HOSPITAL CHRONICLES 2021, 16(1): 10–15

ORIGINAL ARTICLE

Acute Kidney Injury in Patients with COVID – 19 Infection: A Tertiary Referral Hospital Experience

Christina-Danai Skondra[1], Dimitra Kozikopoulou[1], Theodora Oikonomaki[1], Myrto Giannopoulou[1], Glykeria Tsouka[1], Eleni Magira[2], Elias Siempos[2], Stefanos Kokkoris[2], Spyridon Zakynthinos[2], Christaleni Christodoulidou[1]

[1]*Department of Nephrology, «Antonios G. Mpillis», Evagellismos General Hospital, Athens, Greece*
[2]*Department of Intensive Care Medicine, Evagellismos General Hospital, Athens, Greece*

KEY WORDS: *COVID 19, acute kidney injury, renal replacement therapy*

Correspondence to:
Dr. Christina-Danai Skondra
Department of Nephrology,
Evagelismos General Hospital,
45-47 Ipsilantou street,
10676, Athens, Greece
E-mail: christinadsc@hotmail.com

Manuscript received February 12, 2021;
Revised manuscript received May 17, 2021;
Accepted June 23, 2021

ABSTRACT

The emersion of the new coronavirus SARS COV 2 (Severe Acute Respiratory Syndrome Coronavirus 2) was rapidly characterized as a pandemic by WHO. The major manifestation of the virus is respiratory distress; however, the involvement of other organs should not be overlooked. The kidney is one of the most important target organs of the specific virus with acute kidney injury (AKI) described in 5-36% of COVID positive patients and an average 25% within the severely ill.

PURPOSE: The purpose of this study was to consider the incidence of AKI in patients with COVID 19 in our cohort and to better understand risk factors associated with AKI. Further, we wanted to investigate the impact of AKI on survival and in hospital mortality.

METHODS: Patients admitted to Evagelismos General Hospital with confirmed COVID-19 infection from 11th March until 22th May were investigated. Patients 18 years old as well as transplanted patients were excluded from this study. AKI was defined according to the AKI criteria.

RESULTS: From 99 patients with COVID-19 infection, AKI occurred in 41 (41.4%). A total of 44 patients (44.4%) were admitted to Intensive Care Unit (ICU) and 31 of them (70.5%) developed AKI. Of the 44 patients with AKI, 16 (39%) required renal replacement therapy. Hospital mortality, in total, was 16.2% (37% among patients with AKI versus 0.02% among those without AKI, p=0.000).

CONCLUSION: AKI was common among patients hospitalized with COVID 19. AKI was associated with older age, clinical severity and existing CKD.

INTRODUCTION

The outbreak of COVID 19, which was initially reported in Wuhan, China as a rising number of cases of unknown origin pneumonia had rapidly a pandemic spread worldwide. Severe Acute Respiratory Syndrome coronavirus 2 (SARS-COV-2) is a

Conflict of Interest: none declared

novel coronavirus belonging to the already known beta coronavirus cluster associated with the Severe Acute Respiratory Syndrome (SARS) and the Middle East Respiratory Syndrome (MERS) and consists the pathogen of coronavirus disease (COVID 19)[1,2]. Since initial detection more than 140 million cases have been confirmed to date. The clinical spectrum of COVID 19 can range from asymptomatic to severe disease with critical illness and high mortality. Although pulmonary complications are the initial clinical sign and the leading cause of admission to an Intermediate Care Unit (ICU) with a consequent high mortality, many other organs may also be affected. There is growing evidence that acute kidney injury is prevalent in COVID-19 patients and its presence is associated with poor prognosis[3,4]. In already published studies the percentage of patients hospitalized with COVID-19 presenting AKI ranges from 5 to 36 %, while approaches a rate of 90% among patients on mechanic ventilation[3]. In Greece the first case of a 38 year old female patient with travel history to northern Italy was reported on the 26th of February. To date more than 300.000 cases and 3092 deaths have been reported in Greece.

Aim of this study was to define the incidence of AKI among patients with COVID-19 and define predisposing risk factors indicating potential approaches for risk stratification.

