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Kidney damage in COVID-19 patients

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The results of the analysis of case histories of 100 deceased patients (55 women and 45 men), whose cause of death was the syndrome of multiple organ failure due to COVID-19, are presented. The case histories of patients who had no previous renal dysfunction were selected for the analysis. The average age of the patients was 76 years. At the terminal stage of the disease, microhematuria was detected in 27 patients, hypercreatininemia was noted in 17 patients, while the creatinine content in the blood did not exceed 437 μmol / L in any of 100 patients. Oliguria was observed in 9 patients, polyuria – in 43 patients. A possible cause of kidney damage is the damaging effect of SARS-CoV-2 on the proximal convoluted tubules of the nephron. At the same time, in no patient with a severe course of COVID-19, kidney damage did not determine the severity of the condition and was not the cause of death.

Keywords: COVID-19; multiple organ failure; oliguria; polyuria; hypercreatininemia.

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Поражения почек у больных COVID-19

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Приведены результаты анализа историй болезни 100 умерших пациентов (55 женщин и 45 мужчин), причиной смерти которых стал синдром полиорганной недостаточности вследствие коронавирусной инфекции COVID-19. Для анализа были отобраны истории болезни пациентов, ранее не имевших нарушения функции почек. Средний возраст больных составил 76 лет. В терминальной стадии заболевания у 27 пациентов была выявлена микрогематурия, у 17 — отмечена гиперкреатининемия, при этом содержание креатинина в крови ни у одного из 100 пациентов не превышало 437 мкмоль/л. Олигурия отмечена у 9 пациентов, полиурия — у 43 больных. Возможной причиной повреждения почек было поражающее действие коронавируса SARS-CoV-2 на проксимальные извитые канальцы нефрона. При этом ни у одного пациента с тяжелым течением COVID-19 поражение почек не определяло тяжесть состояния и не являлось причиной летального исхода.

Ключевые слова: COVID-19; полиорганная недостаточность; олигурия; полиурия; гиперкреатининемия.

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INTRODUCTION

In December 2019, patients with pneumonia of unknown etiology were identified in the city of Wuhan (China). Within 3 months, outside of China, tens of thousands of people fell ill in 113 countries. In March 2020, the World Health Organization declared a new coronavirus infection (NCI), named Coronavirus Disease 2019 (COVID-19), a pandemic [1, 2]. Such a rapid spread of the infection was due to the high contagiousness and severe disease course. Efforts have been made everywhere to localize the foci of the disease and increase the bed capacity to provide emergency care to patients with NCI [3, 4]. Since the onset of the pandemic, the Ministry of Health of the Russian Federation has issued 12 versions of guidelines for the treatment of NCI. Moreover, all characteristics of the disease course, optimal methods of treatment, and long-term consequences of the infection remain completely unknown, and the effects of the coronavirus on systems and organs, including the kidneys, remain unclear. All this determines the relevance and practical significance of further research of the effects of COVID-19 on the human body.

Severe acute respiratory syndrome coronavirus (SARS-CoV-2) is a new virus related to beta coronaviruses, which are single-stranded RNA viruses [5, 6]. SARS-CoV-2 is highly contagious for humans, with contact and airborne as the main routes of infection. The incubation period lasts from 2 to 14 days [7]. The most common clinical manifestations of NCI are fever (98.6%), fatigue (69.6%), dry cough (59.4%), myalgia (34.8%), shortness of breath (31.2%), nausea, and diarrhea (10.1%) [8]. Mild and moderate courses are noted in 80% of the patients, severe symptoms in 13%–25%, and a life-threatening condition with respiratory and multiple-organ failure, sepsis, and pulmonary embolism in 5.0%–6.1% of the cases. Mortality in NCI is high and varies with different countries, i.e., 7.2% in Italy and 3.8% in China [9, 10].

Damage to kidneys by SARS-CoV-2

SARS-CoV-2 is tropic to many cells in human organs, including angiotensin-converting enzyme 2 (ACE2) receptors. Thus, human ACE2-positive cells are targets of these viruses [11]. Zou et al. [12] revealed up to 4% of ACE2-positive cells in the proximal convoluted tubules of nephrons; thus, the kidneys are at high risk of infection with SARS-CoV-2.

