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RESEARCH ARTICLE

Manifestations of kidney involvement in COVID-19 patients and progression to chronic kidney disease

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ABSTRACT

Introduction. COVID-19 was initially considered a predominantly respiratory infection, with mortality associated with progression of respiratory failure, but currently is recognized as a multisystem disease with a wide range of manifestations. One of the most common complications of COVID-19 is acute kidney injury (AKI), which predominantly evolved to chronic kidney disease (CKD). The objective of the study was to investigate the types of acute kidney injury and their prognostic value in hospitalized patients with COVID-19 with evolution to chronic kidney disease.

Material and methods. The study utilized a comprehensive database of patients admitted to general department of COVID-19 at *Timofei Moşneaga* Republican Clinical Hospital from 2020 to 2022 years (in total 1000 patients). The first part of the study was a retrospective study, focusing on patients with confirmed COVID-19 and lung injury was diagnosed by computer tomography. The second part was a prospective study assessing the prognostic value of inflammatory markers, renal functional status and kidney injury.

Results. AKI occurs in 29.6% of patients with COVID-19. The risk of AKI and CKD is higher in patients with more comorbidities, a more severe course of disease, elevated levels of ASAT/ALAT > 1.6 and hematuria at admission, which significantly increases the risk of progression to CKD. Patients with a history of CKD, and who had ASAT > 40 U/L, ASAT/ALAT > 1.6 and hematuria, experience the onset of AKI before hospitalization. Independent negative predictors of hospital-developed AKI include hypertension, Charlson Comorbidity Index > 4 points, respiratory failure, ASAT/ALAT > 1.6, D-dimers > 250 ng/ml, and hematuria. Hospital mortality in patients with COVID-19 was 20.8%, compared to 8.5% in patients without AKI, and this rate increased to 50% when AKI developed ($p < 0.001$).

Conclusions. Patients who developed AKI during admission had a higher incidence of negative outcomes compared to those with AKI prior to admission. Independent predictors of in-hospital mortality in COVID-19 patients were increased serum CRP. Death in hospitalized patients with COVID-19 and AKI was independently associated with factors such as age > 75 years, history of CKD, admission to Intensive Care Unit, leukocytosis, and ASAT/ALAT > 1.6.

Keywords: chronic kidney disease, acute kidney injury, COVID-19.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Data on the prevalence of acute kidney injury and chronic kidney disease in COVID-19 patients are contradictory and vary widely (from 0.5% to 80.3%) depending on the severity of disease progression and a lot of different factors which remains unknown till now.

The research hypothesis

Clinical evolution of COVID-19 showed a presence of kidney malfunction, therefor it is important to determine evolution and types

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of acute kidney injury and their prognostic value in hospitalized patients with SARS-CoV2 infection with progression to chronic kidney disease.

The novelty added by the manuscript to the already published scientific literature

The article defines that patients who experienced AKI during the acute phase of COVID-19 are at more than 2.5-fold increased risk of death and *de novo* formation or progression of CKD or within 180 days of discharge.

Introduction

Following an increased incidence of respiratory infections that caused respiratory failure in Wuhan, Hubei province, China, in December 2019, researchers identified a new coronavirus, later named by the World Health Organization (WHO) "severe acute respiratory syndrome caused by coronavirus type 2" (SARS-CoV-2). On March 11, 2020, the spread of the virus was declared a pandemic by the WHO. Despite all the progress in diagnosis and treatment as well as active anti-epidemiological measures, the pandemic with a novel coronavirus (COVID-19) has been one of the most urgent public health problems.

COVID-19 was initially considered a predominantly respiratory infection, with mortality associated with the progression of respiratory failure [1, 2]. Currently, COVID-19 is recognized as a multisystem disease with a wide range of manifestations [1-3]. One of the most common complications of COVID-19 is acute kidney injury (AKI). The frequency of AKI, according to different authors, varies greatly and requires further study, including the number of those who required renal replacement therapies also differs [4]. These epidemiological data are necessary for healthcare planning because renal replacement treatment increases patient care costs [5, 6].

The current data on the prevalence of various AKI phenotypes in COVID-19, along with clinical features and the prognostic significance of changes in urinary sediment, proteinuria, and markers of kidney damage in COVID-19 patients are limited. Retrospective studies report that most patients with AKI were already experiencing impaired kidney function upon hospitalization [2, 4, 7]. However, as for now, the prognostic implications and predictors for the development of different AKI phenotypes remain undefined. The study of the predictive role of changes in urinary sediment, proteinuria and biomarkers in the development of acute renal injury and mortality in real clinical practice may become the basis for developing an improved algorithm for managing patients with COVID-19: stratification of patients at risk of developing AKI, identification of high-risk groups requiring frequent monitoring of clinical and laboratory parameters, and adjusting drug treatments.

AKI is a demonstrated risk factor for a poor prognosis in COVID-19 patients [1, 6, 8]. The data from clinical studies confirm the increased risk of hospital mortality in patients with AKI, which underlines the undoubted relevance of the problem. Despite the large number of publications, the prognostic role of AKI among mortality predictors is not completely elucidated.

The consequences of acute kidney injury, incurred in the acute phase of COVID-19, are less studied. The potential impact of AKI on the risk of re-hospitalization, death, and the development or progression of chronic kidney disease (CKD) after discharge from hospital is less well known. The high prevalence of COVID-19 and associated AKI highlights the need to study long-term and renal outcomes for prognosis and patient care planning.