MATERIALS AND METHODS

PATIENTS

In March 2020 and after the first reported cases of COVID-19 infection in Greece, Evagelismos General Hospital was designated as one of the reference hospitals in Athens for treatment of COVID-19 patients. Critically ill patients were hospitalized under isolation precautions in an intensive care unit (ICU) while patients with mild or moderate disease were admitted in an isolated ward. The study was approved from the medical ethical committee of Evagelismos General Hospital (Approval Number 156) while oral consent was obtained from all patients or relatives. The different clinical categories for the severity of the disease and the definition of COVID-19 infection were defined according to the WHO guidelines[5]. Patients younger than 18, those with end stage kidney disease on hemodialysis or peritoneal dialysis and kidney transplant recipients were excluded from the study.

STUDY DEFINITIONS

Symptomatic patients without evidence of viral pneumonia or hypoxia were considered to have mild disease while those with clinical signs of pneumonia such as fever, cough, dyspnea, shortness of breath but no signs of severe pneumonia, including SpO_2 ≥90% on room air had a moderate disease. For severe pneumonia the presence of clinical signs of pneumonia plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress or SpO_2 <90% on room air was mandatory. ARDS, sepsis or septic shock with persistent hypotension despite volume resuscitation requiring vasopressors with organ dysfunction caused by a dysregulated host response to infection were present in critically ill patients.

AKI was identified using KDIGO (Kidney Disease Improving Global Outcomes) definition. Defined when serum creatinine increases by 0.3 mg/dl or more in 48 h or rises to at least 1.5-fold from baseline within 7 days.

The collected information included demographic data, exposure history, medication, comorbidities, chest computer tomography reports and treatment. The day on which symptoms appeared was defined as the onset date. The clinical outcomes were documented until May, the 22nd.

The baseline characteristics on hospital admission are listed on table 1.

STUDY DESIGN AND COHORT

In this retrospective, single center study we analyzed data from electronic medical records. We obtained epidemiological, clinical, laboratory and radiological data and renal outcomes of 99 patients with COVID-19 admitted from March 11th to

TABLE 1. Baseline demographic characteristics, comorbidities and laboratory findings on hospital admission, BMI, body mass index, DM diabetes mellitus, CAD Coronary artery disease, COPD chronic obstructive pulmonary disease, HF heart failure

	COVID +		
	AKI	**non AKI**	**p-value**
Sex (male, %)	31 (75.6)	35 (60.3)	0.08
Age (sd)	69.35 (12)	59.45 (16)	0.001
BMI (sd)	28.2 (3.6)	28.4 (5.8)	NS
DM (%)	12 (29.3)	5 (0.09)	0.01
Dyslipidemia (%)	20 (49)	14 (25)	0.025
CAD (%)	9 (22)	5 (0.09)	0.07
COPD (%)	6 (14.6)	4 (0.07)	NS
HF (%)	12 (29.3)	3 (0.05)	0.001
Smoke (%)	10 (25.6)	11 (21.6)	NS
CKD-EPI (sd) ml/min	64 (27.7)	89.9 (21.85)	0.000
Hb (sd) g/dl	11.98 (2.3)	12.8 (1.85)	0.075
Ferritin (sd) ng/ml	221.6 (195.4)	272.31 (322.3)	NS
CRP (sd) mg/l	13.5 (11.8)	9.1 (10)	0.065

May 22nd. COVID-19 was present on admission or diagnosis was confirmed during hospitalization. Real time PCR (Polymerase chain reaction) testing of a nasopharyngeal sample for COVID-19 was performed either in our hospital or in the Hellenic Pasteur Institute. As primary end point was defined AKI during hospitalization.

STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS 24.0 program. Baseline characteristics were described using mean ± standard deviation (SD) for continuous variables or frequencies with percentage for categorical variables. Continuous variables were compared between groups using the student's *t*-test or ANOVA, as appropriate. Categorical variables were compared between groups using the Chi-squared test. AKI-censored survival outcomes were estimated using the Kaplan–Meier method with significance tested using the log-rank test. Multivariable analysis was performed to adjust for covariates associated with outcomes of interest with $p < 0.05$ in univariate analysis. All *p*-values were two-tailed, and *p*-values of <0.05 were considered significant.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

A total of 99 patients (67% men and 33% women) with confirmed COVID 19 infection were included in the study with mean age (63.57 ± 15.3 years). 44 of the confirmed cases were admitted in an ICU while 55 in an isolated ward. The mean age was 66.56 ± 10.2 years for the ICU patients (35 men, 79.5%) and 61.5 ± 18 for the non ICU patients respectively (Figure 1).

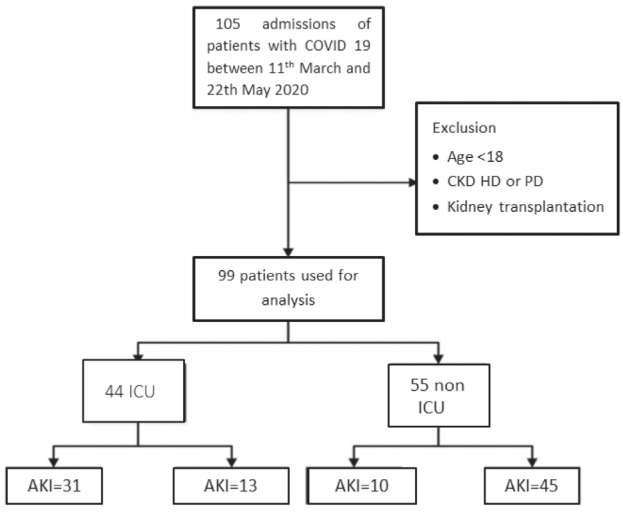

FIGURE 1. Flowchart showing the study population, AKI acute kidney injury, COVID 19, Coronavirus Disease 19.

CLINICAL MANIFESTATIONS AND COMORBIDITIES

The symptoms on admission are shown in Table 2. We studied various baseline characteristics on our cohort. Potential risk factors predicting AKI was the age and the CKD- EPI on admission (p 0.001 and 0.000 respectively). Factors like the median time from symptoms onset, admission, PCR testing to developing AKI or exposure history had no impact on development of AKI.

From the reported comorbidities dyslipidemia and diabetes were positively correlated with AKI (0.025 and 0.010 respectively) while other factors like BMI, sex and smoking had no correlation.

From the symptoms on admission fatigue (p-value 0.031), diarrhea (p-value 0.032), dyspnea (p-value 0.045) and vomiting (p-value 0.028) were positive correlated with AKI in our cohort. All patients with AKI had received an antibiotic pretreatment (p-value 0.000).

LABORATORY AND RADIOLOGICAL PARAMETERS

Extended laboratory testing was performed on admission. Except of the CKD- EPI on admission, which was positively correlated with the development of AKI, the remaining tested laboratory values had no statistical significance with the development of acute kidney injury. On figure 2 is documented the mean creatinine value for ICU and non ICU patients in 5- day intervals. There was a trend for higher ferritin levels on

TABLE 2. primary symptoms on hospital admission and statistical significance.

Primary Symptoms	COVID +		
	ICU (%, total)	Non ICU (%, total)	p-value
Cough	28 (28.3)	32 (32.3)	NS
Sputum	10 (10.3)	8 (8.2)	NS
Anosmia	0	1 (1)	NS
Ageusia	0	1 (1)	NS
Myalgia	2 (2)	2 (2)	NS
Fatigue	11 (11.1)	6 (6.1)	0.057
Diarrhea	4 (4.1)	9 (9.3)	NS
Fever	41 (42.3)	52 (53.6)	NS
Dyspnea	32 (33)	21 (21.6)	0.000
Nausea/Vomit	3 (3.1)	7 (7.2)	NS

admission with severe outcomes but not statistical significant.

All patients had a chest X ray on admission and most of them a Computer tomography during hospitalization. The typical findings were bilateral pulmonary infiltrates in 68.2% of the patients, ground glass opacities in 20.5% and consolidation in 6.8%. Only five patients who were not critically ill and were hospitalized in the isolated ward had no radiological findings.

