICU is high and averages approximately 49% [9]. Li et al. [10] established that 11% of inpatients develop multisystem organ failure (MOF). Acute kidney injury (AKI) in COVID-19 is one of the earliest pathophysiological manifestations of MOF [11]. The mutual influence of impaired lung and kidney functions in COVID-19 forms a mutual burden syndrome (lungs–kidneys).

Cheng et al. [12] revealed an increase in hospital mortality rate from 13.2% to 33.7% when the serum creatinine level increased from 68 ± 16 to 132 ± 39 $\mu\text{mol/L}$. Manifestations of impaired renal function in patients with COVID-19 vary widely from proteinuria and hematuria (44%), isolated hematuria (26.7%) to AKI that require renal replacement therapy (RRT). Richardson et al. [8] studied the treatment outcomes of 5700 patients hospitalized for COVID-19 and found that RRT-requiring AKI occurred in 3.2% of patients in bed departments and 22% of ICU cases.

Yildirim et al. [13] in an observational retrospective study in a cohort of 348 patients verified AKI in 17 (4.9%) patients (according to the criteria of the Kidney Disease: Improving Global Outcomes [KDIGO] initiative [14]), which included 4 (1.3%) patients with stage 1 AKI, 3 (9%) with stage 2, and 10 (76.9%) with stage 3. Similar results were recorded by Chinese researchers (Cheng et al. [12]); AKI was verified in 5.1% of 701 patients hospitalized for

COVID-19. In a retrospective study, Diao et al. [15] revealed the development of AKI in 27.1% of cases (23 of 85 patients hospitalized for COVID-19). The authors also emphasized an increase in the probability of AKI development with age and presence of concomitant pathology. In a meta-analysis, Chen et al. [16] analyzed 20 publications and 6945 patients (China, Italy, UK, and USA) and detected AKI in 8.9% of patients with COVID-19.

The pathophysiological mechanisms for AKI development in COVID-19 are being studied. AKI development in COVID-19 may be based on a combination of prerenal causes because of poor nephron perfusion, decrease in glomerular filtration rate, and renal factors [17]. Upon entry to the human body through the epithelium of the upper respiratory tract, stomach, or intestines, SARS-CoV-2 is transported to the target cell through the cellular angiotensin-converting enzyme 2 receptor (ACE-2). The systemic manifestations of COVID-19 are attributed to the prevalence of ACE-2 in organs (lungs, kidneys, stomach, and intestines) [2, 18]. In the case of immune system failure, the SARS-CoV-2 virus replicates actively through intracellular ACE-2 and destroys the host cell upon entering the extracellular space [19]. Su et al. [20] conducted histopathological studies of the kidneys of 26 patients who died from COVID-19 and found that SARS-CoV-2 affects directly the epithelial cells of the renal tubules and podocytes, thereby causing significant structural damage. Elements of endothelial damage and occlusion of the microvascular bed of the kidneys were also revealed.

The study aimed to examine the clinical and epidemiological aspects of AKI in severe and extremely severe COVID-19 pneumonia.

MATERIALS AND METHODS

This observational prospective study enrolled 117 patients (75 men and 42 women) with severe and extremely severe COVID-19 pneumonia, who were treated in the ICU of Military Clinical Hospital No. 1586 between 2020 and 2022. The inclusion criteria were age 18–80 years and confirmed severe and extremely severe COVID-19 pneumonia. The exclusion criteria were a history of impaired renal function and the presence of oncological diseases.

The study was conducted with the approval of the local ethical committee of the F.P. Haas Moscow Medical and Social Institute and followed the principles of good clinical practice and national standards for the provision of medical care, ensuring the safety and well-being of the study participants who were protected by the ethical principles of the Declaration of Helsinki of the World Medical Association, in compliance with the current legislation of the Russian Federation.

Patients received complex intensive care in accordance with the "Temporary Guidelines: Prevention, Diagnosis, and

¹ United Nations. Naming the coronavirus disease (COVID-19) and the virus that causes it [Electronic resource]. URL: [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it) (accessed: 26.05.2022).

² World Health Organization. WHO Coronavirus (COVID-19) Dashboard [Electronic resource]. URL: <https://covid19.who.int/> (accessed: 12.06.2022).

Treatment of Novel Coronavirus Infection (COVID-19)" that were current at the time of application.

