10.5152/turkjnephrol.2020.4448

Original Article

Turkish Journal of Nephrology

Acute Kidney Injury in SARS-CoV-2 Infected Critically Ill Patients

Kürşat Gündoğan[1], Şahin Temel[1], Burcu Baran Ketencioğlu[2], Belal Rabah[2], Nuri Tutar[2], Murat Sungur[1]

[1]Division of Intensive Care, Department of Medicine, Erciyes University School of Medicine, Kayseri, Turkey
[2]Division of Intensive Care, Department of Chest Diseases, Erciyes University School of Medicine, Kayseri, Turkey

Abstract

Objective: The main objective of this study is to evaluate the frequency of acute kidney injury (AKI) in COVID-19 infected patients who are hospitalized in the intensive care unit (ICU).
Materials and Methods: This study was performed retrospectively on patients above 18 years of age who had a positive polymerase chain reaction (PCR), a typical chest computed tomography (CT) for COVID-19 disease. The patients were hospitalized in the medical ICU and kidney disease improving global outcomes (KDIGO) criteria was used for AKI classification.
Results: We included 16 patients. The median age was 75 years and 88% were male. The most common co-morbid diseases were hypertension (HT) (56%) and cardiovascular disease (CVD) (44%). The median acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were 26 (19-32) and 7 (4-9) respectively. Patients median serum blood urea nitrogen (BUN) and creatinine levels were 27.8 (19.2-44.7) mg/dL, 1.32 (0.97-2.81) mg/dL respectively. According to the KDIGO classification: there was no AKI in 25% of the patients while, 19% stage 1, 12% stage 2 and 44% stage 3 AKI was observed. AKI developed in 75% of the patients.
Conclusion: In this study we detected a high frequency of AKI in SARS-CoV2 infected patients hospitalized in the ICU.
Keywords: Acute kidney injury, COVID-19, critically ill patients, intensive care, SARS-CoV-2

Corresponding Author: Kürşat Gündoğan ✉ kgundogan@erciyes.edu.tr
Received: 02.06.2020 **Accepted:** 16.06.2020

Cite this article as: Gündoğan K, Temel Ş, Baran Ketencioğlu B, Rabah B, Tutar N, Sungur M. Acute Kidney Injury in SARS-CoV-2 Infected Critically Ill Patients. Turk J Nephrol 2020; 29(3): 185-9.

INTRODUCTION

In December 2019 SARS CoV-2 was seen for the first time in Hubei province, Wuhan city, China (1-4). After that the virus quickly spread throughout the world. On the 11th of March 2020 this virus was declared as a pandemic by the World Health Organization (WHO). The SARS CoV-2 virus shows initial signs/symptoms such as fever, cough and dyspnea (3). About 5-14.2% of the patients hospitalized in the ward may later on need to be admitted to the ICU due to deterioration of the clinical condition especially caused by respiratory failure and/or pneumonia (3, 5, 6). As clinical experience and knowledge increased we came to know that SARS Cov-2 infection affects the vascular, cardiac, hepatic and renal organs (7-10). In post-mortem biopsies it was observed that COVID-19 disease not only directly affects the kidneys but also affects them indirectly by causing multiple organ failure (1, 11, 12).

The frequency of AKI in hospitalized SARS CoV-2 infected patients varies from 3-36.6% (4, 8, 11, 13). Kidney involvement in these patients was determined as an increased risk factor for mortality (13, 14). In order to develop future treatments it is important to detect kidney involvement in these patients. There are few studies in which AKI is classified according to the KDIGO guidelines, especially in critically ill patients (1).

The primary objective of this study is to determine the frequency of AKI in ICU hospitalized COVID-19 infected patients.

As for the secondary objective we aim to determine the demographics, laboratory and clinical features of these patients.

MATERIALS AND METHODS

This study was performed in Medical and Pulmonology ICU on COVID-19 positive patients. The medical charts of hospitalized patients who were in the ICU were reviewed retrospectively between 20th of March 2020 and 28th May 2020. The information was obtained from the patient files and the hospital electronic record system. The ethics committee approval was received for this study from the Local Research Ethics Committee of Erciyes University School of Medicine (Approval Date: April 06, 2020; Approval Number: 2020- 199).

