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THE PARTICULARITIES OF ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS WITH COVID-19

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ABSTRACT

Introduction Acute kidney injury (AKI) is a common complication in critically ill patients with COVID-19, associated with increased mortality. This study aimed to evaluate the incidence of acute kidney injury in COVID-19 patients hospitalized in intensive care units, identify risk factors for its development, and determine the impact of AKI on mortality and clinical outcomes.

Material and methods A retrospective cohort study was conducted and included patients with confirmed COVID-19 infection, admitted to the Republican Clinical Hospital "Timofei Moșneaga" between June 01, 2020, and August 31, 2020. The association between potential risk factors and AKI was assessed using relative risk (RR) with 95% confidence intervals (CI).

Results Of the 81 patients included, 20 (24.69%) developed AKI. Significant risk factors associated with AKI included mechanical ventilation (RR = 7.96; 95% CI: 2.86–22.15, p < 0.001) and vasopressor therapy (RR = 4.12; 95% CI: 1.43–11.86, p = 0.009). The mortality rate was significantly higher in patients with AKI compared to those without AKI (90% vs. 36.06%, RR = 2.49; 95% CI: 1.85–3.36, p < 0.001).

Conclusions Acute kidney injury is a severe complication in critically ill COVID-19 patients and significantly increases mortality among patients hospitalized in intensive care units. Identifying modifiable risk factors could help optimize management strategies and improve survival rates.

Keywords Acute kidney injury, COVID-19, risk factors, intensive care units, mortality.

PARTICULARITĂȚILE LEZIUNII RENALE ACUTE LA PACIENȚII ÎN STARE CRITICĂ CU INFECȚIA COVID-19

Introducere Leziunea renală acută (LRA) este o complicație frecventă la pacienții cu COVID-19, fiind asociată cu o mortalitate crescută. În acest studiu, am avut ca obiectiv evaluarea incidenței leziunii renale acute la pacienții cu COVID-19 internați în unitățile de terapie intensivă (UTI), identificarea factorilor de risc în dezvoltarea acesteia și determinarea impactului asupra mortalității și rezultatelor clinice.

Material și metode A fost realizat un studiu retrospectiv de cohortă, care a inclus pacienți cu infecția COVID-19, internați în Spitalul Clinic Republican „Timofei Moșneaga" în perioada 01 iunie 2020-31 august 2020. Asocierea dintre factorii de risc și LRA a fost evaluată utilizând Relative Risk (RR) cu intervale de încredere (CI) de 95%.

Rezultate Dintre cei 81 de pacienți incluși, 20 (24,69%) au dezvoltat LRA. Factorii de risc semnificativi asociați cu LRA au inclus ventilația mecanică (RR = 7,96; 95% CI: 2,86–22,15, p < 0,001) și terapia vasopresoare (RR = 4,12; 95% CI: 1,43–11,86, p = 0,009). Rata mortalității a fost semnificativ mai mare la pacienții cu LRA comparativ cu cei fără (90% vs. 36,06%, RR = 2,49; 95% CI: 1,85–3,36, p < 0.001).

Concluzii Leziunea renală acută este o complicație severă la pacienții cu COVID-19 și crește semnificativ mortalitatea în rândul celor spitalizați în UTI. Identificarea factorilor de risc modificabili ar putea contribui la optimizarea strategiilor de conduită și la îmbunătățirea ratei de supraviețuire.

Cuvinte-cheie Leziune renală acută, COVID-19, factori de risc, unități de terapie intensivă, mortalitate.

INTRODUCTION

Coronaviruses are a large family of viruses that cause diseases ranging from the common cold to more severe illnesses, such as Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome. COVID-19 is a new disease first identified in 2019 (1). Infection with the novel coronavirus (COVID-19) is a pandemic infection caused by the SARS-CoV-2 virus (2). On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic (3).

Clinically, the features of COVID-19 range from asymptomatic disease to acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. The most common clinical features include cough, fever, headache, sore throat, fatigue and dyspnea (4). Although the respiratory system is the major target of COVID-19 (5), the disease can also have repercussions on other organs, including the kidneys (6). Renal involvement in COVID-19 infection is common (7).