Upon admission to the ICU, to determine the severity of the patient's condition and predict a possible lethal outcome, all patients were evaluated using specialized protocols, namely, a protocol for assessing the severity of the patient's condition using the New Early Warning Score (NEWS) scale [21]; a patient's condition assessment protocol to predict 30-day mortality and the need for intensive respiratory or vasopressor support for community-acquired pneumonia based on the systolic blood pressure, multilobar infiltrate, albumin, respiratory rate, tachycardia, confusion, low oxygen, low pH (SMRT-CO) scale [22]; and a protocol for the dynamic assessment of organ failure based on the Sequential Organ Failure Assessment (SOFA) scale [23].

According to the results of the clinical and laboratory assessment based on the KDIGO criteria (Table 1), all patients were distributed into two groups, where group 1 included 96 patients without COVID-19-associated AKI, and group 2 included 21 patients with COVID-19-associated AKI.

Instrumental and laboratory studies were performed in Military Clinical Hospital No. 1586 in accordance with existing standards and protocols. Clinical and laboratory parameters of patients in dynamics were prospectively traced from the moment of hospitalization in the ICU until hospital discharge.

Data were statistically analyzed using descriptive statistics, followed by the determination of the intergroup difference. SPSS Statistics (IBM Corp., Armonk, NY, USA) was used. The significance of intergroup differences was determined by the nonparametric Mann-Whitney *U*-test. Statistical indicators were described as median (Me), and interquartile range as quartile 1 (Q1) and quartile 3 (Q3). Differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

Using the polymerase chain reaction, SARS-CoV-2 was verified in nasal and oropharyngeal swabs in 79 (67.5%) cases. Antibodies to SARS-CoV-2 in the blood serum were detected in the ratio of 59 (50.4%) positive immunoglobulins (Ig) M and 17 (14.5%) negative IgM, 40 (34.1%) positive IgG, and 28 (23.9%) negative IgG. AKI according to KDIGO criteria was verified in 21 (17.9%) patients (stage 1, $n = 10$; stage 2, $n = 4$ cases; stage 3, $n = 7$ patients). Serum creatinine increased in all cases, whereas the volume of urine in three patients decreased. In 22 (18.8%) patients, the serum

creatinine levels were above the norm, but not reaching the diagnostic criteria of KDIGO, which indicates impaired renal function of varying degrees in 43 (36.8%) cases. RRT was initiated in four patients, whereas sessions of prolonged venovenous hemodiafiltration were performed in all cases.

Patients were admitted to the hospital on day 6 (5; 8) from disease onset and in the ICU on day 10 (8; 12) from disease onset; however, no intergroup difference in the time of admission to the hospital and to the ICU from disease onset was found. The duration of treatment in the ICU was 9 (7; 14) days in patients with COVID-19-associated AKI and 6 (4; 10) in patients without COVID-19-associated AKI. After the treatment, in all patients with COVID-19-associated AKI, by the time of hospital discharge, the kidney function was fully restored.

A total of 26 (22.2%) patients died; 11 (52.4%) of them had AKI and 15 (15.62%) had no AKI (Chi-square test, 13.468; $p \leq 0.001$). The immediate causes of death were an acute respiratory failure in 19 patients, sepsis in 2, and heart failure in 5. Invasive mechanical ventilation of the lungs was performed in 23 (19.66%) patients; 14 (66.7%) of them had AKI and 9 (9.38%) had no AKI (Chi-square test 35.810; $p \leq 0.001$).

Statistically significant intergroup differences were found in the scores on the NEWS ($p = 0.000975$), SMRT-CO ($p = 0.011555$), and SOFA ($p = 0.000042$) scales. This may indicate an aggravation of the patient's condition with AKI development, and an increase in the incidence of AKI with the progression of the inflammatory process in the lungs.

The mean age values of patients with and without COVID-19-associated AKI were 65 (58; 71) and 47.5 (41; 55) years, respectively. Patients with COVID-19-associated AKI were statistically significantly older ($p = 0.0001$). The laboratory parameters of the counts of erythrocytes ($p = 0.019419$), leukocytes ($p = 0.047324$), and platelets ($p = 0.001230$), concentration of urea ($p = 0.000007$), and levels of creatinine ($p = 0.0000$), ferritin ($p = 0.048614$), and D-dimer ($p = 0.004496$) differed statistically significantly. This difference indicates more pronounced systemic inflammation in patients with COVID-19-associated AKI.