Data on the prevalence of AKI in COVID-19 patients are contradictory and vary widely (from 0.5% to 80.3%) depending on the severity of disease progression [7, 9, 10]. It has previously been established that AKI is a predictor of poor prognosis in hospitalized patients with COVID-19 [6, 9, 11]. The high prevalence of AKI in the severe COVID-19 group [1, 3, 12] and the increased mortality risk in patients with AKI [4, 13, 14] highlight the need to further explore predictors of kidney damage in this population. Additionally, most studies have investigated the prognosis without considering the timing of kidney failure onset. The purpose of the study is to investigate the types of acute kidney injury and their prognostic value in hospitalized COVID-19 patients who evolve to chronic kidney disease.

Material and methods

The study utilized a comprehensive database of patients admitted to general department of COVID-19 at *Timofei Moşneaga* Republican Clinical Hospital since 2020 to 2022 years, and included 1000 patients. The study consists of two parts. The first part was a retrospective study, which included hospitalized adult patients with confirmed COVID-19 and lung injury according to computer tomography (CT) scan of the chest (favorable opinion of the Research Ethics Committee, minutes №6 from 18.05.2023). Clinical and demographic characteristics of patients are presented in Table 1. The exclusion criteria were: repeated hospitalization, hospitalization less than 48 hours, acute surgical pathology, transfer to another hospital, single measurement of serum creatinine during hospitalization.

Table 1. Clinical and demographic characteristics of patients (n = 1000).

Parameter	Result
Men, (%)	49.2%
Age, years, Me (IQR)	68 (54; 79)
BMI, kg/m^2, M±SD in 828 patients	30±5
Obesity, n (%)	400 (48)
Overweight, n (%)	284 (33)
DM, n (%)	261 (26)
Of them, DM type 2, n (%)	255 (98)
HTA, n (%)	711 (71.1)
From them controlled HTA, n (%)	594 (83)
Anamnesis oncology, n (%)	97 (10)
Of them, relapse at the time of hospitalization, n (%)	46 (47)
Atrial fibrillation, n (%)	153 (15.3)
CKD, n (%)	137 (13.7)
Ischemic heart disease, n (%)	171 (17.1)
Chronic obstructive pulmonary disease, n (%)	67 (6.7)
Cirrhosis, n (%)	12 (1.2)
Charlson Comorbidity Index, CCI, Me (IQR)	3 (2; 5)

***Note**: IQR – interquartile range; Me – median; BMI – body mass index; HTA* – arterial hypertension; CKD – chronic kidney disease; *CCI – Charlson Comorbidity Index; DM – diabetes mellitu*s.

The second part of the paper is a prospective study of the prognostic value of inflammatory markers (CRP), renal function test (serum creatinine) and kidney injury (hematuria, proteinuria) in the development of AKI and hospital mortality, general and renal outcomes in patients who developed AKI in the acute phase of COVID-19.

In all patients, admission physical examination data (saturation O_2 (SpO_2), blood pressure and heart rate) and data on home treatment and therapeutic interventions received during hospitalization were evaluated.

In all patients, a complete blood count was performed (with erythrocyte count, hemoglobin, leukocytes, lymphocytes, platelets), a biochemical analysis of blood with determination of the level of CRP, parameters of renal function (creatinine, electrolytes, GFR estimation using CKD-EPI from 2012), liver function tests (ALAT, ASAT, total bilirubin, albumin), in some patients procalcitonin, lactate dehydrogenase (LDH), ferritin, uric acid, coagulation profile with determination of the level of D-dimer and fibrinogen and urinalysis. Data from laboratory examinations of patients are presented in Table 2. All laboratory parameters were investigated in a local laboratory. Proteinuria was defined as the presence of more than 0.3 g/l of protein in urine. Hematuria was defined as the presence of more than three erythrocytes in the high-power field, leukocyturia - more than four leukocytes in the high-power field.

Assessment of kidney function. Changes in serum creatinine levels according to KDIGO 2012 criteria were used to detect and evaluate the severity of acute kidney injury. Baseline serum creatinine was defined as the lowest serum creatinine value at the time of admission or, if available, the last serum creatinine value within 6 months prior to hospitalization. 2 phenotypes of AKI have been defined – out-of-hospital and hospital acute kidney injury. Patients who were admittedwith AKI or those who developed AKI within the first 48 hours were considered to have out-of-hospital AKI. Hospital AKI was defined as any recorded AKI after 48 hours in hospital. Recovery of baseline renal function was considered positive dynamics of serum creatinine (± 2.5% of normal or baseline) until the end of hospitalization (discharge or death). Transient AKI was considered when AKI resolved within 48 hours, and persistent AKI was considered when it resolved between 48 hours and seven days after onset. Acute kidney injury was defined as an acute malfunction that had not resolved within seven days. A tendency to recover initial renal function was defined as a decrease in serum creatinine by 25% of its maximum value.