Although initial reports from China suggested relatively low rates of renal involvement, subsequent reports from Europe and the USA indicate much higher rates of acute kidney injury, particularly in the intensive care unit (ICU) setting (8), with an incidence ranging from 0.5% to 80% (9). Patients with COVID-19 have increased need for renal replacement therapy, ICU admission and mechanical ventilation (10). Current research suggests that mortality among hospitalized patients with renal impairment is higher compared to those without renal impairment (7, 8, 10).

During the COVID-19 pandemic, our institution observed a notable increase in COVID-19 hospitalizations. At the same time, we noticed an alarming number of COVID-19 patients who developed acute kidney injury.

This study aimed to evaluate the incidence of acute kidney injury in COVID-19 patients hospitalized in intensive care units, identify risk factors for its development, and determine the impact of AKI on mortality and clinical outcomes.

MATERIAL AND METHODS

Study setting

The study was approved by the institutional ethics committee, and authorization was obtained to access patient records and archives.

A retrospective cohort study was conducted, including 81 patients with confirmed COVID-19 hospitalized in the intensive care units at the Republican Clinical Hospital “Timofei Moșneaga” between June 1, 2020, and August 31, 2020.

Study population

The inclusion criteria for the study were: patients with COVID-19, diagnosed by real-time PCR technique and admitted to the Republican Clinical Hospital “Timofei Moșneaga” during the study period. Exclusion criteria were patients aged < 18 or >80 years, chronic kidney disease stage IV-V, patients transfer to other institutions and monitoring for less than 48 h, or insufficient clinical data for evaluation.

Patients were followed from hospital admission until discharge or death. AKI was considered the primary exposure, while mortality, ICU length of stay, and need for renal replacement therapy were the main outcomes of inter-

est. Patients who did not develop AKI were defined as group I (No AKI) and patients who developed AKI were defined as group II (With AKI). The study design is illustrated in Figure 1.

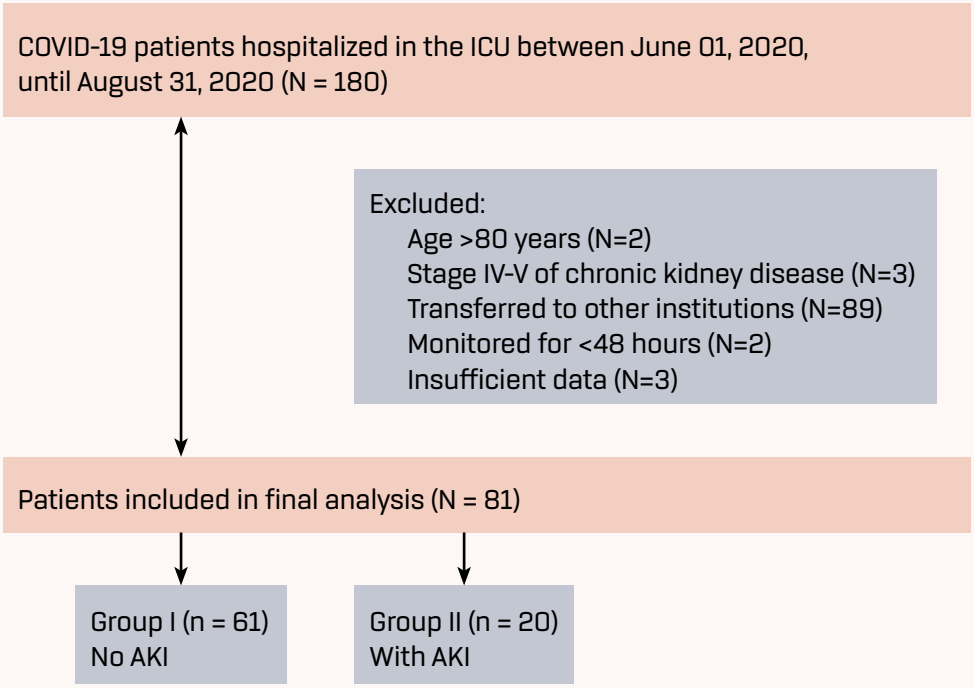

Figure 1. Study design.