Patients included were over 18 years of age, hospitalized in the ICU for more than 24 hours, diagnosed with COVID-19 disease with positive PCR test and with a typical chest CT. Patients diagnosed with pneumonia in the ICU with a negative COVID-19 test and an atypical/vague chest CT were excluded.

On the day of hospitalization the age, sex, Glasgow coma scale (GCS), APACHE II score and co-morbid diseases were recorded. Upon ICU hospitalization blood tests were performed and white blood count (WBC), lymphocyte count, hemoglobin, platelet count, BUN, creatinine, sodium (Na), potassium (K), ferritin, D-dimer, troponin, fibrinogen, C-reactive protein (CRP) and procalcitonin results were recorded.

The medications given to the patient were recorded as COVID-19 specific medications and other drugs. The duration of mechanical ventilation (MV), need for renal replacement treatment therapy, SOFA score, PaO2/FiO2 index, need for prone positioning, use of cytokine filter, total length of ICU stay and mortality were also recorded.

Diagnosis

COVID-19 diagnosis was verified by at least two positive real-time PCR tests and by one positive antibody test. Laboratory confirmation for SARS-Cov-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction (RTPCR) assay of nasal, pharyngeal swabs or endotracheal aspirate according to the WHO guideline (15). According to the Radiological Society of North America classification, patients with a typical COVID-19 chest CT were considered as disease positive (16).

Whether these patients developed AKI was examined every day during their days of ICU stay. AKI was diagnosed according to KDIGO criteria (17).

Statistical Analysis

All statistical analyses were calculated using the IBM Statistical Package for the Social Sciences software version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Data was reported as interquartile range, median (IQR, 25%-75%) for all parameters. The chi-square test was used to determine significant differences in rates between categorical variables. $p<0.05$ was considered statistically significant.

RESULTS

Sixteen patients were enrolled in the study 12 (75%) of whom had a positive PCR and the other 4 (25%) patients had a typical COVID-19 chest CT. The median age was 75 (65-77) years and 88% of the patients were male. The most common co-morbid diseases were HT (56%) and CVD (44%). The median APACHE II and SOFA scores were 26 (19-32) and 7 (4-9) respectively. Patient's median BUN and creatinine levels were 27.8 (19.2-44.7) mg/dL and 1.32 (0.97-2.81) mg/dL. Median ferritin level was 579 (342-916) ng/mL. The median WBC and lymphocyte count were 6.39 (4.76-12.19) 10^3/µL and 0.97 (0.58-1.30) 10^3/µL, respectively. When the blood gas was analyzed upon ICU hospitalization the median Pa02/Fi02 ratio was 181 (112-250).

All patients received hydroxychloroquine therapy, 75% of the patients received oseltamivir and 88% received favipiravir. All patients received azithromycin and/or levofloxacin which are drugs used in the treatment of atypical bacterial infection.

During follow-up, 9 patients (56%) were placed in the prone position. Immune plasma treatment was applied to 5 patients (31%). MV was performed on 13 patients (88%) and 6 patients (38%) needed renal replacement therapy. The median length of ICU stay was 14 (7-20) days. ICU mortality rate was 62%. Detailed demographic, laboratory and clinical information are given in Table 1.

When the patients were evaluated according to the KDIGO classification: while AKI did not develop in 25% (4 patients), stage 1 AKI in 3 patients (19%), stage 2 AKI in 2 patients (12%) and stage 3 AKI in 7 patients (44%) were detected (Figure 1). During follow-up, 75% of patients developed AKI. Survivors and no survivors were compared according to AKI staging but no statistically significant difference was seen between them ($p=0.098$). Six (38%) of the patients who developed AKI stage 3 died (Table 2).

Main Points

- The rate of AKI was found to be high in SARS-CoV-2 infected critically ill patients.
- SARS-CoV-2 infected critically ill patients has older age and male gender.
- The most common co-morbid disease were HT and CVD.
- SARS-CoV-2 infected critically ill patients ICU mortality rate has been observed higher than other ICU patients.

