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Acute Kidney Injury Incidence, Risk Factors and Effects on Mortality in Critically ill COVID-19 Patients: A Retrospective Cohort Study

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ABSTRACT

Objective: Acute kidney injury (AKI) is a common condition in critically ill patients, especially those with severe infections, and associated with increased morbidity and mortality. While the main features associated with COVID-19 are extensive alveolar damage and acute respiratory failure, another common complication in patients infected with SARS-CoV-2 is AKI. There is increasing evidence that it affects the kidneys in particular. It was aimed to investigate the frequency and risk factors of AKI development in critically ill COVID-19 patients.

Material and Methods: Between March 15th, 2020 and June 1st, 2021, patients with COVID-19 who were admitted to the intensive care unit(ICU) for more than 24 hours were included in the study and analysed, retrospectively. Patients were grouped according to whether they developed AKI according to KDIGO criteria during the first week of their ICU stay and compared for risk factors.

Results: There were 206 patients who met the inclusion criteria, of whom 120 had developed AKI during the first week of admission. Patients in AKI group were older with a median age of 70.5 years (p<0.001). The median APACHEII and SOFA scores were higher in the AKI group (20 and 5, respectively, p<0.001). Hypertension was the most common comorbidity and was more frequent in AKI patients (69%, p<0.001), invasive mechanical ventilation (IMV) and vasopressor requirements were more common in AKI patients (78%, p<0.001 and 66%, p<0.001, respectively). In 31 (26%) patients with AKI, renal replacement therapy was required. Mortality rate was higher in AKI patients (68%, p<0.001). Logistic regression analyses revealed hypertension (OR=2.71, %95CI=1.23-5.95, p=0.013) and IMV (OR= 8.15, %95 CI= 3.35-19.83, p< 0.001) as risk factors for AKI.

Conclusion: AKI is a poor prognostic condition commonly seen in critically ill COVID-19 patients. The rate of AKI development is higher in patients with hypertension and those who need invasive mechanical ventilation. The development of AKI has been associated with high mortality in critically ill COVID-19 patients.

Key words: Acute renal failure, ICU, SARS-CoV2, outcome

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a global and still ongoing pandemic. In coronavirus disease (COVID-19) the main feature of the disease is respiratory failure, whereas there are studies that report respiratory failure accompanied by other organ failures, especially renal failure (1-5).

Acute kidney injury (AKI) is a frequent clinical problem in critically ill patients, especially those with severe infections (6). COVID-19 related AKI may develop due to many different mechanisms, including decreased renal perfusion as a result of hemodynamic instability, hypoxemia, hypovolemia, sepsis, and drugs (5). Additionally, COVID-19 itself can cause AKI by a specific mechanism: through ACE receptors those over-expressed in renal cells that bring about tubular cell injury, cause increased thrombotic events, or elevation of proinflammatory cytokines (5, 7, 8).

AKI existence is associated with increased mortality and morbidity in critically ill patients. In this regard, determining the risk factors for the development of AKI can give the advantage of a chance to prevent it as well as to decrease morbidity and mortality of patients.

In this study, we aimed to evaluate the incidence of and risk factors for AKI development in critically ill COVID-19 patients who were admitted to an intensive care unit (ICU) and its association with ICU mortality.

Materials and Method

We performed a single-center retrospective cohort study in patients that were admitted to pandemic ICU between March 15, 2020 and June 1, 2021 and had tested positive for SARS-CoV-2 by real-time RT-PCR in respiratory fluids and/or nasopharyngeal swaps. Patients with end-stage kidney disease, ICU stay shorter than 24 hours and age under 18 years was excluded. The study was approved by Ministry of Health of the Turkish Republic and Institutional Local Ethic Committee (date February 23, 2021 and number 2021/211).

We examined clinical laboratory findings, and medical records retrospectively. We gathered demographic data, comorbidities (diabetes mellitus, hypertension, atherosclerotic heart disease, malignancy, congestive heart failure, chronic obstructive lung disease), exposition to nephrotoxic agents (nonsteroidal anti-inflammatory drugs, intravenous contrast agents, aminoglycoside, colistin, and vancomycin), Sequential Organ Failure Assessment (SOFA) score at ICU admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, laboratory parameters (neutrophil to lymphocyte ratio-NLR, C-reactive protein, d-dimer, ferritin, admission creatinine), need for vasopressors infusion, invasive mechanical ventilation requirement, arterial oxygen partial pressure to fractional inspired oxygen ratio (PaO_2/FiO_2 ratio), steroid treatments received in the ICU, length of ICU stay and survival outcome 28 days after ICU admission.