Staging of acute kidney injury was performed by serum creatinine level, according to the Kidney Disease Improving Global Outcomes (KDIGO) classification. Thus, an increase in serum creatinine (SCr) values by 1.5-1.9 times from baseline was classified as AKI stage I, an increase in SCr by 2-2.9 times from baseline was classified as AKI stage II, and an increase in SCr by 3 times from baseline or a decrease in GFR to 35 ml/min/1.73 m^2 was classified as AKI stage III.

Data collection and research tools

Data were extracted from the electronic patient records and compiled into an electronic database. The following data were collected: patients' demographics, duration of hospitalization, mode of discharge, comorbidities (cardiovascular disease, cerebrovascular disease, chronic kidney disease, diabetes, body mass index), treatments administered and the impact of aggressive factors on renal function during intensive care unit admission (mechanical ventilation, renal replacement therapy, vasoactive therapy, antiviral and nephrotoxic medication.

Data analysis

Continuous variables were analyzed using the Student's t-test, while categorical variables were assessed using the chi-square test or Fisher's exact test, as appropriate. Relative risk (RR) with 95% confidence intervals (CI) was calculated to evaluate associations between AKI and potential risk factors. Statistical significance was defined as $p < 0.05$.

RESULTS

Patient Characteristics

The age of the study participants ranged from 29 to 77 years, with a mean of 58.8 ± 10.6 years. The age distribution is shown in Figure 2.

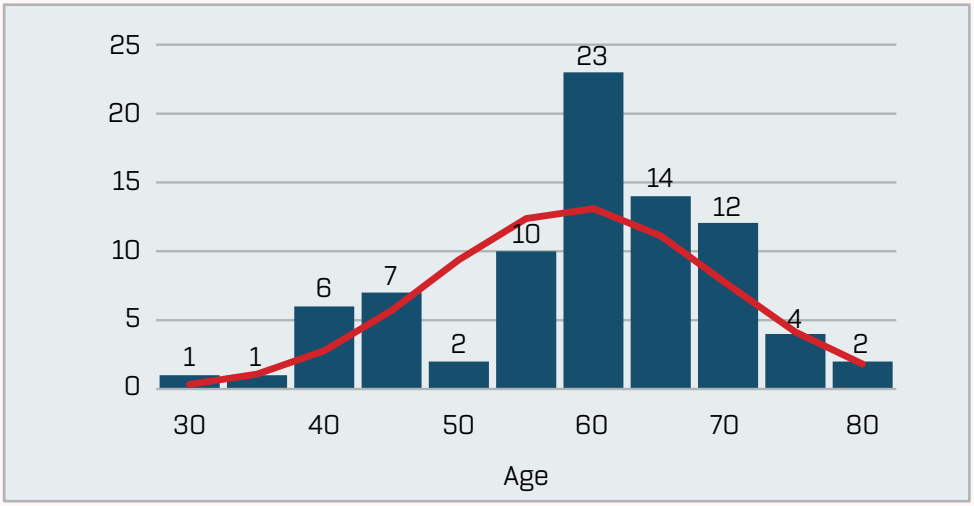

Figure 2. Distribution of subjects according to age.

Thus, Figure 2 shows that most of the subjects included in the study were aged between 60-70 years, indicating that elderly patients develop severe forms of COVID-19, requiring follow-up and treatment in intensive care units.

Of the 81 patients included in the study, 49 (60.49%) were men and 32 (39.50%) were women. Various studies have reported that the rate of COVID-19 infection is relatively similar in both males and females, but the mortality rate is higher (1.5 to 2.5 times) in males. Studies have suggested that sex-based differences in hormonal and immune response may be responsible for the higher mortality in men. Similarly, sexual dimorphism is also common in acute kidney injury. In AKI, males had 2.19 times higher rate of developing AKI than females (11). In our study, also the mortality rate among the subjects included in the study was higher in males (72.2% vs. 27.8%).