The nephrotoxic effect of coronavirus was already known in 2005 from the publication of Chu et al. [13], who reported the development of acute renal failure (ARF) in a group of patients with coronavirus infection, which led to death in more than 90% of cases. ARF in COVID-19 occurs in 5%–15% of cases. According to Cheng et al. [14], who examined 710 patients with NCI, 44% had proteinuria and hematuria, 26.7% noted only hematuria, and 15.5% had hypercreatininemia. Based on the analysis of the case histories of 200 patients with COVID-19, Zhou et al. [15] noted proteinuria in 59% of the patients, hematuria in 44%, and an increase in the level of creatinine in the blood in 10%. Mortality in patients with ARF was 5.3 times higher than in individuals without ARD, and ARF developed in the late disease stages. Proteinuria, hematuria, and hypercreatininemia are thought to be unfavorable predictors of disease outcomes. The significance of kidney damage in NCI also reflects the fact that in the 12th version of the temporary guidelines "Prevention, diagnostics, and treatment of new coronavirus infection COVID-19" dated September 21, 2021, the renal clinical and morphological masks of COVID-19 are separately allocated. In patients who died from COVID-19, their kidneys demonstrated ischemic changes caused by impaired microcirculation in the medulla, diapedetic hemorrhages in the glomeruli, proliferation of mesangial cells, and thickening of the basement membrane, and granular, hyaline-droplet dystrophy, up to necrosis, and lymphoid infiltration are observed in the tubules [16]. These morphological changes are characteristic of a systemic inflammatory response. Despite close attention to kidney damage in NCI, many questions remain unanswered. Thus, there is no clear answer to the question, is the kidney damage in patients with NCI the result of a primary, direct viral lesion of the kidney, or is it mediated by other factors? Secondary damage can be associated with a "cytokine storm" and other immune disorders, intoxication, hemolysis, oxygen starvation of the nephron due to respiratory failure, vascular and thrombotic disorders, and side effects of drug therapy.

This retrospective study aimed to identify the aspects of renal function impairment in patients with severe NCI.

MATERIALS AND METHODS

A retrospective assessment of the functional and morphological state of the kidneys of patients with confirmed NCI, whose cause of death was intoxication and multiple-organ failure syndrome, was performed. We analyzed the case histories of 100 patients (55 women and 45 men) who died in the period from January 1, 2021, to June 3, 2021. On average, the

patients were 76 years old. Given their serious condition, the majority of the patients (60%) were admitted directly to the intensive care unit, bypassing the emergency department.

In this study, the inclusion criteria were the presence of SARS-CoV-2 infection, confirmed by polymerase chain reaction, intoxication, and multiple-organ failure syndrome as the direct cause of death. The exclusion criteria were severe somatic pathology and its complications that can lead to death without SARS-CoV-2 infection (such as acute myocardial infarction, acute cerebrovascular accident, pancreatitis, and extensive purulent lesions of the skin and fatty tissue), concomitant oncological diseases, pulmonary embolism, and renal dysfunction before SARS-CoV-2 infection. Status assessment of the kidney was based on the analysis of laboratory parameters (creatinine and urea), daily urine output, presence of hematuria, and results of the morphological examination of the kidneys.

RESULTS AND DISCUSSION

In the analysis of 100 case histories, microhematuria was noted in 27 patients following SARS-CoV-2 infection. Microhematuria was transient, and assessment of its source was not possible, especially considering the presence of a urethral catheter and intake of anticoagulants. Hypercreatininemia was noted in 17 patients; the average plasma creatinine level in these patients was 200 ± 24 μmol/L. Moreover, in 83 patients, the blood creatinine level was within the normal range (reference value, 62–115 μmol/l). Interestingly, none of the 100 patients who died from multiple-organ failure had creatinine levels in the blood exceeding 437 μmol/L. This indicates that kidney damage in patients with severe NCI is not considered the leading contributor of the severity of the patient's condition and death. The analysis of laboratory parameters revealed that the level of urea increases faster than that of creatinine. Thus, compared with the reference values, the level of creatinine increased by two times, while that of urea increased by three times or more. A possible reason for this circumstance is that patients with severe NCI showed signs of intoxication, i.e., an increase in urea level is a laboratory sign of intoxication, whereas creatinine is an indicator of total renal function.