AKI is defined by as any of the following: Increase in serum creatinine by 0.3mg/dL or more within 48 hours or Increase in serum creatinine to 1.5 times baseline or more within the last 7 days or urine output less than 0.5 mL/kg/h for 6 hours according to KDIGO guidelines (9).

Patients were categorized depending on whether they developed AKI or not on admission or in the first week of ICU stay. The primary end point was to evaluate the incidence and risk factors for AKI development and the secondary outcome was to evaluate association between AKI and ICU mortality.

Statistical Analysis

Statistical analysis of the data was performed with the Statistical Package for Social Science for Windows (SPSS) v.22. Continuous variables were presented as medians [quartile 25%–quartile 75%] and categorical variables as numbers and percentages. Continuous variables were compared using a Mann-Whitney U test. Categorical data were compared AKI development the x2 test or Fisher's exact test. The independent predictors of ICU mortality were identified using logistic regression including the factors with a p value under 0.10 in the univariate analysis. The association measures were calculated (adjusted odds ratio) with a confidence interval of 95%. A *p*-value of <0.05 was considered statistically significant.

Results

Between March 15, 2020 and June 1, 2021, a total of 254 critically ill patients were admitted to the pandemic ICU. Of them 218 patients' real-time RT-PCR for SARS-CoV-2 were positive. Twelve patients did not meet the study inclusion criteria. After all, 206 patients were included to the study. Figure 1 shows the flow chart of the patients included to the study. The median age was 67 years [56-76] and 62% were male. The median APACHE II and SOFA scores were 16 [12-23] and 3 [2-6], respectively. The most common comorbidities recorded were diabetes mellitus (36%), hypertension (56%) and coronary artery disease (33%).

In 120 patients AKI developed in the first week of ICU admission. The patients with AKI were older (70 vs 60 years, p <0,001) and had a higher incidence of hypertension (69% vs 37%, p<0.001), diabetes mellitus (41% vs 28%, p = 0.04) and coronary artery disease (40% vs 23%, p <0.01) (Table 1). Patients with AKI had more severe illness as determined by APACHE II (20 vs 13, p <0.001) and SOFA (5 vs 2, p <0.001) scores. The PaO_2/FiO_2 ratio, that is the severity of acute hypoxic respiratory failure, was similar in the two groups (107 vs 130 mmHg, p = 0.15). However, the requirement for invasive mechanical ventilation (78% vs 29%, p <0.001) and vasopressor therapy (66% vs 40%, p<0.001) was higher in the AKI group. The percentages