The most common comorbidity was cardiovascular disease (81.48%), followed by obesity (48.14%), diabetes (38.27%), cerebrovascular disease (20.98%), enterocolitis (20.98%) and chronic kidney disease (CKD) (2.46%) (fig. 3).

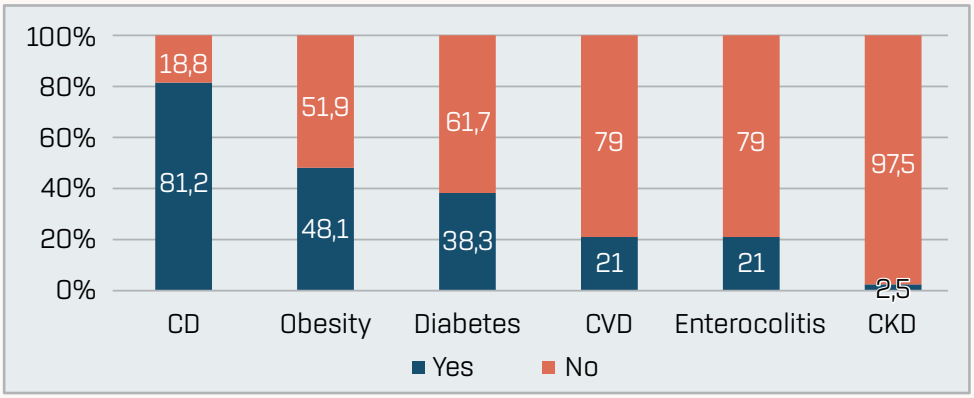

Figure 3. Comorbidities of the patients, %.

Legend: CD – cardiac disease, CVD – cerebrovascular disease; CKD – Chronic Kidney Disease.

Treatments

Out of all patients, 85.18% received nephrotoxic medication, 59.25% were intubated, 41.97% received antiviral medication, 34.56% vasopressor treatment and 30.86% diuretics. Renal replacement therapy required 4 patients (20%).

Clinical characteristics and treatments administered to patients during hospitalization in intensive care units are shown in Table 1.

Table 1. Clinical characteristics and treatment of COVID-19 patients.

Characteristics	All patients, n = 81	Patients with AKI, n = 20	Patients without AKI, n = 61	P value
Demographic Data				
Age, mean (range)	58.8 (29-77)	64.7 (55-72)	56.85 (29-77)	<0,001
Male sex, n (%)	49 (60.49%)	14 (70%)	35 (57.37%)	0.32
Duration of hospitalization, days (range)	18.89 (5-46)	18.71 (7-46)	18.03 (5-45)	0.78
Chronic Diseases, n (%)				
Cardiovascular diseases	66 (81.48%)	18 (90%)	48 (78.68%)	0.25
Chronic kidney disease	2 (2.46%)	1 (5%)	1 (1.63%)	0.42
Cerebrovascular diseases	17 (20.98%)	3 (15%)	14 (22.95%)	0.55
Diabetes	31 (38.27%)	9 (45%)	22 (36.06%)	0.45
Obesity	39 (48.14%)	11 (55%)	28 (4.9%)	0.47
Enterocolitis	17 (20.98%)	4 (20%)	13 (21.31%)	1.00
Treatments, n (%)				
Mechanical ventilation	48 (59.25%)	19 (95%)	29 (47.54%)	<0.001
Renal replacement therapy	4 (20%)	4 (20%)	-	-
Diuretics	25 (30,86%)	16 (80%)	9 (14.75%)	<0.001
Vasopressor treatment	28 (34.56%)	13 (65%)	15 (24.59%)	<0.001
Nephrotoxic medication	68 (85.18%)	17 (85%)	45 (73.77%)	0.38
Antiviral treatment	34 (41.97%)	14 (70%)	20 (32.78%)	0.002

Note: Statistical significance was assessed between groups (patients with AKI and patients without AKI) using the two-tailed Student's t-test for continuous variables (e.g., age, duration of hospitalization) and the chi-square test or Fisher's exact test for categorical variables, depending on the expected frequencies. Statistically significant differences (p < 0.05) are indicated in bold. AKI – acute kidney injury.