Table 2. Laboratory data of COVID-19 patients at admission (n = 1000)

Parameter	Result
Serum creatinine, µmol/L, Me (IQR)	91 (78; 115)
GFR CKD-EPI, ml/min, Me (IQR)	65 (48; 82)
Sodium, mmol/L, Me (IQR)	138 (135; 141)
Potassium, mmol/L, Me (IQR)	4.13 (3.76; 4.57)
CRP, mg/L, Me (IQR)	73 (29; 125)
ASAT, U/L, Me (IQR)	34 (25; 51)
ALAT, U/L, Me (IQR)	24 (16; 41)
ASAT/ALAT, Me (IQR)	1.38 (1,03; 1,86)
Total bilirubin, mmol/L, Me (IQR)	10.2 (7.5; 14)
Serum albumin, g/L, Me (IQR)	34 (30.8; 37)
WBC, 10^9, Me (IQR)	6.1 (4.5; 8.3)
Lymphocytes, 10^9, Me (IQR)	1 (0.7; 1.4)
Hemoglobin, g/L, Me (IQR)	130 (118; 143)
Platelets, 10^9, Me (IQR)	194 (152; 255)
D-Dimers, ng/ml, Me (IQR), available in 814 patients	311 (164; 597)
Hematuria, n (%)	144 (15.5)
Leukocyturia, n (%)	212 (22.8)
Proteinuria, n (%)	279 (30)

***Note**: IQR – interquartile range; Me – median; GFR CKD-EPI – Equations for Glomerular Filtration Rate; WBC* – white blood cell; CRP – C-reactive protein; *ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase.*

Assessment of the degree of lung injury by CT of the chest. The degree of lung injury was estimated by CT of the chest: CT-1 lesion from 1 to 25% of the lungs, CT-2 – 26-50%, CT-3 – 51-75% and CT-4 more than 75% of the volume of lung lesion.

Assessment of long-term results. Overall long-term outcomes (death from any cause within 180 days, readmission to hospital within 30 days) were assessed by telephone contact and data were available for 691 (87%) of discharged patients.

Long-term renal outcomes were assessed by analyzing data on mean serum creatinine within 180 days of discharge, which were available in 446 (56%) of discharged patients. The progression of CKD was considered as a change from baseline to more severe in line with current recommendations [2-4].

Statistical analysis of study results. The statistical processing of the obtained data was performed with the help of StatSoft STATISTICA 9.0 application software packages. Distribution verification was performed using

the Shapiro-Wilk W-criterion criterion. The quantitative variables were described as M and SD (for the normal distribution) or as Me and IQR (for the asymmetric distribution). The significance of differences between two groups in quantitative variables was assessed using the Mann–Whitney U criterion. Qualitative variables were represented by absolute (n) and relative (%) values. All variables for which significance of differences between groups was demonstrated were included in multivariate regression analysis, where 95% OR and CI were determined using logistic regression. The thresholds for quantitative predictors were established based on the correlation of marginal probabilities with the selected limit score. Multinomial logistic regression was performed to examine potential predictors of out- and out-of-hospital AKI. Mortality predictors were assessed using multivariate Cox regression and 95% OR and CI were calculated.

Results

Study of prevalence, severity, phenotypes, risk factors and predictors of AKI. In hospitalized patients with COVID-19 and lung injury, AKI was determined in 296 (29.6%) cases. 56% had stage I of AKI, 26% stage II and 18% stage III according to KDIGO 2012 criteria. 61% (n = 182) of patients with kidney dysfunction were admitted to hospital with impaired renal function or developed it within 48 hours of admission. 36% had transient kidney dysfunction and 29% had persistent kidney dysfunction. It was found that 55.7% of kidney dysfunction patients did not recover their initial kidney function by the end of hospitalization. Less than 20% of patients, whose renal function was compromised during admission and did not tend to restore serum creatinine, tended to recover renal function at discharge.

As a result of the study of risk factors for AKI, patients who developed AKI, as opposed to patients without AKI, were found to be older (74 (54; 82) vs 63 (52; 73) years, respectively, p < 0.0001), had more frequent comorbidities: HTA (86% vs 65%, p < 0.001), DM (33% vs 23%, p = 0.001), cardiovascular disease (CVD) (26% vs 14%, p < 0.001), CKD (23% vs 9%, p < 0.001), history of oncological diseases (17% vs 7%, p < 0.001) and Charlson Comorbidity Index, CCI higher (5 (3; 6) vs 3 (1; 4), scores, p < 0.0001), more frequently administered renin-angiotensin-aldosterone system inhibitors (41 % vs 32 %, p = 0.02), loop diuretics (10 % vs 4 %, p < 0.001), statins (14 % vs 10 %, p = 0.006). Inpatient respiratory failure (56% vs 39%, p < 0.001), more severe maximal lung injury were also more frequently observed among patients with AKI (CT-3 39% vs 27%, p < 0.001; CT-4 11 % vs 3.6 %, p < 0.001). Laboratory data of patients with and without AKI are presented in Table 3.

According to multivariate regression analysis, independent predictors of AKI occurrence were DM (OR 1.79, 95% CI 1.13-2.83), HTA (OR 1.98, 95% CI 1.08-3.63), oncology history (OR 2.56, 95% CI 1.27-5.14), Charlson index > 4 points (OR 2.05, 95% CI 1.12-3.74), respiratory failure (OR 2.05, 95% CI 1.34-3.13), lymphopenia (OR 1.65, 95% CI 1.04-2.60), ASAT/ALAT>1.6 (OR 1.88, 95 % CI 1.22-2.89) and hematuria (OR 2.17, 95 % CI 1.24-3.81) on admission.