A statistically insignificant intergroup difference was noted in C-reactive protein (CRP) ($p = 0.059913$), hemoglobin ($p = 0.116489$), total protein ($p = 0.203566$), and lymphocytes ($p = 0.176277$). The lack of an

Table 1. Stages of AKI according to KDIGO criteria

Таблица 1. Стадии ОПП согласно критериям KDIGO

Stage	Serum creatinine	Urine output
1	1.5–1.9 times higher than baseline or increase by $\geq 26.5 \mu\text{mol/L}$	$< 0.5 \text{ mL/kg/h}$ for 6–12 h
2	2–2.9 times higher than baseline	$< 0.5 \text{ mL/kg/h}$ for $\geq 12 \text{ h}$
3	3 times higher than baseline or increase to $\geq 4 \text{ mg/dL}$ ($\geq 353.6 \mu\text{mol/L}$), or start of renal replacement therapy	$< 0.3 \text{ mL/kg/h}$ for $\geq 24 \text{ h}$ or anuria for $\geq 12 \text{ h}$

intergroup difference in maximum concentrations of the systemic inflammatory marker CRP (173.8 mg/L in patients with COVID-19-associated AKI (63.1; 203.5); 118.1 mg/L (58.65; 166.15) in patients without COVID-19-associated AKI; $p = 0.059913$) can be due to the use of biologically active therapy (actemra and olumiant) in 101 (86.3%) patients and hormonal therapy (metypred, dexamethasone, prednisolone) in 100% of the patients, which was performed both before admission to the ICU and under ICU conditions.

In general terms, all clinical, laboratory, and instrumental parameters of the patients examined are presented in Table 2. A statistically significant relationship was found between the incidence of AKI in COVID-19 and comorbidities,

which may indicate a more severe COVID-19 in patients with AKI. Comorbidities detected in the examined patients are presented in Table 3.

Kidney function was impaired in 43 (36.8%) patients with severe and extremely severe COVID-19 pneumonia, AKI was recorded in 21 (17.9%) of these patients, and the increase in serum creatinine was higher than the norm, but not reaching the KDIGO diagnostic criteria, in 22 (18.3%) patients. The results indicate a significant prevalence of kidney damage in patients with severe and extremely severe COVID-19 pneumonia.

In general, our data are in good agreement with the results of many international researchers. Qian et al. [24] and Wang et al. [25] indicate that according to

Table 2. Clinical, laboratory, and instrumental indicators of the examined patients, *Me* (Q1; Q3)

Таблица 2. Клинические, лабораторные и инструментальные показатели обследуемых больных, *Me* (Q1; Q3)

Indicator	Patients		
	All	Without COVID-19-associated AKI	With COVID-19-associated AKI
Age, years	49 (43; 62)	47.5 (41; 55)*	65 (58; 71)
Men/women, <i>n</i>	75/42	66/30	9/12
Mortality, <i>n</i> (%)	26 (22.2%)	15 (15.62%)	11 (52.4%)
Terms of admission to the hospital from disease onset, days	6 (5; 8)	6 (5; 8)	6.5 (2; 8)
Terms of admission to the ICU from disease onset, days	10 (8; 12)	10 (8; 12)	10 (7; 12)
Duration of treatment in the ICU, days	7 (5; 11)	6 (4; 10)	9 (7; 14)
Duration of hospitalization, days	21 (12; 28)	21 (12; 28)	22 (12; 30)
Severity of patients' condition according to the NEWS scale, score	10 (8; 11)	9 (8; 11)*	12.5 (10; 13)
Severity of patients' condition according to the SMRT-CO scale, score	4 (4; 5)	4 (4; 4)*	5 (4; 6)
Severity of patients' condition according to the SOFA scale, score	3 (2; 5)	3 (2; 4)*	7 (4; 9)
Hemoglobin, g/L	127 (115; 139)	127.5 (116.5; 139.5)	120.5 (83; 132)
Erythrocytes, $10^{12}/L$	4.33 (3.86; 4.65)	4.41 (3.935; 4.685)	4.07 (2.69; 4.34)
Urea, mmol/L	8.55 (6.7; 12.1)	7.7 (6.6; 10.4)*	17.25 (11.6; 20.2)
Creatinine, $\mu\text{mol}/L$	104 (94; 129)	99.5 (94; 104)*	174.5 (156; 309)
CRP, mg/L	134.25 (62; 175.9)	118.1 (58.65; 166.1)	173.8 (63.1; 203.5)
Total protein, g/L	54.7 (51; 59.5)	55 (52; 60)	52 (51; 55)
Ferritin, $\mu\text{g}/L$	560.9 (102; 708.3)	102 (102; 579.5)*	596.35 (102; 711)
Leukocytes, thousand units/ μL	7.05 (5.76; 8.92)	6.65 (5.38; 8.41)*	8.45 (6.95; 10.7)
Lymphocytes, %	3.5 (2; 7)	4 (2; 8)	2.5 (1; 4)
D-dimer, mg/L	2.19 (0.66; 7.67)	1.55 (0.61; 4.53)*	9.995 (2.78; 10)
Platelets, thousand units/ μL	165 (120; 220)	178 (147; 224)*	99 (51; 123)