Acute kidney injury and risk factors

Of the 81 patients, 20 patients (24.69%) had acute kidney injury, of which 5 developed stage I AKI (25%), 7 (35%) developed stage II and 8 (40%) stage III, according to the KDIGO classification (fig. 4). Among the patients with AKI and available urine analysis, 65% had proteinuria, and 45% had hematuria. In a prospective cohort study that included 701 hospitalized patients infected with COVID-19, the prevalence of proteinuria and hematuria on hospital admission was 44 and 27%, respectively (12).

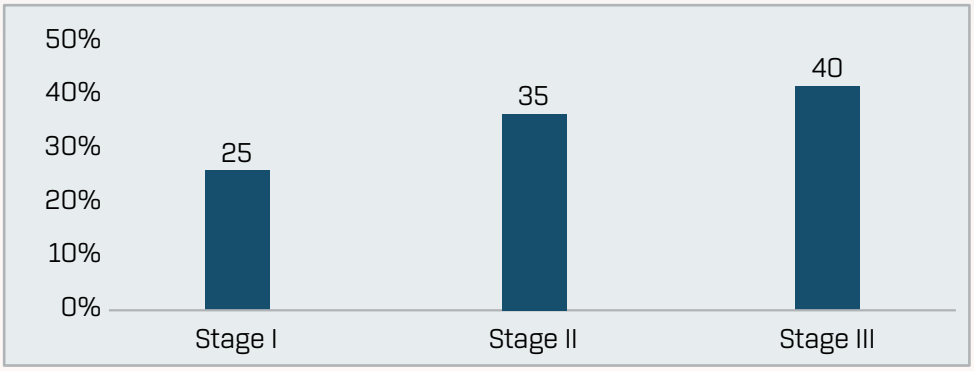

Figure 4. Staging of acute kidney injury, %.

Significant risk factors for the development of acute kidney injury during hospitalization were mechanical respiration and vasopressor therapy (tab. 2).

Table 2. Risk Factors for Acute Kidney Injury in patients with COVID-19.

Risk factor	Relative Risk (RR)	95% CI	p-value
Male sex	1.37	0.67–2.81	0.49
Mechanical ventilation	7.96	2.86–22.15	**<0.001**
Vasopressor therapy	4.12	1.43–11.86	**0.009**
Obesity	1.24	0.57–2.70	0.58
Diabetes mellitus	1.25	0.56–2.78	0.58

Note: *Relative Risk (RR) with 95% confidence intervals (CI) was calculated to assess the association between risk factors and the development of acute kidney injury (AKI). Statistically significant differences (p < 0.05) are indicated in bold.*

Male patients had a 1.37 times higher risk of developing AKI compared to female patients; however, this association was not statistically significant (RR = 1.37; 95% CI: 0.67–2.81, p = 0.49). Patients requiring mechanical ventilation had a 7.96 times higher risk of developing AKI and a statistically significant association was observed (RR = 7.96; 95% CI: 2.86–22.15, p < 0.001). The use of vasopressors was associated with a 4.12 times higher risk of AKI, which was statistically significant (RR = 4.12; 95% CI: 1.43–11.86, p = 0.009). Obesity was not significantly associated with an increased risk of AKI (RR = 1.24; 95% CI: 0.57–2.70, p = 0.58). Diabetes mellitus was not significantly associated with AKI in this cohort (RR = 1.25; 95% CI: 0.56–2.78, p = 0.58).

Complications and Mortality

The most common complication during hospitalization was disseminated intravascular coagulation (DIC) syndrome (33.3%), followed by secondary infections (30.9%), liver injury (29.6%), sepsis (19.8%), septic shock (14.8%), and cardiac injury (11.1%) (tab. 3).

Table 3. Complications and outcomes of patients with COVID-19.