Table 3. Laboratory data at admission by presence of AKI

Parameter	Without AKI (n = 704)	With AKI (n = 296)	p
Leukocytes in blood, 10^9, Me (IQR)	5.9 (4.5; 7.8)	7 (4.9; 9.8)	<0.0001
Lymphocytes, 10^9, Me (IQR)	1.1 (0.8; 1.4)	0.8 (0.6; 1.2)	<0.0001
Hemoglobin, g/l, Me (IQR)	132 (121; 144)	125 (111; 140)	<0.0001
Platelets, 10^9, Me (IQR)	196 (154; 259)	190 (142; 241)	0.02
Serum creatinine, µmol/L	86 (74; 101)	126 (95; 166)	<0,0001
Potassium, mmol/L	4.12 (3.8; 4.5)	4,2 (3.7; 4.7)	0.3
CRP, mg/L	64 (23; 112)	101 (54; 157)	<0.0001
ASAT, U/L	33 (24; 47)	38 (26; 55)	0.002
ASAT/ALAT	1.29 (0.98; 1.72)	1.64 (1.24; 2.27)	<0.0001
Total bilirubin, µmol/L	10 (7.3; 13)	11 (7.8; 15)	0.04
Albumin, g/L	35 (32; 38)	32 (28; 36)	<0.0001
LDH, U/L*	325 (248; 451)	442 (306; 603)	<0.0001
Ferritin, ng/ml**	459 (209; 657)	604 (389; 703)	0.002
D-Dimers, ng/ml#	262 (144; 477)	480 (250; 1016)	<0.0001
Hematuria, n (%)	68 (10)	76 (26)	<0.001
Leukocyturia, n (%)	126 (18)	86 (29)	<0,001
Proteinuria, n (%)	171 (24)	108 (36)	<0.001

***Note**: IQR – interquartile range; Me – median;* CRP – C-reactive protein; *ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase, LDH – lactate dehydrogenase; * - available to 378 patients; ** - available to 340 patients; # - available in 814 patients.*

Comparative analysis of clinical characteristics and prognosis of in hospital and out-of-hospital AKI. After comparative analysis of demographic parameters, no significant differences between groups were identified in terms of gender, obesity frequency, diabetes, HTA, atrial fibrillation, CVD and oncological history. Patients with hospital-acquired AKI were older (78 (67; 83) vs 72 (62; 80), years, p = 0.002), although belonging to the same age group, had a higher Charlson index (5 (4; 6) vs 4 (3; 6), scores, p = 0.02). When comparing anamnestic renal function data, there were no differences in the incidence of CKD and mean serum creatinine prior to hospitalization. No significant differences were found when analyzing differences between groups in pre-admission treatment. When comparing clinical data at admission, no statistically significant differences were found in the incidence of respiratory failure and hemodynamic disorders. When studying differences in laboratory data at admission, patients with AKI that occurred out-of-hospital and those that developed AKI during hospitalization, showed no differences in frequency of changes in blood count, levels of inflammatory markers, liver dysfunction and clotting disorders, frequency of changes in urine summary examination. Maximum laboratory mean values during for in-hospital and out-of-hospital AKI are presented in Table 4.

Table 4. Maximum laboratory average values during hospitalization for in- and out-of-hospital AKI.

Parameter, Me (IQR)	Out-of-hospital AKI (n = 182)	Hospital AKI (n = 114)	p
Leukocytes > $10x10^9$, n (%)	99 (54)	86 (75)	<0.001
Lymphocytes min, 10^9	0.6 (0.4; 0.9)	0.4 (0.3; 0.7)	0.0002
Lymphocytes < $1,2x10^9$, n (%)	157 (86)	108 (95)	0.02
Creatinine max, μmol/L	163 (130; 245)	198 (128; 294)	0.1
Potassium max, mmol/L	5 (4.4; 5.8)	5.1 (4.42; 5,9)	0.4
CRP max, mg/L	151 (96; 234)	206 (146; 270)	0.002
ASAT max, U/L	53 (33; 94)	62 (42; 120)	0.04
Total bilirubin max > 21 μmol/L, n (%)	39 (21)	40 (35)	0.01
D-Dimers max, ng/ml	1317 (417; 3396)	2079 (780; 5150)	0.009

***Note**: AKI – acute kidney injury; IQR – interquartile range; Me – median;* CRP – C-reactive protein; *ASAT – aspartate aminotransferase; min – minimum values during hospitalization; max – maximum values during hospitalization*

Maximum lung involvement (8% vs. 7%, p < 0.05) and progression of lung injury volume (39% vs. 26%, p = 0.03) were observed more frequently in patients with hospital AKI compared to developed AKI until hospitalization. Patients who developed AKI during hospitalization were more likely to experience transfer to the intensive care unit (59% and 41%, p < 0.05), initiation of artificial pulmonary ventilation (49% and 33%, p < 0.05), and hospital mortality (73% and 36%, p < 0.001) than those who had acute kidney injury to hospitalization.

Estimation of prognostic value of inflammatory markers, renal functional status and kidney injury for AKI occurrence and death during hospitalization. The incidence of AKI within the group was 24%, 56% had stage I, 25% stage II and 19% stage III. Patients with AKI compared to the group without AKI were found to have higher serum CRP (114 (66; 194) vs 68 (35; 105), mg/L, p = 0.01), serum creatinine (143 (107; 173) vs 85 (76, 100), μmol/L, p < 0.0001), erythrocytes in urine (3.5 (0; 10) vs 0 (0; 1), p = 0.04) and protein in urine (0.3 (0.2; 0.5) vs 0 (0; 0,15), g/L, p = 0,0003). After regression analysis using 7 separate models, proteinuria (p = 0.02), CRP (p = 0.03) and serum creatinine (p = 0.001) showed significant associations with AKI, whereas hematuria was not statistically significant.