Table 1. Patients demographic, laboratory and clinical characteristics

	Patients N=16
Age (IQR), year	75 (65-77)
Gender, n(%)	
Male	14 (88)
Female	2 (12)
Co-morbid disease, n(%)	
HT	9 (56)
DM	4 (25)
CVD	7 (44)
COPD	2 (12)
CRF	2 (12)
Malignancy	2 (12)
APACHE II score (IQR)	26 (19-32)
SOFA score (IQR)	7 (4-9)
GC score (IQR)	6 (3-15)
BUN (IQR), mg/dL	27.8 (19.2-44.7)
Creatinine (IQR), mg/dL	1.32 (0.97-2.81)
Na (IQR), mmol/L	137 (133-139)
K (IQR), mmol/L	4.44 (3.99-4.78)
Ferritin (IQR), ng/mL	579 (342-916)
D-Dimer (IQR), µg/L	990 (612-3402)
Fibrinojen (IQR), µg/L	408 (305-580)
Troponin (IQR), ng/mL	0.025 (0.011-0.208)
Hb (IQR), g/dL	12.55 (11.05-14.75)
WBC (IQR), 10^3/µL	6.39 (4.76-12.19)
Lenfosit (IQR), 10^3/µL	0.97 (0.58-1.30)
Thrombosit (IQR), 10^3/µL	177.5 (109.5-229.75)
CRP (IQR), mg/L	80.68 (44.0-11.75)
Procalcitonin (IQR), ng/mL	0.230 (0.067-0.330)
PaO_2/FiO_2	181 (112-250)
Hidroksicloroquine, n (%)	16 (100)
Oseltamivir, n (%)	12 (75)
Azitromicin/Levofloxacin, n (%)	16 (100)
Favipiravir, n (%)	14 (88)
Lopinavir/Ritanavir, n (%)	6 (38)
Prone position, n (%)	9 (56)
Convelecan plasma, n (%)	5 (31)
Cytokine filters, n (%)	3 (19)
Need for MV, n (%)	13 (81)
Renal replasman therapy, n(%)	
IHD	3 (19)
CVVHDF	3 (19)
Length of ICU stay, (IQR) day	14 (7-20)
ICU mortality, n (%)	10 (62)

IQR: interquartile range (25%-75%); HT: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; GC: Glasgow coma scale; BUN: blood urea nitrogen; Na: sodium; K: potassium; WBC: white blood cell; CRP: C-reactive protein; MV: mechanical ventilation; IHD: intermittent hemodialysis; CVVHDF: continuous veno-venous hemodiafiltration; ICU: intensive care unit

Table 2. Comparison of survivor and non-survivor patients according to AKI classification

	Survivor N=6	Non-survivor N=10	p
AKI stage, n (%)			
Normal	3 (19)	1 (6)	
Stage 1	2 (12)	1 (6)	0.098
Stage 2	0 (0)	2 (12)	
Stage 3	1 (6)	6 (38)	

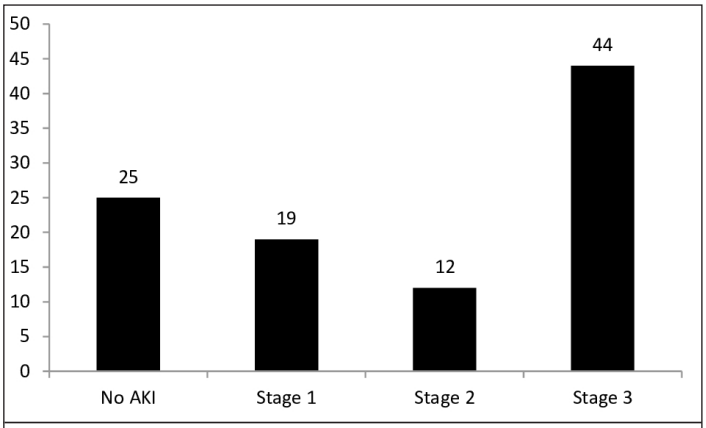

Figure 1. According to KDIGO guideline AKI classification patients with SARS-CoV-2 infection

DISCUSSION

In this study, AKI frequency was classified according to the KDIGO criteria in critically ill patients diagnosed with COVID-19 disease followed in the ICU. AKI stage 1 was detected in 19% of patients, stage 2 was detected in 12% of patients and stage 3 in 44% of patients.