Variable	All patients, N = 81	Patients with AKI, N = 20	Patients without AKI, N = 61	RR	95% CI	p-value
Complications, n (%)						
Sepsis	16 (19.75%)	11 (55%)	5 (8.19%)	6.71	2.60–17.30	**<0.001**
Septic shock	12 (14.81%)	10 (50%)	2 (3.27%)	15.29	3.60–64.90	**<0.001**
DIC	27 (33.33%)	7 (35%)	20 (32.78%)	1.07	0.55–2.08	0.84
Cardiac injury	9 (11.11%)	6 (30%)	3 (3.7%)	8.11	2.25–29.20	**<0.001**
Liver injury	24 (29.62%)	12 (60%)	12 (19.67%)	3.05	1.75–5.32	**<0.001**
Secondary infections	25 (30.86%)	11 (55%)	14 (22.95%)	2.40	1.40–4.10	**<0.01**
Discharge type, n (%)						
In-hospital death	40 (49.38%)	18 (90%)	22 (36.06%)	2.49	1.85–3.36	**<0.001**
Discharged	41 (50.61%)	2 (10%)	39 (63.93%)	0.16	0.04–0.60	**<0.01**

Note: DIC – disseminated intravascular coagulation.

The relative risk (RR) of developing complications was significantly higher in patients with AKI compared to those without AKI. Patients with AKI had a 3.05 times higher risk of liver injury compared to those without AKI (60% vs. 19.67%, RR = 3.05; 95% CI: 1.75–5.32, $p < 0.001$). The risk of cardiac injury was 8.11 times higher in patients with AKI (30% vs. 3.7%, RR = 8.11; 95% CI: 2.25–29.20, $p < 0.001$). Patients with AKI had a 2.40 times higher risk of developing secondary infections (55% vs. 22.95%, RR = 2.40; 95% CI: 1.40–4.10, $p < 0.01$). The risk of sepsis was 6.71 times higher in patients with AKI (55% vs. 8.19%, RR = 6.71; 95% CI: 2.60–17.30, $p < 0.001$). Patients with AKI had a 15.29 times higher risk of septic shock compared to those without AKI (50% vs. 3.27%, RR = 15.29; 95% CI: 3.60–64.90, $p < 0.001$).

The mortality rate was significantly higher in patients with AKI compared to those without AKI (fig. 5). Patients with AKI had a 2.49 times higher risk of in-hospital mortality (90% vs. 36.06%, RR = 2.49; 95% CI: 1.85–3.36, $p < 0.001$). The mortality rate also increased with the severity of AKI, as classified by the KDIGO staging system. Among AKI patients, mortality was highest in stages II-III ($p<0.05$) (fig. 6). For stage I AKI, the mortality rate was 60% (RR = 1.66; 95% CI: 1.10–2.50, $p = 0.02$). For stage II AKI, the mortality rate was 85.71% (RR = 2.38; 95% CI: 1.65–3.42, $p < 0.001$). For stage III AKI, the mortality rate was 100% (RR = 2.77; 95% CI: 2.10–3.65, $p < 0.001$).

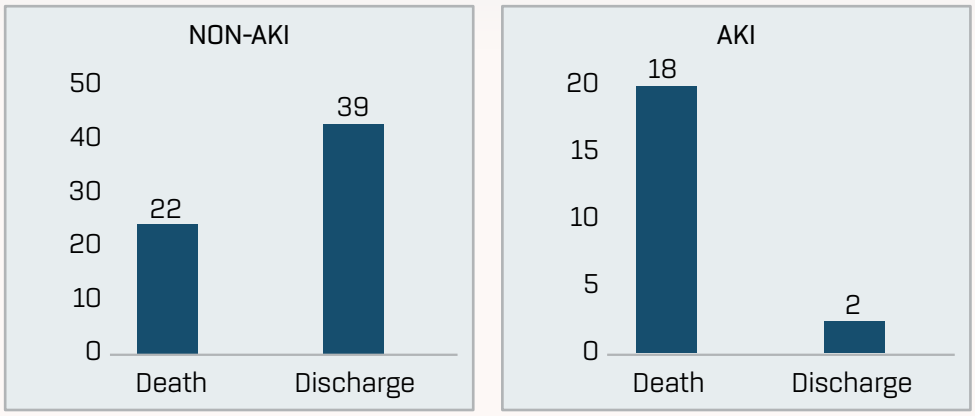

Figure 5. Patient mortality rate, n.