After comparing groups of surviving vs. deceased patients, deceased patients had higher levels of proteinuria at admission (0.2 (0.15; 0.5) vs 0.12 (0; 0.25), g/L, p = 0.03) and serum creatinine (136 (86; 167) vs 86 (79; 107), μmol/L, p = 0.05) and CRP (147 (99; 149) vs 65 (35; 105), mg/L, p = 0.0009). After performing regression analysis using 5 separate models for each predictor, CRP and serum creatinine showed significant associations with mortality, whereas proteinuria was not statistically significant. The optimal limit values for the above biomarkers for predicting hospital mortality were determined based on the correlation of marginal probabilities with the selected cut-off score.

Analysis of short-term outcomes and mortality predictors in hospitalized patients with COVID-19. The median duration of hospitalization was 11 (9; 15) days. 248 (24.8%) patients were in intensive care for at least one day, 136 (13.6%) patients underwent invasive ventilatory support, 89 (8.9%) – required vasopressor support. Thromboembolic complications occurred in 6% of patients. Renal replacement therapy was performed in 10 (1%) patients. 208 (20.8%) patients died in hospital. Mortality was higher in intensive care compared to the general profile ward (56 % vs. 9 %, p < 0.001). Mortality was significantly higher in the acute kidney injury group (50% vs 8.5%, p < 0.001).

Patients who died in hospital were found to be older (79 (67; 85) vs 64 (52; 73), years, p < 0.0001), more frequently had comorbidities, were admitted with respiratory failure (58% vs 41%, p < 0.001), were admitted to intensive care (67% vs 14%, p < 0.001) and had AKI (71% vs 19%, p < 0.001). It was established that during hospitalization, patients who died had higher leukocytosis (80% vs 23%, p < 0.001), lymphopenia (96% vs 69%, p < 0.001), hemoglobin below 120 g/l (41% vs 24%, p < 0.001) compared to survivors, platelets below $150x10^9$ (48% vs 28%, p < 0.001), hypoalbuminemia (97% vs 66%, p < 0.001), hematuria (27 % vs 11 %, p < 0.001), leukocyturia (33 % vs 18 %, p < 0.001) and proteinuria (37 % vs 26 %, p < 0.001), had higher CRP levels (210 (146; 285) vs 97 (50; 151), mg/L, p < 0.0001), serum creatinine (174 (112; 276) vs 93 (80; 115), p < 0.0001), ASAT (70 (41; 122) vs 41 (28; 65), U/L, p < 0.0001), ASAT/ALAT (1.91 (1.28, 2.57) vs 1.14 (0.84; 1.57), p < 0.0001), total bilirubin (16.5 (11; 27) vs 12 (9; 16), μmol/L, p < 0.0001), D-Dimers (2664 (907; 7047) vs 271 (187; 780), ng/ml, p < 0,0001). Age over 75 years (OR 2.27, 95% CI 1.58-3.27), Charlson comorbidity index > 5 points (OR 1.78, 95% CI 1.17-2.72), AKI (OR 1.65, 95% CI 1.11-2.46), leukocytosis (OR 2.69, 95% CI 1.80-4.01), lymphopenia (OR 2.44, 95% CI 1.03-5.79), CRP increase > 100 mg/L (OR 2.08, 95 % CI 1.27-3.42) and ASAT/ALAT > 1.6 (OR 2.68, 95 % CI 1.89-3.78) during hospitalization were independent predictors of mortality according to multivariate Cox regression.

Patients who died with AKI more frequently had transient renal impairment (50.5% vs 22%, p < 0.001), more severe renal injury (stage I 37% vs 76%, p < 0.001, stage II 35% vs 21%, p = 0.03, stage III 28% vs 3%, p < 0.001) and less frequently had recovery of baseline renal function by the end of hospitalization (14% vs 74%, p < 0,001).

After comparing discharged and deceased AKI patients, patients in the second group were older (79 (68; 85) vs 70 (61; 78) years, p < 0.0001), more had hypertension (91% vs

82%, p = 0.02) and CVD (28% vs 18%, p = 0.04), more had respiratory failure at admission (62% vs 50%, p = 0.04) and hospitalized in intensive care units (73% vs 23%, p < 0.001). Laboratory maximums during hospitalization were analyzed in relation to hospital mortality in patients with AKI and data are presented in Table 5. Deceased patients with AKI and those who recovered showed no differences in the frequency of changes in urinary sediment, proteinuria at admission.

Table 5. Maximum laboratory values in patients with AKI by mortality rate.

Parameter, Me (IQR)	Survivors with AKI (n = 148)	Deaths with AKI (n = 148)	p
Leukocytes > $10x10^9$, n (%)	62 (46)	123 (83)	<0.001
Lymphocytes < $1.2x10^9$, n (%)	123 (83)	142 (96)	<0.001
Hemoglobin < 120 g/L, n (%)	77 (52)	93 (63)	0.06
Platelets < $150x10^9$, n (%)	53 (36)	74 (50)	0.01
Creatinine max, µmol/L	147 (119; 189)	243 (158; 307)	<0.0001
Sodium min, mmol/L	135 (131; 138)	136 (131; 140)	0.04
Potassium max > 5.1 mmol/L, n (%)	49 (33)	80 (54)	0.001
CRP max, mg/L	124 (84; 187)	227 (152; 296)	<0.0001
ASAT max, U/L	48 (30; 73)	76 (43; 182)	<0.0001
ASAT/ALAT max	1.45 (1.04; 1.93)	1.98 (1.42; 2.69)	<0.0001
Total bilirubin max, µmol/L	13 (10; 21)	16 (11; 28)	0.006
Albumin min, g/L	29 (24; 33)	23 (19; 27)	<0.0001
Procalcitonin max, ng/ml*	0.24 (0.09; 0.7)	1.4 (0.4; 6.8)	0.0002
LDH max, U/L**	404 (273; 571)	660 (440; 967)	<0.0001
D-Dimers max, ng/ml	717 (323; 2521)	2711 (1247; 6085)	<0.0001
Fibrinogen max, g/L	6.9 (5.4; 7.6)	7 (5.5; 7.9)	0.5