Note: * differences when compared with patients with COVID-19-associated AKI, $p < 0.05$.

Table 3. Concomitant diseases in the examined patients**Таблица 3.** Сопутствующие заболевания у обследуемых больных

Disease	Patients with COVID-19-associated AKI	Patients without COVID-19-associated AKI	<i>p</i>
Alimentary-constitutional obesity	1	12	0,307
Diabetes mellitus	2	2	0,090
Ischemic heart disease	3	11	0,718
Postinfarction cardiosclerosis of unknown age	1	0	0,032
Arterial hypertension	6	18	0,313
Chronic heart failure	0	7	0,202

various sources, the epidemiological aspects of kidney damage in COVID-19 widely range from 0.5% to 36.6% and depend on the COVID-19 course, direct nephrotropic and nephrotoxic effects of the virus, hypoxia, and shock development. Richardson et al. [8] studied the treatment outcomes of 5700 inpatients with COVID-19 and reported that RRT was performed in 3.2% ($n = 81$) of the cases in hospital bed departments and 22% of ICU cases. In a meta-analysis (54 publications, 30,639 patients), Silver et al. [26] reported that AKI occurred in 28% of their patients with COVID-19, and the cumulative need for RRT was 9%. In the resuscitation cohort, AKI occurred in 46% of the cases, and RRT was performed in 19%. Chan et al. [27] reported that in a cohort of 3993 inpatients with COVID-19, AKI was confirmed in 1835 (46%) patients, of whom RRT was initiated in 347 (18.9%). According to the KDIGO criteria, AKI was distributed as stage 1 in 39% of cases, stage 2 in 19%, and stage 3 in 42%. Moreover, 976 (24%) patients were admitted in the ICU, and AKI was verified in 754 (76%) patients in the ICU. Kanbay et al. [28] indicated that among 100 patients, 81 (81%) patients with COVID-19 who were resuscitated developed AKI (according to KDIGO criteria, stage 1, $n = 44$; stage 2, $n = 10$; stage 3, $n = 27$). Shakked et al. [29] revealed that of 52 patients with COVID-19 seeking medical help in the emergency department, 22 (42.3%) developed AKI, including 8 (36.4%) patients who required RRT.

Pei et al. [30], based on the results of a retrospective single-center study of 467 patients with COVID-19, noted that AKI (according to KDIGO criteria) developed in 4.7% of inpatients with COVID-19. Moreover, 65.8% of patients were diagnosed with proteinuria, and 41.7% had hematuria, which indicates a large proportion of kidney damage in patients with COVID-19. The authors also concluded that patients with COVID-19-associated AKI had a higher mortality rate of 11.2% (28 of 251) than the 1.2% (1 of 82) in patients without COVID-19-associated AKI. Similarly, Chan et al. [27] concluded and revealed that the mortality rates were 50% and 8% among patients with and without COVID-19-associated AKI, respectively.

No statistically significant intergroup difference was found in the treatment duration of patients in the ICU (9 and 6 days in patients with and without COVID-19-associated AKI, respectively). In our opinion, the finding that more patients with COVID-19-associated AKI died than patients without COVID-19-associated AKI (52.4% and 15.62%, respectively) may indicate a more severe COVID-19 in patients with AKI.