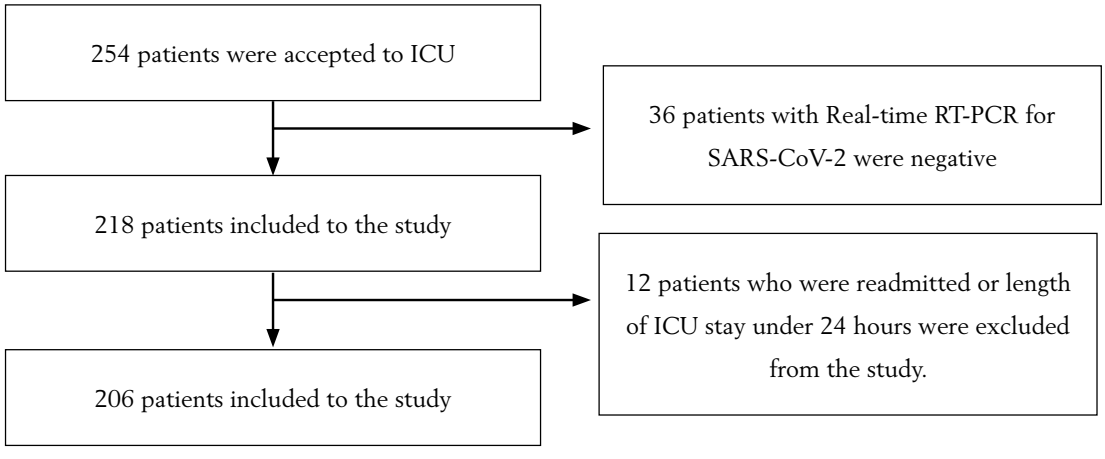

Figure 1. Flow diagram of patient selection and including to the study

Table 1. Patients' clinical characteristics and laboratory parameters

	AKI (n=120)	Non-AKI (n=86)	Total (n=206)	p
Age, years*	70 [63-77]	60 [49-72]	67 [56-76]	<0.001
Male**	74 (32)	54 (63)	128 (62)	0.87
APACHE II score*	20 [15-26]	13[10-18]	16 [12-23.5]	<0.001
SOFA score*	5 [3-7]	2 [2-4]	3 [2-6]	<0.001
Comorbidities**				
HT	83 (69)	31(37)	114 (56)	<0.001
DM	49 (41)	23 (28)	72 (36)	0.04
CAD	49 (40)	19 (23)	68 (33)	<0.01
Malignancy	23 (19)	13 (15)	36 (17)	0.45
CHF	20 (17)	8 (10)	28 (14)	0.12
COPD	17 (14)	17 (20)	34 (16)	0.28
Invasive mechanical ventilation**	94 (78)	25 (29)	119 (58)	<0.001
Vasopressor requirement**	79 (66)	34 (40)	113 (55)	<0.001
Steroid treatment**	84 (70)	63 (73)	147 (71)	0.61
Nephrotoxic agents**	73 (61)	27 (31)	100 (49)	<0.001
PaO_2/FiO_2, mmHg*	107 [66-166]	130 [83-193]	110 [75-171]	0.15
NLR*	10.5 [5-19]	9.4 [6-14]	10.1 [5.7-18.4]	0.32
CRP, mg/L*	128 [81-188]	116 [74-171]	119 [77-180]	0.38
D-dimer, ng/mL*	673 [331-2071]	398 [271-848]	512 [299-1193]	0.01
Ferritin, ng/mL*	503 [265-1086]	485 [260-1285]	494 [265-1099]	0.93
Admission creatinine, mg/dL*	1 [0.8-1.4]	0.8 [0.6-0.9]	0.9 [0.7-1.2]	<0.001
Length of ICU stay, days*	9 [6-24]	13 [5-18]	11 [6-22]	<0.01
Mortality**	81 (68)	10 (12)	91 (44)	<0.001

*median [25-75 percentiles] ** n (%)
Nephrotoxic agents include nonsteroidal anti-inflammatory drugs, intravenous contrast agent, aminoglycoside, colistin and vancomycin.
APACHE: Acute Physiology and Chronic Health Evaluation, **SOFA:** Sequential Organ Failure Assessment, **HT:** Hypertension, **DM:** Diabetes Mellitus, **CAD:** Coronary Artery Disease, **CHF:** Congestive Heart Failure, **COPD:** Chronic Obstructive Lung Disease, **CRP:** C-reactive Protein, **ICU:** Intensive Care Unit

of patients who received steroids were similar in both groups. On admission, patients with AKI had higher creatinine (1mg/dl vs 0.8 mg/dl, p<0.001) and D-dimer (673ng/ml vs 398 ng/ml, p=0.01) levels. C-reactive protein levels, ferritin levels, and neutrophil-lymphocyte ratio were similar in both groups. The clinical characteristics and laboratory parameters of all patients are presented in Table 1. In 31(26%) patients renal replacement therapy was required.

ICU mortality was higher in patients with AKI (68% vs 12%, p<0,001).

In univariate analysis (without adjustment), age, comorbidities (hypertension, and coronary artery disease), severity scores (APACHE II and SOFA), D-dimer, requirement on admission, vasopressor use, invasive mechanical ventilation, were revealed to be associated (p <0.1) with AKI (Table 1). In the multivariable logistic regression analysis, after including the variables mentioned above, hypertension (OR= 2.71, %95 CI=1.23- 5.95, p= 0.013), and need for invasive mechanical ventilation (OR= 8.15, %95 CI= 3.35-19.83, p<0.001) were found to be independently associated with AKI development (Table 2).