***Note**: AKI – acute kidney injury; IQR – interquartile range; Me – median;* CRP – C-reactive protein; *ALAT – alanine aminotransferase; ASAT – aspartate aminotransferase, LDH – lactate dehydrogenase; * - available in 96 patients; ** - available in 160 patients.*

According to multivariate regression analysis, patients with AKI who were 75 years > years of age (OR 1.93, 95% CI 1.33-2.79), CKD (OR 1.67, 95% CI 1.12-2.49) were admitted to Intensive Care Department (OR 3.34, 95% CI 2.06-5.41), leukocytosis > $10x10^9$ (OR 2.09, 95% CI 1.32-3.30) and AST/ALT > 1.6 (OR 2.21, 95% CI 1.54-3.17) during hospitalization, all of these factors were independent predictors of mortality.

Assessment of the prognostic character of AKI in relation to long-term outcomes. For the analysis of long-term outcomes, 691 patients were evaluated, of which 554 (80%) patients did not have AKI during the acute period of COVID-19 and 137 (20%) had AKI. Patients who sustained acute kidney injury and were discharged were older (71 (62; 78) vs 64 (52; 73) years, p < 0.0001), more had HTA (82.5% vs 66%, p < 0.001), CVD (25% vs 12%, p < 0.001), atrial fibrillation (18% vs 9%, p = 0.008), cancer (17.5% vs 6.7%, p < 0.001) and CKD (18% vs 9%, p = 0.002), Charlson index higher (4 (3 (3; 5) vs. score 3 (1; 4), p < 0.0001), more admitted to intensive care (23% vs. 10%, p < 0.001) and radiologically had CT-3 and CT-4 (38% vs. 25%, p < 0.05). According to the Cox multivariate regression, as predictors of death from any cause within 180 days of discharge, only the Charlson index (OR 1.46, 95% CI 1.19-1.79) and acute kidney injury (OR 2.83, 95% CI 1.28-6.26) sustained in the acute phase of COVID-19 were predictors. At discharge, 792 patients were monitored, 446 (56%) patients had serum creatinine levels examined within 180 days of discharge. Clinical and demographic characteristics of patients are presented in Table 6.

Table 6. Clinical and demographic characteristics of patients who underwent AKI and in whom renal function was assessed after discharge.

Parameter	Patients without AKI (n = 343)	Patients with AKI (n = 103)	p
Men, n (%)	195 (57)	41 (39)	0.002
Age, years, Me (IQR)	65 (56; 73)	71 (61; 76)	0.006
Obesity, n (%)	157/314 (50)	49/89 (55)	0.4
DM, n (%)	90 (26)	34 (32)	0.2
HTA, n (%)	245 (72)	83 (78)	0.09
Angiotensin-converting enzyme inhibitors, n (%)	132 (39)	37 (35)	0.9
CVD, n (%)	51 (15)	26 (25)	0.02
Charlson Index, Points, Me (IQR)	3 (2; 4)	4 (3; 5)	0.0002
Anamnesis oncology, n (%)	26 (8)	18 (17)	0.003
Atrial fibrillation, n (%)	43 (13)	21 (20)	0.05
CT-3 and above, n (%)	78 (23)	38 (36)	0.005
Admission to Intensive Care Department, n (%)	34 (10)	26 (25)	<0.001

***Note:** AKI – acute kidney injury; IQR – interquartile range; CVD – cardiovascular disease*

Data on GFR were divided into two groups, at discharge and over 180 days, and are presented in Table 7.

It was found that in patients who developed AKI during hospitalization, the incidence of a decrease in GFR was higher by more than 10% compared to GFR at discharge (33% vs 18%, p < 0.05), by more than 20% compared to GFR at discharge (22% vs 6%, p < 0.001) and formation of *de novo* chronic kidney disease or progression of pre-existing CKD (35% vs 15%, p < 0.001) 180 days after discharge from hospital.

Table 7. Mean GFR values at discharge and over 180 days of follow-up

Parameter, n (%)	On discharge		During 180 days	
	Discharged without AKI (n = 343)	Discharged with AKI (n = 103)	Discharged without AKI (n = 343)	Discharged with AKI (n = 103)
GFR CKD-EPI > 60 ml/min	272 (79)	60 (58)**	269 (78)	56 (54)**
GFR CKD-EPI from 59 to 45 ml/min	50 (15)	24 (23)*	50 (15)	23 (22)
GRF CKD-EPI from 44 to 30 ml/min	19 (5,5)	10 (10)	21 (6)	18 (17)**
GFR CKD-EPI < 30 ml/min	2 (0,5)	9 (8)**	3 (1)	6 (5)*

***Note**: GFR CKD-EPI – Equations for Glomerular Filtration Rate; *p < 0.05, **p < 0.001 – the significance of differences between patients with AKI*

Similarly, according to multivariate regression analysis, age > 65 years (OR 4.29, 95% CI 1.96-9.38), Charlson index > 4 points (OR 2.44, 95% CI 1.30-4.59) and AKI development (OR 2.54, 95% CI 1.46-4.43) were predictors of *de novo* CKD or its progression within 180 days.