Most of the patients were elderly with the mean age was 75 years with significant male dominance (88%). HT and CVD were the most common co-morbid diseases. The median APACHE II score was 26 and ICU mortality rate was 62%. Severe clinical course with high mortality and high AKI frequency is expected considering the severity of the disease.

In a study conducted by Cheng et al. (13) on 701 hospitalized COVID-19 patients, AKI frequency was found to be 5.1%. AKI was detected in 1.9% stage 1, 1.3% stage 2 and 2% stage 3 patients. The average age of the patients was 63 years and HT was seen in 33.4% of the patients. Only 10.4% of the patients were admitted to the ICU and the mortality rate was 16.1%. Their patient's severity and comorbidities were less than our patients. This may explain the high AKI frequency and mortality in our patients.

AKI was examined according to KDIGO criteria in a study by Hirsch et al. (8), which included 13 academics and 5449 patients from community hospitals. AKI was detected in 1993 (36.6%) of the

patients. In this study, 46.5% stage 1, 22.4% stage 2 and 31.1% AKI stage 3 patients were seen. 14.3% of the patients required renal replacement therapy. Older age, diabetes mellitus (DM), HT, CVD, black race, MV requirement and vasopressor drug use were determined to be the risk factors for AKI development in their study. The patient characteristics of this study are similar to ours. ICU admission were required in 25.6% of the patients and 21.1% needed MV. In addition, risk factors for AKI detected by Hirsch et al. (8) were also observed in our patients. In a study done in China, COVID-19 positive 34 ICU patients were examined (1), it was shown that renal failure was more common in patients with MV requirement. Patient characteristics included in this study are also similar to ours.

In Turkey, treatment of COVID-19 patients is regulated by guidelines published by the Ministry of Health COVID-19 Science Board (18). We applied the treatment protocols according to the scientific board guidelines. The antivirals and antibiotics used to prevent secondary bacterial infections may cause renal toxicity. All patients received hydroxychloroquine, azithromycin and/or levofloxacin treatment. More than half of the patients received oseltamivir and favipiravir. Less than half received lopinavir/ritonavir. These drugs may have contributed to AKI development.

Hemodynamic instability, multiple organ failure, hypotension and shock are conditions that contribute to AKI development.

In our study, median SOFA score was 7 and 81% of patients were intubated. The patients had moderate ARDS upon ICU admission (PaO2/Fi02: 181), 56% of them needed prone positioning and 38% received renal replacement therapy. The previously mentioned characteristics show that our patients were clinically unstable and that may contribute to the high AKI rate.

In a multi-center study conducted in accordance with KDIGO criteria in ICU non-COVID-19 patients, AKI frequency in critically ill patients was found to be 57.3% and it was found to increase mortality (19). In post-mortem studies, it has been shown that SARS CoV-2 infection directly damages the kidney (11, 12). The reason for the high rate of AKI in our patients may be caused both by hemodynamic instability and direct viral effect.

The number median length of ICU stay of our patients was 14 days, and the mortality rate was 62%. In our previous studies from the same ICU, the average hospitalization duration was 6 days (20). In addition, the overall patient mortality of our intensive care unit is 38% (20). Intensive care days and mortality rates of patients followed with COVID-19 infection were higher than other ICU patients.

The study being single centered and a small number of patients has significant limitations. Moreover, detailed medication uses such as antibiotics, sedatives, and analgesics which may cause AKI, and sepsis which may cause multiple organ failure, were not evaluated. Post-mortem biopsy was not performed on the patients. Detailed risk analysis for mortality was not performed because the low number of patients.

CONCLUSION

As a result of this study, the rate of AKI was found to be high in critically ill patients who were followed up in the ICU with the diagnosis of COVID-19. To better determine the etiology of AKI, detailed studies and analysis with more patient population should be done.