CLINICAL OUTCOMES

AKI was reported in 41 COVID patients (41.4%), 31 of them (31.3% of our total cohort) hospitalized in the ICU. The mean age of the COVID patients who developed AKI was 69.35±12.1 years, statistically significant higher from COVID patients who did not develop an AKI (59.45 ± 16.1 y, p-value 0.001). The same age difference was also reported to the ICU patients with those presenting AKI being older than the patients who preserved their kidney function (p 0.035). 47% developed AKI stage I, 3% AKI Stage II and 50% AKI Stage III. The mean time of development of AKI after hospital admission was 8.3±10.3 days for the whole cohort and for the ICU patients was 12.37±10 days.

Sixteen patients required renal replacement therapy. All of them were critically ill. The modality utilized was continuous renal replacement therapy (CRRT). The mean time of initiation of CRRT from the onset of respiratory failure and mechanic ventilation was 2.32±5.12 days.

From the ICU 27 patients (61.4%) developed sepsis, 19 (43.2%) septic shock defined as persistent hypotension despite volume resuscitation requiring vasopressors with organ dysfunction caused by a dysregulated host response to infection. All of them developed respiratory failure and required mechanic ventilation. All mentioned factors were positively correlated with AKI (p-value 0.000). The days from admission until sepsis onset and consequently the severity of the disease were negative correlated with presence of AKI (p value 0.037). 15 patients from our cohort died (16.2%), 14 of them in ICU.

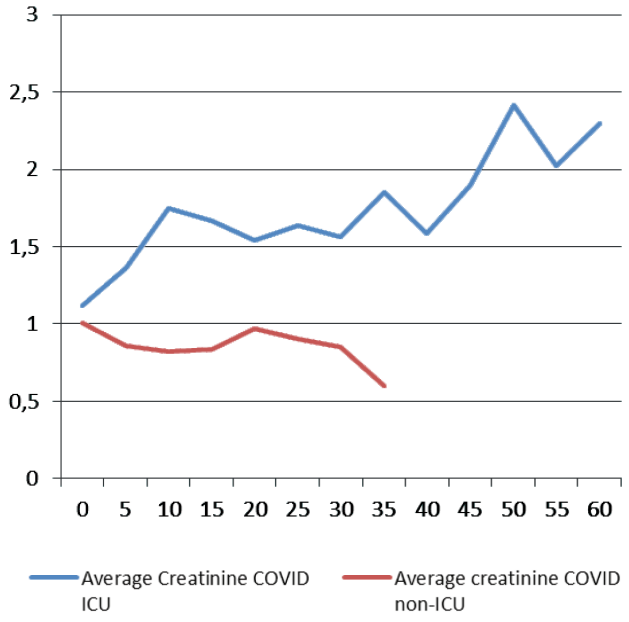

FIGURE 2. Course of average creatinine values for ICU and non ICU patients in 5-day intervals after admission.

DISCUSSION

Although SARS COV 2 preferentially affects the respiratory tract, kidney involvement is frequent with clinical presentation ranging from mild proteinuria and hematuria to progressive acute kidney injury[6]. In CRTs the percentage of acute kidney injury varies from 5 to 36 %[3,7]. This variation may be explained in part by varying populations and percentage of severely ill patients in the cohorts or hospital practices and differences on admission threshold.

In our cohort 41% of the admitted patients with COVID 19 developed AKI while 44% of them were critically ill. 16% of COVID patients with AKI died. The impact of AKI on mortality was demonstrated in previous reports showing that the proportion of patients with severe outcomes is high in patients with AKI and severe disease. The incidence of AKI was higher in older patients and in those with elevated baseline creatinine (p value 0,001 and 0,000 respectively) suggesting that greater age and kidney disease on admission are both associated with poor outcomes, finding in keeping with previous studies[6]. A prospective study in China with 701 patients admitted in a tertiary teaching hospital showed that AKI occurred in 5.1% while the incidence of in hospital death was higher for patients with elevated baseline creatinine on admission[4]. Most of the cases of AKI occurred within 7 days.