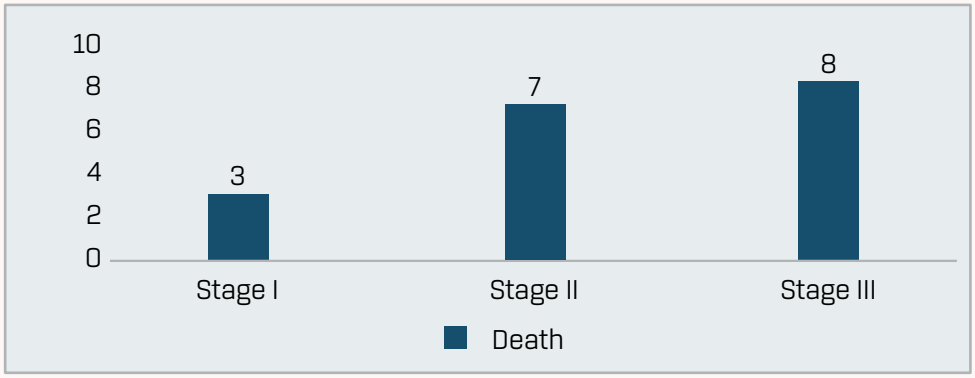

Figure 6. Mortality rate by AKI staging, n.

DISCUSSIONS

This study has several limitations, including its retrospective design and relatively small sample size, which may limit the generalizability of the findings.

According to previous studies, risk factors associated with the development of acute kidney injury include: advanced age, multiple comorbidities (particularly diabetes, hypertension, and cardiovascular disease), high body mass index, non-O blood group, and African American race (13). Chronic kidney disease (CKD) is a well-recognized risk factor for AKI in hospitalized patients (8). AKI occurred nearly three times more often in patients with pre-existing kidney disease (11.4% vs. 4%) (13) and has been identified as the most relevant risk factor for AKI requiring renal replacement therapy in critically ill COVID-19 patients (8). Higher rates of AKI have consistently been documented in critically ill populations (13).

Additional factors associated with an increased risk of AKI on admission include leukocytosis, leukopenia, elevated inflammatory markers (ferritin, C-reactive protein [CRP], D-dimer), severity of COVID-19, viremia, respiratory status, hypovolemia, rhabdomyolysis, medications (e.g., NSAIDs), and non-respiratory involvement such as diarrhea. Risk factors for AKI developing during hospitalization include the use of vasopressors, mechanical ventilation, and fluid overload or hypovolemia (12). Nephrotoxic medications may also contribute, particularly antibiotics, antiviral therapy, and traditional medicines (14).

The pathogenesis of kidney injury in COVID-19 is multifactorial (6). Both direct and indirect mechanisms have been implicated (7), such as hemo-

dynamic disturbances, endothelial dysfunction, hypercoagulation, altered microcirculation, nephrotoxic exposure, the impact of invasive mechanical ventilation (15), local and systemic inflammatory response, and renin-angiotensin-aldosterone system (RAAS) imbalance (6). However, there is emerging evidence that additional infection-specific factors also play an important role (15).

Our findings align with previous studies showing that AKI is a significant predictor of mortality in critically ill COVID-19 patients. Mechanical ventilation and vasopressor therapy were major contributors to AKI development.

CONCLUSIONS

1. Acute kidney injury is a serious complication in critically ill COVID-19 patients and is strongly associated with increased mortality.
2. Early identification of high-risk patients, particularly those requiring mechanical ventilation and vasopressor therapy, is crucial for timely intervention.
3. This study emphasizes the importance of continuous monitoring and personalized treatment strategies to reduce the risk of AKI and improve outcomes in hospitalized COVID-19 patients.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICAL APPROVAL

The study was approved by the Research Ethics Committee of the State University of Medicine and Pharmacy “Nicolae Testemitanu” (Decision no. 76, of 14.11.2022).

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