Table 2. Regression analysis results of risk factors for AKI development

Risk factor	OR	95% CI	p
Invasive mechanical ventilation	8.15	3.53-19.83	<0.001
Hypertension	2.71	1.23-5.95	0.013

In univariate analysis (without adjustment), age, comorbidities (hypertension, diabetes mellitus, coronary artery disease, chronic heart failure and malignancy), severity scores (APACHE II and SOFA), NLR, d-dimer, creatinine on admission, PaO_2/FiO_2, nephrotoxic agents, vasopressor use, invasive mechanical ventilation, renal replacement therapy were revealed to be associated (p <0.1) with ICU mortality (Table 3). In the multivariate logistic regression analysis, invasive mechanical ventilation requirement (OR= 31.65, %95 CI=6.53- 153.49, p<0.001), vasopressor treatment (OR= 4.20, %95 CI=1.24-14.19, p= 0.02), and acute kidney injury existence (OR= 9.03, %95 CI=2.86-28.56, p<0.001) were revealed as independent risk factors for mortality (Table 4).

Discussion

In this retrospective observational study, we determined that 58% of critically ill COVID-19 patients were diagnosed with AKI. Although patients with AKI had higher hypertension, diabetes mellitus and atherosclerotic heart disease incidence, only hypertension was established as a risk factor for AKI development. In addition, invasive mechanical ventilation requirement was found as a risk factor for AKI development. Furthermore, AKI was associated with increased mortality and length of ICU stay.

The rate of AKI incidence in the literature is reported to be between 20-80 % (1, 2, 5, 10-13). This range could be the result of divergent patient groups that were included in the studies. Patients who were admitted to the ICU had higher rates of

Table 3. Survivors' and non-survivors' clinical characteristics and laboratory parameters

	Total (n=206)	Survivors (n=115)	Non-survivors (n=91)	p
Age, years*	67 [56-76]	63 [51-72]	71[64-78]	<0.001
Male**	128 (62)	70 (61)	58 (64)	0.67
APACHE II score*	16 [12-23.5]	14 [10-18]	21 [16-28]	<0.001
SOFA score*	3 [2-6]	2 [2-4]	5.5 [4-8]	<0.001
Comorbidities**				
HT	114 (55)	55 (48)	59 (65)	0.02
DM	72 (35)	32 (28)	40 (44)	0.02
CAD	68 (33)	28 (24)	40 (44)	<0.01
Malignancy	36 (17)	13 (11)	23 (25)	<0.01
CHF	28 (14)	10 (9)	18 (20)	0.02
COPD	34 (16)	16 (14)	18 (20)	0.26
AKI**	120 (58)	39 (34)	81 (89)	<0.001
Invasive mechanical ventilation**	119 (58)	32 (28)	87 (96)	<0.001
Vasopressor requirement**	113 (55)	40 (35)	73 (80)	<0.001
Renal replacement therapy**	31 (15)	2 (2)	29 (32)	<0.001
Steroid treatment**	147 (71)	86 (75)	61 (67)	0.22
Nephrotoxic agents**	100 (49)	38 (33)	62 (68)	<0.001
PaO_2/FiO_2, mmHg*	110 [75-171]	136 [85-197]	94 [60-133]	<0.01
NLR*	10.1 [5.7-18.4]	9.5 [5.7-14.9]	11.3 [5.3-21.5]	0.06
CRP, mg/L*	119 [77-180]	116 [75-173]	130 [80-189]	0.58
D-dimer, ng/mL*	512 [299-1193]	433 [281-848]	811 [348-2448]	<0.01
Ferritin, ng/mL*	494 [265-1099]	479 [227-1144]	571 [272-1091]	0.44
Admission creatinine, mg/dL*	0.9 [0.7-1.2]	0.8 [0.7-1]	1.0 [0.8-1.4]	<0.01
Length of ICU stay, days*	11 [6-22]	9 [5-17]	16 [7-35]	<0.01

*median [25-75 percentiles] **n (%)
Nephrotoxic agents include nonsteroidal anti-inflammatory drugs, intravenous contrast agent, aminoglycoside, colistin and vancomycin.
APACHE: Acute Physiology And Chronic Health Evaluation, **SOFA:** Sequential Organ Failure Assessment, **HT:** Hypertension, **DM:** Diabetes Mellitus, **CAD:** Coronary Artery Disease, **CHF:** Congestive Heart Failure, **COPD:** Chronic Obstructive Lung Disease, **AKI:** Acute Kidney Injury, **PaO_2/FiO_2:** Arterial Oxygen Partial Pressure to Fractional Inspired Oxygen Ratio, **NLR:** Neutrophil to Lymphocyte Ratio, **CRP:** C-reactive Protein, **ICU:** Intensive Care Unit