Clinical manifestations of ARF in the form of oliguria and subsequent polyuria did not correspond to laboratory parameters. Oliguria was noted only in nine patients, and their decrease in diuresis was accompanied by an increase in the level of creatinine in the blood, which indicates glomerular damage and decreased glomerular filtration. The overwhelming majority of patients entered the intensive care unit in an already serious condition, and the oliguric stage of ARF development could proceed outside the intensive care unit, where daily diuresis was considered. If polyuria is present, we could only state hypercreatininemia. Thus, we suggested that hypercreatininemia was present in the remaining 8 of 17 patients with an increase in creatinine level in the blood. Moreover, the results of this study suggest that it is not possible to determine the exact incidence of ARF if all classical stages of this syndrome had occurred. Altogether, in this study, polyuria was recorded in 43 patients. The question arises about the discrepancy between the number of patients with oliguria and polyuria, since these symptoms are successive stages of ARF. We consider two possible explanations for this phenomenon. First, polyuria arose as a stage of ARF, but we did not observe the oliguric stage, and second, ACE2-positive cells in the proximal convoluted tubules of the nephron, which are targets of SARS-CoV-2, were affected. As a result, water reabsorption was impaired, the volume of excreted urine increased, but an increase in creatinine level was not recorded, since it is filtered by the glomeruli.

Thus, SARS-CoV-2 may directly affect the renal parenchyma in nephrons located in proximal convoluted tubules. In this case, the function of the kidney as an organ of excretion is not substantially affected, and the viral lesion does not cause renal failure. This assumption requires further research, including morphological studies.

Histological examination did not reveal specific signs of kidney damage, which could be attributed to the direct damage to the nephron caused by SARS-CoV-2. All changes were nonspecific and represented parenchymal dystrophy, microcirculation disorder, and cyanotic induration of the kidneys. These changes were noted in all clinical cases and were not specific, especially in older patients.

CONCLUSIONS

In patients without renal failure prior to SARS-CoV-2 infection in cases of severe NCI complicated by multiple-organ failure ARF develops in 17% and is not the leading symptom complex that determines the severity of the patient's condition and disease outcomes. The assumption about the direct damaging effect of SARS-CoV-2 on the proximal convoluted tubules of the nephron requires further study, including morphological analysis. The histological examination of the kidneys revealed no specific signs of direct damage to the renal tissue caused by SARS-CoV-2.

ADDITIONAL INFORMATION

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REFERENCES

1. Kul'chavenja EV, Holtobin DP, Nejmark AI. The working of the urology department during the covid-19 epidemic. *Urology Reports (St. Petersburg).* 2020;10(4):301–307. DOI: 10.17816/uroved52792
2. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 51 Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf
3. Iacobucci G. COVID-19: all non-urgent elective surgery is suspended for at least three months in England. *BMJ*. 2020;368: m1106. DOI: 10.1136/bmj.m1106
4. Naspro R, Da Pozzo LF. Urology in the time of corona. *Nat Rev Urol*. 2020;17:251–253. DOI: 10.1038/s41585-020-0312-1
5. Zumla A, Chan JF, Azhar EI, et al. Coronaviruses – drug discovery and therapeutic options. *Nat Rev Drug Discov*. 2016;15(5):327–347. DOI: 10.1038/nrd.2015.37
6. He F, Deng Y, Li W. Coronavirus Disease 2019: what we know? *J Med Virol.* 2020;92(7):719–725. DOI: 10.1002/jmv.25766
7. Zumla A, Niederman MS. The explosive epidemic outbreak of novel coronavirus disease 2019 (COVID-19) and the persistent threat of respiratory tract infectious diseases to global health security. *Curr Opin Pulm Med.* 2020;26(3):193–196. DOI: 10.1097/MCP.0000000000000676
8. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11)1061–1069. DOI: 10.1001/jama.2020.1585
9. Kupferschmidt K, Cohen J. China's COVID-19 strategy work elsewhere? *Science*. 2020;367(6482):1061–1062. DOI: 10.1126/science.367.6482.1061
10. Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. *JAMA.* 2020;323(14):1335. DOI: 10.1001/jama.2020.4344
11. Lin L, Lu L, Cao W, Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection – a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect.* 2020;9(1):727–732. DOI: 10.1080/22221751.2020.1746199
12. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med.* 2020;14(2):185–192. DOI: 10.1007/s11684-020-0754-0
13. Chu KH, Tsang WK, Tang CS, et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome. *Kidney Int.* 2005;67(2):698–705. DOI: 10.1111/j.1523-1755.2005.67130.x
14. Cheng Y, Luo R, Wang K, et al. Kidney impairment is associated with inhospital death of COVID-19 patients. *Kidney Int.* 2020;97(5):829–838. DOI: 10.1016/j.kint.2020.03.005
15. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054–1062. DOI: 10.1016/S0140-6736(20)30566-3
16. Rybakova MG, Karev VE, Kuznecova IA. Anatomical Pathology of Novel Coronavirus (COVID-19) Infection. First Impressions. *Arkhiv Patologii.* 2020;82(5):5–15. DOI: 10.17116/patol2020820515

