

COVID-19-INDUCED KIDNEY INJURY – ANALYSIS AND PROGNOSIS

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Abstract

There is much data that the kidney may be a vulnerable organ in the cases with SARS-CoV-2 infection. Acute kidney injury (AKI) is the frequent and typical manifestation in COVID-19 associated with high mortality. In most cases the diagnosis AKI is identified by the higher values of the serum creatinine (sCr). A retrospective analysis of 120 positive patients, hospitalized in Military Medical Academy (MMA), Sofia in the period from October to December of 2021, has been conducted. The average age of the patients admitted for treatment with COVID-19 (69 male, 51 female) is 63.4 years, 70% of the patients have had accompanying diseases, 61% have been discharged from the hospital and 39% have died. The laboratory monitoring of the kidney indicators of all admitted patients shows that 34% had increased values of the serum creatinine while 44% had increased values of the blood urea nitrogen (BUN). The data from the urinal analysis show the presence of hematuria in 32% of the cases and proteinuria in 27.5% of the cases. A high frequency in the death cases had an AKI. Older age and comorbidities may aggravate the risk of renal injury in COVID-19 patients. The severe forms of COVID-19, forcing hospitalization, are often accompanied by a kidney dysfunction. AKI is a negative prognosis for survival in the cases of the infected by SARS-CoV-2.

Key words: COVID-19, acute kidney injury, serum creatinine, proteinuria, hematuria

Introduction. Observations show that the discovered at the end of 2019 new coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus) has an incredible potential to strike down every organ directly without

tissue tropism or indirectly with immunomediated inflammation. The kidney tissue is a specific target for SARS-CoV-2. Kidney injuries are frequently observed as well as serious complications in the cases of hospitalized and critically ill patients with COVID-19. The kidney can be affected in three ways by acute kidney injury (AKI), proteinuria and hematuria. According to the meta-analysis the frequency of AKI in the cases of patients hospitalized with COVID-19 may vary from 5.5% in China to 28.6% in the USA [1]. AKI is reported as the most frequent and typical manifestation of COVID-19-associated nephropathy (COVAN) [2]. AKI is associated with a prolonged hospitalization and worse clinical results as well as increased use of health care resources. Among the hospitalized patients for treatment in the intensive care unit (ICU) with COVID-19 76% have been documented to have had AKI. Furthermore, the registered cases of diseased patients who have developed AKI are 54.24%, which is significantly higher than those who have not developed AKI [3].

The pathophysiology of AKI in the cases of COVID-19 is complex and multifactorial, suggesting a biphasic model of kidney injury, in the beginning of the disease or occurring at a later stage. Both early and late forms of AKI were associated with an increased risk of in-hospital mortality [4]. The kidney is being struck down on a level of glomeruli, proximal tubules, and vascular endothelium. The angiotensin-converting enzyme 2 (ACE-2), which is the functional receptor of the virus, has a key role in the infection. ACE-2 mediates the penetration of SARS-CoV-2 in the targeted cells by connecting the S1 subunit of the spike glycoprotein (S). ACE-2 is highly expressed in the proximal tubular cells and podocytes (100 times more compared to the lungs). Furthermore, ACE2 has an expressed biological activity as a component of renin–angiotensin–aldosterone system (RAAS) and works as a key regulator of the cardiac function and the control of blood pressure. SARS-CoV-2 encourages the disbalanced activation of RAAS which gives an unfavourable reflection on the cardiovascular system, conditions violations in the renal hemodynamics and the endothelial dysfunction. Among the discussed mechanisms of the kidney injury is the development of acute ischemic tubular necrosis, cytokine storm, a direct cytopathic effect of SARS-CoV-2 on the kidney parenchyma, collapsing glomerulopathy, prerenal azotemia (intravascular volume deficit), microvascular thrombosis, use of nephrotoxic medications. The induced by the virus cytokine storm, which is a systematic hyperinflammatory aperture with discharge of inflammatory mediators, affects directly or indirectly the kidney function, conditioning the development of hypoxia, shock, and rhabdomyolysis. Interleukin-6 (IL-6) is a key mediator in the immune response, while the participation of the complement boosts the development of endotheliitis, as the inflammatory process includes glomeruli and tubules. The activation of the coagulation system negatively affects the microcirculation. Microthrombi in various organs, including the kidney, in SARS-CoV-2 infection, have been observed. A recently reported series in 26 autopsies of patients with COVID-19 showed

acute tubular injury of varying severity and prominent microvascular obstruction [5]. The development of AKI, in the severe courses of the disease, is the result of the multi-organ failure due to the cytokine storm [6].