The mean time period from the symptoms onset to development of AKI in our cohort was 12.37±10.7. Monitoring of kidney function and awareness of AKI is therefore important and earlier admission or consultancy of a health care professional may prevent negative clinical outcomes

The pathogenesis of AKI could be the result of the synergistic effect of the renal tropism of SARS COV-2 and the cytokine induced systemic inflammatory response in severe disease. Acute tubular necrosis (ATN) has been the predominant lesion described in multiple histopathologic series.

Arterial underfilling and tissue hypoxia due to multiorgane failure and shock and also drug toxicity and administration of contrast fluid as well as additive prerenal factors through volume depletion could contribute to development of AKI. Autopsy studies have confirmed with immunohistochemistry the presence of SARS-CoV-2 nucloeocapsid protein in the renal tubule[8,9]. Moreover, the receptor of SARS-CoV-2, (angiotensin converting enzyme) ACE2 was found to be upregulated in patients with COVID-19. The viral spike protein

binds to ACE 2 receptors and this interaction facilitates entry of the virus in the human cells. ACE 2 gene is expressed in the kidney[10] while Wrapp et al described that the affinity of SARS COV 2 to the ACE2 receptor is 10-20 times higher than the one of SARS COV[11]. The role of cytokine releasing syndrome in developing of AKI is still to be elucidated.

The contribution of each of the previously announced factors to the pathogenesis of AKI is still to be clarified.

We confirmed that several comorbidities were independent risk factors for AKI.

Nineteen (19) % of patients in our study had diabetes Typ II, 43% hypertension and 17% Coronary Heart Disease. Variations in the prevalence of comorbidities have been reported in previous reports[17]. (Three) 3% of our patients were treated with ACE inhibitors (ACEI) and 28% with Angiotensin receptor blockers (ARB) according to the current guidelines. Both drug groups are shown to increase the ACE2 expression in the kidney and the heart (2-5 fold)[18,19]. It still remains controversial whether the use of these drugs could predispose to more severe illness. Angiotensin II is catalyzed by ACE 2 to angiotensin (1-7) with anti-inflammatory and vasodilatory effects[20]. Many studies could not support a negative prognosis while other studies have suggested that ACE inhibitors may upregulate the expression of ACE2, exacerbate the anti-inflammatory effects and lead to more severe infection[21-23].

Our data could not support worse outcomes for patients in ACEI or ARB. The official statement by the European Society of Hypertension (ESH) and Cardiology (ESC) is the critical use of these agents in patients with reduced renal function and hemodynamic instability. From the other side, RAAS blockers should not be discontinued when indicated in stable patients with confirmed COVID 19 infection.

From the patients with AKI in our study 16 (39%) required RRT, which was delivered as continuous renal replacement therapy (CRRT). All of the patients needed CRRT were hospitalized in the ICU. From the non ICU patients only one developed AKI Stage III but did not need renal replacement therapy.

The proportion of patients needed CRRT ranges from 1.5-9 % in cohorts, while in severely ill patients the percentage can rise to 5.2-25 %[1,6,13].

Ronco et al describe the extracorporal modalities used for blood purification[14].

CRRT or slow low efficiency dialysis (SLED) if available has been practiced in many sepsis patients on mechanic ventilation. Intermittent hemodialysis is not preferred in the setting of isolation and the hemodynamic instability presenting in severely ill patients[15]. Cytokine adsorption columns for patients with cytokine releasing syndrome and their potential in removing inflammatory agents can be used for the treatment of severe COVID-19[16].

Our study has some notable limitations. Incomplete documentation and lacking data of the exposure history and the symptoms on admission especially in cases diagnosed in outpatient setting was due to the retrospective design of our study inevitable. At the time of data extraction 5 severely ill patients were still hospitalized and the outcomes considered were the outcomes of the time of the analysis. Moreover we did not have access to urine analysis results and therefore we could not provide data regarding proteinuria and hematuria. Due to the relatively short observation period we were unable to obtain long term outcomes.

CONCLUSION

The incidence of AKI in COVID 19 patients is high and is associated with comorbidities such as diabetes and chronic kidney disease. Hospital mortality and severe outcomes are significantly higher in AKI patients.

Patients with COVID 19 should be closely monitored during hospitalization for the development of AKI. Further studies may elucidate new markers for early detection of kidney damage and determine a more effective clinical approach.