Table 4. Regression analysis results of risk factors for mortality

Risk factor	OR	95% CI	p
Invasive mechanical ventilation	31.65	6.53-153.49	<0.001
Vasopressor treatment	4.21	1.14-14.19	0.02
Acute kidney injury	9.03	2.86-28.56	<0.001

AKI than those were hospitalized at the wards (5). Some of the studies included all COVID-19 patients who were admitted to the hospital whereas this study constituted of critically ill patients with higher risk of organ failure. As well as those including critically ill patients reported similar AKI incidence rates, even some of them had higher rates (1-3, 10, 12, 14). Additionally, some studies planned to evaluate patients according AKI stage and reported the incidence of AKI stage II-III or only AKI stage III (3, 13). We could not define AKI stages as a consequence of missing urine output data.

Evaluation of risk factors is important to tailor monitoring and set up prevention, as well as to improve early treatment schemes for patients who will benefit the most from intervention. In a retrospective cohort from Brasil, Doher et al reported higher baseline creatinine levels, diuretic use and invasive mechanical ventilation as risk factors for AKI development in COVID-19 patients (2). In another retrospective multicenter study from Paris, Geri et al. showed that chronic kidney disease existence, need for invasive mechanical ventilation as well as administration of vasopressors at day 1 were risk factors for AKI (1). Hirch et al. expressed that, patients who needed mechanical ventilation developed AKI at a significantly higher rate than those who did not need mechanical ventilation (89.7% vs 21.7%) in a multicenter cohort study from New York (11). In addition, they reported older age, hypertension, male sex as risk factors for AKI development (11). In a retrospective study, Chaibi et al described a critically ill patients' group with COVID-19 in which invasive mechanical ventilation requirement was associated with a higher incidence of KDIGO stage III AKI (26%) (15). Still, some studies reported that older age, nephrotoxic drug administration and need for vasopressor treatment as risk factors for AKI (1, 3, 14). In univariate analysis these factors were significantly higher in AKI patients but in multivariate analysis these factors were not significant. It was

shown that invasive mechanical ventilation requirement and/or hypertension were risk factors for AKI development in our retrospective cohort. Invasive mechanical ventilation requirement can be a clue for more severe disease. Furthermore, positive pressure ventilation can be a cause of hemodynamic instability and subsequently a decrease in renal perfusion which creates a tendency for AKI.

We know that AKI, especially in critically ill patients, is associated with increased mortality. In their retrospective cohort of 339 COVID-19 patients, Marques et al. expressed that AKI which occurred during hospital admission was an independent predictor of mortality (13). In another prospective study Piñeiro et al. demonstrated higher mortality rate in COVID-19 patients with AKI (16). In this study mortality rate was reported as 50% and patients with AKI had a longer ICU stay compared to patients without AKI (16). Similarly our study revealed that mortality was higher in patients with AKI (68% vs 12%) and length of ICU stay was longer than patients without AKI.

There are some limitations in our study. First, as a result of the retrospective design urine output data were missing in this cohort. As a consequence of the lack of urine output information of the patients the actual incidence of AKI may have been underestimated Second, we could not define AKI stages. However, we included only critically ill patients and we tried to include most of the confounders related to the patient and treatments applied in the ICU related to AKI development. Third, it was a single center study which was performed in a university hospital. Thus, this study can not be generalized, since it could include selection bias.

Conclusion

We found that AKI had a higher incidence in critically ill COVID-19 patients, as well it was associated with higher mortality. Hypertension and invasive mechanical ventilation requirement were found to be independent risk factors for AKI development. Especially in critically ill patients with AKI, close monitoring is needed for patients with risk factors to decrease mortality.

AUTHOR CONTRIBUTIONS:

Concept: LF, IAT, NDA; **Design:** LF, NDA; **Supervision:** LF, NDA; **Data Collection and/or Processing:** LF, IAT, NDA; **Analysis and/or Interpretation**: LF,NDA; **Literature Search:** LF, IAT; **Writing Manuscript**: LF, IAT; **Critical Review:** LF, NDA.

Ethics Committee Approval: Ankara University Ethical Committee date February 23, 2021 and number 2021/211

Informed Consent: Retrospective study

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

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