Old age, comorbidity, genetic predisposition (APOL1), elevated inflammatory and coagulation biomarkers (CRP, ferritin, D-dimer) have been pointed out among the risk factors for AKI [7]. Reports from China, Italy and USA show that hospitalized patients with COVID-19 are often older and have pre-existing chronic diseases such as hypertension and diabetes mellitus [8]. The high mortality observed in comorbid and elderly patients may be related to a reduction in renal functional reserve. Complications in patients with diabetes and hypertension are more often observed due to the vascular endothelium being primarily damaged. Independent variables for AKI development were the presence of CKD and requirement for ventilator support [9]. Patients with chronic kidney disease (CKD) have suppressed immunity and worsened kidney function. The course of COVID-19 in the cases of CKD conditions a higher risk of fatal outcome [10]. Patients with CKD in advanced stages, chronic kidney failure (CKF), on hemodialysis or needing kidney transplantation, with heavily suppressed immunity and significantly worsened kidney functions are especially vulnerable. Meanwhile, CKF conditions for simultaneously elevated risk of blood clotting and bleeding. Furthermore, excessive positive pressure ventilation administered to patients with COVID-19 potentially leads to adverse hemodynamic effects of decreased cardiac output, which amplifies renal hypoperfusion [11]. The development of AKI is accompanied by an increase of the nitrogen fractions (serum creatinine, urea nitrogen) and oligoanuria, requiring kidney-replacement therapy. Active kidney function monitoring is recommended with the idea of early discovery of kidney injury. Creatinine is excreted through the kidneys in quantities proportional to the serum content. Some authors define the development of AKI based on the discovery of increased values of the serum creatinine [12]. Renal function is usually evaluated by measuring the serum creatinine level. Creatinine is a more reliable indicator of renal function than BUN because it is less influenced by other factors. Research shows that patients with increased values of the baseline sCr are frequently admitted in ICU which suggests that the kidney affection at the beginning of the disease directs towards clinical deterioration [13]. COVID-19 associated nephritis is described in the cases of critically ill patients who need intensive care. The proteinuria and hematuria are frequently observed findings, which is why a urinal analysis is recommended [14]. The present epidemiological data confirms that AKI is among the factors that have important prognostic meanings. The recovery of the kidney function is observed in almost half of the patients who have survived AKI while the fast counter development of AKI is related to a better prognosis. The reason for the continuous kidney dysfunctions in the cases with COVID-19 is unknown. It is considered possible, similarly to the development of pulmonary fibrosis, that the occurrence of tubulointerstitial fibrosis conditions the progression of AKI to CKD.

Materials and methods. Patients and samples. This research, with descriptive design, presents the results of 120 patients (69 male, 51 female), with an average age of 63.4 years, hospitalized in MMA-Sofia in the period from October 1 to December 31, 2021, with laboratory confirmed diagnosis COVID-19. All patients with a positive PCR test for SARS-CoV-2 have had their main kidney functions (serum creatinine, urea, urinalysis) dynamically tracked. In this research, the levels of serum creatinine and urea nitrogen, were described and renal dysfunction was evaluated among COVID-19 patients between the period of admission and discharge, or the death exit. Suitable for research clinical samples (respiratory and serum) have been taken and analyzed complying with the rules for good laboratory practice and according to the established standard operating procedures. An evaluation of the age, premorbid and laboratory profile of the hospitalized patients with COVID-19 has been made, as the frequency of kidney injury and the in-hospital mortality have been established.

Results. For the chosen period for the research in MMA-Sofia 120 patients, with an average age of 63.4 years (age range from 22 to 94 years), with COVID-19 have been hospitalized. The male part of the patients hospitalized is higher than that of the female, 57.5% for the male compared to 42.5% for the female. The analysis of the electronic medical records of the patients shows that 70% of them had accompanying diseases (57% hypertension, 29% diabetes mellitus, 11% chronic renal failure, 11% oncological disease, 4% autoimmune disease, 4% chronic lung disease, 3% obesity). Regarding the prognosis 61% of the patients with COVID-19 have been discharged from the hospital and 39% have died (Table 1). The average length of hospital stay for deceased patients was 10 days (2–24 days). The average age of the patients with severe clinical course of COVID-19 and fatal ending is 72.4 years of age while those who have been discharged from the hospital have an average age of 58.2 years. Most of the patients who have died had documented acute kidney injury and one or more accompanying diseases.

Deviations in the laboratory indicators of the kidney functions – elevated serum creatinine ($\mu\text{mol/l}$), elevated urea nitrogen (mmol/l), proteinuria and hematuria have been discovered among the hospitalized patients with COVID-19. The

T a b l e 1
Hospitalized COVID-19 patients – general data

COVID-19 patients	<i>n</i> (%) / average	Men / average	Women / average
Overall hospitalized patients	120 – 63.4 y	69 (57.5%) – 61.6 y	51 (42.5%) – 67.8 y
Discharged patients	73 (61%) – 58.2 y	43 (62%) – 55.4 y	30 (59%) – 61 y
Patients who died	47 (39%) – 72.4 y	26 (37.6%) – 67.7 y	21 (41%) – 74.7 y
Comorbidities	84 (70%)	47 (68%)	37 (73%)
Without comorbidities	36 (30%)	22 (32%)	14 (27%)

T a b l e 2

Laboratory indicators of the kidney function in the cases of hospitalized patients with COVID-19

Laboratory indicators of renal function	Hospitalized patients = n (%)	Discharged patients	Patients who died
Elevated sCr ($\mu\text{mol/l}$)	41 (34%)	1	40
Elevated BUN (mmol/l)	53 (44%)	10	43
Hematuria	38 (32%)	–	38
Proteinuria	33 (27.5 %)	–	33