Discussion

Given the heterogeneity of the data, even though there are standardized AKI criteria recognized by the global medical community, the true prevalence of deteriorating kidney function in patients with COVID-19 is not fully understood. Thus, the pathogenesis of kidney damage in SARS-CoV-2 infection is multifactorial. First, SARS-CoV-2 can exert a direct cytopathic effect on the kidney. This is supported by the detection of coronavirus fragments in the urine of SARS-CoV-2-infected patients determined by polymerase chain reaction [1, 3, 15]. As mentioned above, SARS-CoV-2 uses ACE2 to enter the host cell [2]. Therefore, the most common symptom in patients with CKD and COVID-19 was proteinuria, which is the result of direct damage to podocytes due to ACE2 expression [2, 11, 16], a fact also mentioned in our study. Literature data highlight the presence of hematuria in 20% of patients infected with COVID-19 [4, 17], a value comparable to the value in our study. The authors explain the pathogenesis of hematuria as a consequence of endotheliitis leading to coagulopathy and destruction of the filtration barrier in the renal corpuscles [2, 17-19]. Some authors, including ourselves, believe that the occurrence of proteinuria and hematuria in a COVID-19 patient are independent predictors of the development of the critical stage of the disease [6, 13, 20]. Similarly, literature data also indicate that AKI has been diagnosed in patients with COVID-19 more frequently than cardiovascular (23%) and liver (23%) diseases [11-14, 21]. Of the patients who developed AKI due to coronavirus infection, one in four patients required continuous hemodialysis, and 12 (80%) patients died within the first week of admission [2, 5, 9, 22].

In a large study from the UK, more than half (51%) of patients with AKI had stage 1, 13% had stage 2, and 36% had stage 3 AKI [11], similar results to our study. In another trial from the United States, which included more than 9,000 patients, the incidence of AKI was 39.9%, of which 43% had stage 1, 22% had stage 2, and 36% had stage 3 [9, 15]. This differed in terms of comorbidity compared to our study, but overall were similar. In another retrospective analysis from Scotland, which included 554 hospitalized patients with COVID-19, the incidence of AKI was 60.6%, with the majority of AKI cases corresponding to stage 3 (55.8%) [17]. In a meta-analysis of 13 studies that reported the severity of AKI, the majority (44%) of patients with AKI had stage one, 19% had stage two, and 34% had stage three [13]. This suggest a hypothesis of predominance of comorbidities influencing the degree and severity of kidney damage in SARS-CoV2 infection.

A clinical trial based in a hospital in Wuhan (n = 701) showed that 5.1% of patients admitted for antiviral treatment developed acute kidney injury [23]. Among these patients at admission, 43.9% had proteinuria, 26.7% had hematuria, 13-14% had elevated serum creatinine levels, and glomerular filtration rate was less than 60 ml/min. Also, the results of scientific studies conducted by reputable experts clearly demonstrate that SARS-CoV-2 infection can provoke the development of chronic kidney disease [24, 25]. While it is still difficult to assess the long-term effects of the pandemic, these effects are likely to contribute to an increased incidence of chronic kidney disease.

Conclusions

Acute kidney injury occurs in 29.6% of patients hospitalized with COVID-19. In more than half of cases, kidney dysfunction corresponds to the first stage of AKI, begins before hospitalization, and does not recover until discharge. The risk of AKI is higher in patients with more comorbidities and a more severe course of disease. Patients with history of CKD, AKI often starts before hospitalization. Independent negative predictors of hospital-developed AKIs were HTA, Charlson index > 4 points, respiratory failure, ASAT/ALAT > 1.6, D-Dimers > 250 ng/ml, and hematuria on admission. In patients who underwent AKI in the acute phase of COVID-19, the risk of death and either *de novo* formation of CKD, or progression of existing CKD within 180 days of discharge, is more than 2.5 times higher.

Competing interests.

None declared.

Patient consent.

Obtained.

Ethics approval.

The study was approved by the Research Ethics Committee of *Nicolae Testemițanu* State University of Medicine and Pharmacy (minutes no.6 from 18.05.2023).

Authors' contribution.

Study conception and design: TR, LG, EC, ER. Data acquisition: TR, ZA, CG. Analysis and interpretation of data: TR, ER, ZA, CG. Drafting of the manuscript: TR, ER, ZA. Significant manuscript review with significant intellectual involvement: LG, EC, ER. All authors approved the final version of the manuscript.