Kanbay et al. [28] determined that in a cohort of 770 inpatients with COVID-19, AKI developed in 92 (11.9%). A statistically significant intergroup difference was found in the treatment duration in the ICU; thus, the average duration of inpatient treatment was 16 days in patients with COVID-19-associated AKI and 9.9 days in those without COVID-19-associated AKI ($p < 0.001$). Statistically significant intergroup differences were noted in the ICU admission rate, development of a cytokine storm, and mortality rate (63% vs. 20.7%, $p < 0.001$; 25.9% vs. 14%, $p = 0.009$; and 47.2% vs. 4.7%, $p < 0.001$, among those with and without COVID-19-associated AKI, respectively). This is also evidenced by the statistically significant intergroup difference in the scores on the NEWS, SMRT-CO, and SOFA scales. This may indicate, as mentioned earlier, the aggravation of the patient's condition with AKI development and an increase in AKI incidence with the progression of the inflammatory process in the lungs. Extreme damage to the lungs (acute respiratory distress syndrome) and kidneys (AKI) in severe and extremely severe pneumonia initiate mutual aggravation of acute respiratory and renal failure with impaired water and electrolyte balance (hyperhydration and hyperkalemia), acid-base balance of mixed genesis (respiratory and metabolic), hypoxia of mixed genesis, accumulation of uremic toxins, and additional synthesis of cytokines in cases of invasive lung ventilation was initiated [31].

Our conclusion that the probability of kidney damage in COVID-19 increases with age is fully confirmed by Diao et al. based on the effect of age on the development of COVID-19-associated AKI [15]. The authors showed that the incidence of AKI in different age groups varied, i.e., 65.22% in patients

aged ≥ 60 years and 24.19% in patients aged < 60 years ($p < 0.001$). Fisher et al. [32] made similar conclusions, who confirmed that age > 50 years affects the development of COVID-19-associated AKI. In a total cohort of 3345 patients, AKI developed in 1903 (56.9%) cases. The authors also indicate that an independent risk factor for the development of COVID-19-associated AKI is the male sex and the Negroid race.

Diao et al. [15] draw attention to the statistically significant relationship between the incidence of AKI in COVID-19 and concomitant diseases (69.57% in their presence, 11.29% in their absence, $p < 0.001$), ischemic heart disease (21.74% in its presence; 4.84% in its absence; $p = 0.018$), and hypertension (39.13% in its presence, 2.90% in its absence; $p = 0.0007$). This is also in full agreement with our data (Table 2).

Thus, AKI is registered in almost every fifth patient with severe and extremely severe COVID-19 pneumonia, aggravates the condition of patients, and increases mortality. Physicians' apprehensive attitude to AKI, early diagnostics, and timely nephroprotective treatment may reduce the possibility of adverse outcomes of the disease.

CONCLUSIONS

1. AKI developed in 17.9% of patients with severe and extremely severe COVID-19 pneumonia, and an increase in serum creatinine above the normal level, but not reaching the diagnostic criteria for KDIGO (the serum creatinine level was 1.5–1.9 times higher than the baseline or an increase of

$\geq 26.5 \mu\text{mol/L}$, the volume of urine excreted $< 0.5 \text{ mL/kg/h}$ for 6–12 h) in 36.8% of the patients.

2. The probability of kidney damage in COVID-19 increases with age (mean age of patients with COVID-19-associated AKI is 65 (58; 71) years and those without COVID-19-associated AKI is 47.5 (41; 55) years; $p = 0.0001$).

3. The condition severity according to scores on scales (NEWS, $p = 0.000975$; SMRT-CO, $p = 0.011555$; SOFA, $p = 0.000042$) in patients with severe and extremely severe COVID-19-associated AKI, is statistically significantly higher than those in patients without COVID-19-associated AKI.

4. Among patients with COVID-19-associated AKI, statistically significant ($p < 0.001$) more pronounced manifestations of systemic inflammation are detected (leukocytes, $p = 0.047324$; platelets, $p = 0.001230$; ferritin, $p = 0.048614$; and D-dimer, $p = 0.004496$).

5. The overall mortality rate was 22.2% ($n = 26$), while significantly more ($p < 0.001$) deaths occurred in patients with COVID-19-associated AKI than in those without COVID-19-associated AKI (52.4% and 15.62%, respectively).

6. Invasive mechanical ventilation of lungs was performed in 23 (19.66%) patients; 14 (66.7%) of them had COVID-19-associated AKI and 9 (9.38%) patients had no COVID-19-associated AKI (Chi-square test 35.810; $p \leq 0.001$).

7. The treatment duration in the ICU was 9 (7; 14) days for patients with COVID-19-associated AKI and 6 (4; 10) days for patients without COVID-19-associated AKI. After the treatment, in all patients with COVID-19-associated AKI, by the time of discharge from the hospital, the kidney function was fully restored.)

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