Ethics Committee Approval: The ethics committee approval was received for this study from the Local Research Ethics Committee of Erciyes University School of Medicine (Approval Date: April 06, 2020; Approval Number: 2020-199).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.G., N.T., M.S., Ş.T.; Design - K.G., M.S., Ş.T., N.T.; Supervision - K.G., M.S.; Resources - Ş.T., K.G., B.B.K., B.R.; Materials - Ş.T., K.G., B.B.K., B.R., N.T.; Data Collection and/or Processing - Ş.T., K.G.., B.B.K.; Analysis and/or Interpretation - K.G., M.S., N.T., B.B.K., Ş.T.; Literature Search - K.G., Ş.T., N.T.; Writing - K.G., M.S., Ş.T., N.T., B.B.K.; Critical Reviews - K.G., M.S., N.T., B.R., Ş.T.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Zheng Y, Sun LJ, Xu M, Pan J, Zhang YT, Fang XL, et al. Clinical characteristics of 34 COVID-19 patients admitted to intensive care unit in Hangzhou, China. J Zhejiang Univ Sci B 2020; 21: 378-87. [Crossref]
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet (London, England) 2020; 395: 1054-62. [Crossref]
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 382: 1708-20. [Crossref]
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet (London, England) 2020; 395: 507-13. [Crossref]
5. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. Jama 2020; 323: 2052-9. [Crossref]
6. Temel S, Gundogan K, Ulger B, Arican H, Bulut K, Sari A, et al. Characteristics and outcomes of patients infected with SARS-CoV-2 admitted to intensive care units: Erciyes University covid-19 center experience. Erciyes Med J. 2020. doi: 10.14744/etd.2020.00907. [Crossref]

7. Lai CC, Ko WC, Lee PI, Jean SS, Hsueh PR. Extra-respiratory manifestations of COVID-19. Int J Antimicrob Agents 2020 May 22. doi: 10.1016/j.ijantimicag.2020.106024. [Epub ahead of print]. [Crossref]
8. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, et al. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020 May 16. doi: 10.1016/j.kint.2020.05.006. [Epub ahead of print]. [Crossref]
9. Ng JJ, Luo Y, Phua K, Choong A. Acute kidney injury in hospitalized patients with coronavirus disease 2019 (COVID-19): A meta-analysis. J Infect. 2020 May 8. doi: 10.1016/j.jinf.2020.05.009. [Epub ahead of print]. [Crossref]
10. Fanelli V, Fiorentino M, Cantaluppi V, Gesualdo L, Stallone G, Ronco C, et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care 2020; 24: 155. [Crossref]
11. Rossi GM, Delsante M, Pilato FP, Gnetti L, Gabrielli L, Rossini G, et al. Kidney biopsy findings in a critically ill COVID-19 patient with dialysis-dependent acute kidney injury: A case against "SARS-CoV-2 nephropathy". Kidney Int Rep. 2020 May 17. doi: 10.1016/j.ekir.2020.05.005. [Epub ahead of print]. [Crossref]
12. Su H, Yang M, Wan C, Yi LX, Tang F, Zhu HY, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020. doi: j.kint.2020.04.003 [Crossref]
13. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020; 97: 829-38. [Crossref]
14. Hassanein M, Thomas G, Taliercio J. Management of acute kidney injury in COVID-19. Cleve Clin J Med. 2020 May 20. doi: 10.3949/ccjm.87a.ccc034. [Epub ahead of print]. [Crossref]
15. WHO Team. Clinical management of COVID-19: Interim guidance. WHO. 2020: Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19
16. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America expert consensus statement on reporting chest CT findings related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. J Thorac Imaging. 2020 Apr 28. doi: 10.1097/RTI.0000000000000524. [Epub ahead of print]. [Crossref]
17. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract 2012; 120: c179-84. [Crossref]
18. Kurulu TCSBB. Türkiye Cumhuriyeti Sağlık Bakanlığı COVID-19 (SARS-CoV-2 enfeksiyonu) rehberi. 2020: 1-95.
19. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: The multinational AKI-EPI study. Intensive Care Med 2015; 41: 1411-23. [Crossref]
20. Gundogan K, Akbudak IH, Bulut K, Temel S, Sungur M, Guven M, et al. Thiamin status in adults receiving chronic diuretic therapy prior to admission to a medical intensive care unit: A pilot study. Nutr Clin Pract 2019; 34: 565-71. [Crossref]