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References

1. Tran VT, Porcher R, Pane I, Ravaud P. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun. 2022;13(1):1812. doi: 10.1038/s41467-022-29513-z.
2. Legrand M, Bell S, Forni L, Joannidis M, Koyner JL, Liu K, et al. Pathophysiology of COVID-19-associated acute kidney injury. Nat Rev Nephrol. 2021;17(11):751-764. doi: 10.1038/s41581-021-00452-0.
3. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022;22(4):e102-e107. doi: 10.1016/s1473-3099(21)00703-9.
4. Seeßle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al. Persistent symptoms in adult patients 1 year after coronavirus disease 2019 (COVID-19): a prospective cohort study. Clin Infect Dis. 2022;74(7):1191-1198. doi: 10.1093/cid/ciab611.
5. Chung EYM, Palmer SC, Natale P, Krishnan A, Cooper TE, Saglimbene VM, et al. Incidence and outcomes of COVID-19 in people with CKD: a systematic review and meta-analysis. Am J Kidney Dis. 2021;78(6):804-815. doi: 10.1053/j.ajkd.2021.07.003.
6. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-436. doi: 10.1038/s41586-020-2521-4.
7. Lumlertgul N, Pirondini L, Cooney E, Kok W, Gregson J, Camporota L, et al. Acute kidney injury prevalence, progression and long-term outcomes in critically ill patients with COVID-19: a cohort study. Ann Intensive Care. 2021;11(1):123. doi: 10.1186/s13613-021-00914-5.
8. Ji W, Huh K, Kang M, Hong J, Bae GH, Lee R, et al. Effect of underlying comorbidities on the infection and severity of COVID-19 in Korea: a nationwide case-control study. J Korean Med Sci. 2020;35(25):e237. doi: 10.3346/jkms.2020.35.e237.
9. Flythe JE, Assimon MM, Tugman MJ, Chang EH, Gupta S, Shah J, et al. Characteristics and outcomes of individuals with pre-existing kidney disease and COVID-19 admitted to intensive care units in the United States. Am J Kidney Dis. 2021;77(2):190-203.e191. doi: 10.1053/j.ajkd.2020.09.003.
10. Henry BM, Lippi G. Chronic kidney disease is associated with severe coronavirus disease 2019 (COVID-19) infection. Int Urol Nephrol. 2020;52(6):1193-1194. doi: 10.1007/s11255-020-02451-9.
11. Sullivan MK, Lees JS, Drake TM, Docherty AB, Oates G, Hardwick HE, et al. Acute kidney injury in patients hospitalized with COVID-19 from the ISARIC WHO CCP-UK Study: a prospective, multicentre cohort study. Nephrol Dial Transp. 2022;37(2):271-284. doi: 10.1093/ndt/gfab303.
12. Jana KR, Yap E, Janga KC, Greenberg S. Comparison of two waves of COVID-19 in critically ill patients: a retrospective observational study. Int J Nephrol. 2022;2022:3773625. doi: 10.1155/2022/3773625.
13. Dadras O, Afsahi AM, Pashaei Z, Mojdeganlou H, Karimi A, Habibi P, et al. The relationship between COVID-19 viral load and disease severity: a systematic review. Immun Inflamm Dis. 2022;10(3):e580. doi: 10.1002/iid3.580.
14. Davies MA, Morden E, Rosseau P, Arendse J, Bam JL, Boloko L, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection during resurgence driven by Omicron lineages BA.4 and BA.5 compared with previous waves in the Western Cape Province, South Africa. medRxiv. 2022. doi: 10.1101/2022.06.28.22276983.
15. Groppa L, Agachi S, Sasu B, Rotaru L, Pascari-Negrescu A, Russu E, Dutca L, Sasu D. Afectarea renală în maladia COVID-19: sinteză de literatură = Kidney involvement in COVID-19 disease: review article. Mold J Health Sci. 2020;(2):4-16. Romanian, English.
16. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. Lancet. 2022;399(10323):437-446. doi: 10.1016/s0140-6736(22)00017-4.
17. Bell S, Campbell J, Watters C, O'Neil M, Almond A, Buck K, et al. The impact of Omicron on outcomes following infection with SARS-CoV-2 in patients with kidney failure in Scotland. Clin Kidney J. 2023;16(1):197-200. doi: 10.1093/ckj/sfac173.
18. Liakopoulos V, Roumeliotis S, Papachristou S, Papanas N. COVID-19 and the kidney: time to take a closer look. Int Urol Nephrol. 2022;54(5):1053-1057. doi: 10.1007/s11255-021-02976-7.
19. Jewell PD, Bramham K, Galloway J, Post F, Norton S, Teo J, et al. COVID-19-related acute kidney injury: incidence, risk factors and outcomes in a large UK cohort. BMC Nephrol. 2021;22(1):359. doi: 10.1186/s12882-021-02557-x.
20. Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. J Am Soc Nephrol. 2021;32(11):2851-2862. doi: 10.1681/asn.2021060734.
21. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021;397(10270):220-232. doi: 10.1016/s0140-6736(20)32656-8.
22. Petersen EL, Goßling A, Adam G, Aepfelbacher M, Behrendt CA, Cavus E, et al. Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: the Hamburg City Health Study COVID programme. Eur Heart J. 2022;43(11):1124-1137. doi: 10.1093/eurheartj/ehab914.
23. Li D, Liao X, Ma Z, Zhang L, Dong J, Zheng G, et al. Clinical status of patients 1 year after hospital discharge following recovery from COVID-19: a prospective cohort study. Ann Intensive Care. 2022;12(1):64. doi: 10.1186/s13613-022-01034-4.
24. Al Rumaihi K, Khalafalla K, Arafa M, Nair A, Al Bishawi A, Fino A, et al. COVID-19 and renal involvement: a prospective cohort study assessing the impact of mild SARS-CoV-2 infection on the kidney function of young healthy males. Int Urol Nephrol. 2022;55(1):201-209. doi: 10.1007/s11255-022-03301-6.
25. Yende S, Parikh CR. Long COVID and kidney disease. Nat Rev Nephrol. 2021;17(12):792-793. doi: 10.1038/s41581-021-00487-3.