СПИСОК ЛИТЕРАТУРЫ

1. Кульчавеня Е.В., Холтобин Д.П., Неймарк А.И. Работа урологического отделения во время эпидемии COVID-19 // Урологические ведомости. 2020. Т. 10, № 4. С. 301–307. DOI: 10.17816/uroved52792
2. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 51. Режим доступа: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf. Дата обращения: 01.10.2021.
3. Iacobucci G. COVID-19: all non-urgent elective surgery is suspended for at least three months in England // BMJ. 2020. Vol. 368. P. m1106. DOI: 10.1136/bmj.m1106
4. Naspro R., Da Pozzo L.F. Urology in the time of corona // Nat Rev Urol. 2020. Vol. 17. P. 251–253. DOI: 10.1038/s41585-020-0312-1
5. Zumla A., Chan J.F., Azhar E.I., et al. Coronaviruses – drug discovery and therapeutic options // Nat Rev Drug Discov. 2016. Vol. 15, No. 5. P. 327–347. DOI: 10.1038/nrd.2015.37
6. He F., Deng Y., Li W. Coronavirus Disease 2019: what we know? // J Med Virol. 2020. Vol. 92, No. 7. P. 719–725. DOI: 10.1002/jmv.25766
7. Zumla A., Niederman M.S. The explosive epidemic outbreak of novel coronavirus disease 2019 (COVID-19) and the persistent threat of respiratory tract infectious diseases to global health security // Curr Opin Pulm Med. 2020. Vol. 26, No. 3. P. 193–196. DOI: 10.1097/MCP.0000000000000676
8. Wang D., Hu B., Hu C., et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China // JAMA 2020. Vol. 323, No. 11. P. 1061–1069. DOI: 10.1001/jama.2020.1585
9. Kupferschmidt K., Cohen J. China's COVID-19 strategy work elsewhere? // Science. 2020. Vol. 367, No. 6482. P. 1061–1062. DOI: 10.1126/science.367.6482.1061
10. Livingston E., Bucher K. Coronavirus disease 2019 (COVID-19) in Italy // JAMA. 2020. Vol. 323, No. 14. P. 1335. DOI: 10.1001/jama.2020.4344
11. Lin L., Lu L., Cao W., Li T. Hypothesis for potential pathogenesis of SARS-CoV-2 infection – a review of immune changes in patients with viral pneumonia // Emerg Microbes Infect. 2020. Vol. 9, No. 1. P. 727–732. DOI: 10.1080/22221751.2020.1746199
12. Zou X., Chen K., Zou J., et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection // Front Med. 2020. Vol. 14, No. 2. P. 185–192. DOI: 10.1007/s11684-020-0754-0
13. Chu K.H., Tsang W.K., Tang C.S., et al. Acute renal impairment in coronavirus-associated severe acute respiratory syndrome // Kidney Int. 2005. Vol. 67, No. 2. P. 698–705. DOI: 10.1111/j.1523-1755.2005.67130.x
14. Cheng Y., Luo R., Wang K., et al. Kidney impairment is associated with inhospital death of COVID-19 patients // Kidney Int. 2020. Vol. 97, No. 5. P. 829–838. DOI: 10.1016/j.kint.2020.03.005
15. Zhou F., Yu T., Du R., et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study // Lancet. 2020. Vol. 395, No. 10229. P. 1054–1062. DOI: 10.1016/S0140-6736(20)30566-3
16. Рыбакова М.Г., Карев В.Е., Кузнецова И.А. Патологическая анатомия новой коронавирусной инфекции COVID-19. Первые впечатления // Архив патологии. 2020. Т. 82, № 5. С. 5–15. DOI: 10.17116/patol2020820515

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