* serum creatinine (sCr) – reference values: male (74–130 $\mu\text{mol/l}$), female (58–100 $\mu\text{mol/l}$)

* blood urea nitrogen (BUN) – reference values: 2.8–8.3 mmol/l

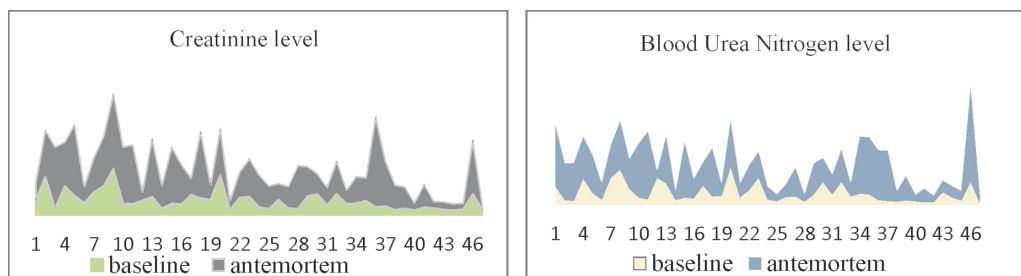


Fig. 1. Dynamics of laboratory parameters creatitnie and blood urea nitrogen

highest registered baseline values of serum creatinine are up to 514 $\mu\text{mol/l}$ and those of urea nitrogen up to 47 mmol/l . During the hospitalization of the patients, the dynamic monitoring of those crucial indicators of the kidney function showed that maximum value of the serum creatinine was 972 $\mu\text{mol/l}$ and of the urea nitrogen 111.2 mmol/l . The increase of the serum creatinine (40/47) and the urea nitrogen (43/47) in the cases of the patients with fatal ending of the disease is significantly higher (Fig. 1). The urinal analysis shows that 32% have had hematuria and 27.5% have had proteinuria (Table 2).

Discussion. The data from different countries present a varying frequency of acute kidney injury among the hospitalized patients with COVID-19. The results from a large scale research conducted by the Imperial College London shows that among the patients with COVID-19 in the ICU in the period from March to July of 2020 those who had pre-existing CKD or have developed AKI in hospitals have had higher hospital mortality [10]. The authors have tracked the clinical outcome in the cases of 372 patients with an average age of 59 years from which 58% have had kidney disorders. Of those 372 patients 45% have developed AKI during their hospitalization, 13% have medical history with kidney diseases, and 37% have passed away. The focused observations of the clinical-laboratory presentation of COVID-19 point towards the presence of significantly increased

values of the serum creatinine and connected to AKI hospital mortality of patients with COVID-19. A large prospective study covering 701 Chinese patients with COVID-19 establishes increased values of the creatinine and urea nitrogen already at the admittance in the hospital in 14.4% of the cases and 13.1% of the cases [13]. Proteinuria and hematuria may be reported in about 40% of patients with COVID-19 at hospital admission [15]. Urinalysis can detect the early renal impairment in patients with COVID-19 [16]. AKI is a marker for the severity of the illness and a negative prognostic factor for survivability in the cases of hospitalized patients with COVID-19. Many reports have highlighted age-related and chronic comorbidities differences in health outcomes. In accordance with the results from other research we have established a higher risk of fatal ending of the disease with older age, presence of accompanying diseases, and acute kidney injury which has occurred. The increased values of the serum creatinine and urea nitrogen as well as the presence of proteinuria and hematuria point to a renal infection. The increase of the serum creatinine (40/47) and the urea nitrogen (43/47) in the cases of the patients with fatal ending of the disease is significantly higher compared to that of those who have been discharged from the hospital (1/73 и 10/73). On admission to the hospital, of the group of deceased patients, 15 had normal creatinine values and 17 had normal blood urea nitrogen values. They developed AKI in the course of the disease during the hospital stay. The registered hospital mortality in the cases of patients hospitalized with COVID-19 is 39%. Age is an independent risk factor for severe course of illness or fatal ending. The deceased patients are older (average age of 72.4 years) while the discharged from the hospital are mainly in active age (average age of 58.2 years). Regarding the presence of accompanying diseases, the difference between the group of the deceased (46/47) and the discharged from the hospital (35/73) is significant. Most patients who have died from the disease have had acute kidney injury, some of them also had underlying chronic kidney disease – 13%, unlike the patients discharged from the hospital. The identification of potential risk factors causing unfavourable clinical outcomes in the case of positive for COVID-19 patients is significant for the survivability. The kidney is a vulnerable organ in case of infection with SARS-CoV-2 which causes the necessity for active monitoring of the liver function and adequate treatment being conducted. The involvement of the kidney in the inflammatory process worsens the course and prognosis of COVID-19.

Conclusion. The prevalence of acute kidney injury in severely and critically ill patients with COVID-19 is common and is considered an independent risk factor for increased mortality. In-hospital mortality is directly related to advanced age and the chronic comorbidities of the patient. Kidney involvement in hospitalized COVID-19 patients has been associated with an unfavourable outcome.

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