REFERENCES

1. Zhu N, Zhang D, Wang W et al. A novel coronavirus from patients with coronavirus in China. *NEJM* 2020; 382:727–733.
2. Sun P, Lu X, Xu C et al. Understanding of COVID-19 based on current evidence. *J Med Virol* 2020; 92:548–551.
3. Hirsch JS, Ng JH, Ross DW et al. Acute kidney injury in patients hospitalized with COVID 19. *Kidney International* 2020; p.p. 209-218.
4. Cheng Y, Luo R, Wang K et al. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney International* 2020; p.p. 829-838.
5. *WHO*. Clinical management of severe acute respiratory infection when novel coronavirus (2019 nCOV2) infection is suspected: interim guidance. 2020, January.
6. Huang C, Wang Y, Li X, et al Clinical features of patients infected with COVID 19 novel infection in Wuhan, China. *Lancet* 2020; 395:467-506.
7. Mohamed MMB, Lukitsch I, Torres-Ortiz AE et al**.** Acute kidney injury associated with coronavirus disease in Urban, New Orleans. *Kidney Int* 2020; 360.
8. Hua Su, Ming Yang, Cheng Wan et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; 98:219-227.
9. Diao B, Wang C, Wang R et al, Human kidney is a target for novel severe acute respiratory syndrome virus (SARS COV 2). *Nat Commun* 2020; 12:2506.
10. Sreedhar Adapaa J, Avantika Chennab, Mamtha Balla et al. *COVID-19* Pandemic Causing Acute Kidney Injury and Impact in Patients woth chronic kidney disease and renal Transplantation. *J Clin Med Res* 2020; 12:352-361.
11. Wrapp D, Wang N, Corbett KS et al. Cryo-EM structure of

the 2019 nCOV Spike in the prefusion conformation. *Science* 2020; 367:1260-1263.
12. Liu R, Miller J. China approves use of Roche drug in battle against coronavirus complications. *Reuters* 2020.
13. Guan WJ, Ni ZY, Hu Y et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *NEJM* 2020; 382:1708-1720.
14. Ronco C, Navalesi P, Vincent JL et al.Coronavirus epidemic: preparing for extracorporeal organ support in intensive care. *Lancet Resp Med* 2020; 8:240-241.
15. Expert opinion on CRRT application in the treatment of new coronavirus. National Center for Professional Medical Quality Management and Control of Nephropathy, blood purification therapy and engineering Technology Branch of the Chinese Medical Advocacy Council and the blood purification therapeutic Comittee of the Army. 2020.
16. Gang Chen, Yangzhong Zhou, Jie Ma et al. Is there a role for blood purification therapies targeting cytokine storm syndrome in critically severe COVID-19 patients? *Renal Failure,* 2020;42:483-488.
17. Remuzzi A, Remuzzi G. COVID-19 and Italy: what's next. *Lancet* 2020; 395:1225-1228.
18. Ishiyama Y, Gallagher PE, Averill DB, Tallant AE, Brosnihan BK, Ferrario CM. Upregulation of angiotensin converting enzyme 2 after myocardial infarction by blockade of angiotensin II receptors. *Hypertension* 2004; 43:970-976.
19. Ferrario CM, Jessup J, Chappell MC et al. Upregulation of angiotensin converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin converting enzyme. *Circulation* 2005; 111:970-976.
20. Li XC, Zhang J, Zhuo JL et al. The vasoprotective axes of the renin-angiotensin system: physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacol Res* 2017; 125:21-23.
21. Mancia G, Rea F, Ludergnani M et al. Renin-angiotensin-aldosterone blockers and the risk of COVID 19. *N Engl J Med* 2020. NEJMoa2006923
22. de Abajo FJ, Rodríguez-Martín S, Lerma V et al. Use of renin-angiotensin-aldosterone system inhibitors and risk of COVIS 19 requiring admission to hospital: a case population study. *Lancet* 2020; 395:1705-1714.
23. Peng Z, Zhang, Lihua Zhu et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID 19. *Circ Res* 2020; 126:1671-1681.