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CLINCAL STUDY

Contrast-induced acute kidney injury in COVID-19 patients

Gucun M[1], Isik ME[2]

Department of Nephrology, University of Health Sciences, Koşuyolu High Specialization Research and Traning Hospital, Istanbul, Turkey. **gcn_2001@yahoo.com**

ABSTRACT
BACKGROUND: This study aims to evaluate the CI-AKI following emergency percutaneous coronary intervention in patients with COVID-19 infection.
METHODS: Forty-two COVID-19 patients who underwent emergency PCI due to the diagnosis of acute coronary syndrome were included in the study. Mean age was 63±14.76 and males accounted for 81 % (34/42). Contrast-induced acute kidney injury (CI-AKI) was defined as absolute increase in serum creatinine level by 0.3 mg/dL above baseline within 48 hours of contrast exposure. Patients were divided into two groups according to CI-AKI development following coronary angiography.
RESULTS: CI-AKI developed in 33.3 % (14/42) of the patients. Pre-procedure e-GFR (p=0.028), serum albumin levels (p=0.021), and ejection fraction (p=0.039) were lower in the CI-AKI group. Whereas the platelet/lymphocyte ratio was significantly lower in the non-CI-AKI group (p=0.010).
CONCLUSIONS: Our study results demonstrated that patients suffering from COVID-19 had a high risk of CI-AKI development following coronary angiography *(Tab. 1, Ref. 36)*. Text in PDF *www.elis.sk*
KEY WORDS: COVID-19, contrast-induced acute kidney injury, coronary angiography.

Introduction

Coronavirus disease 2019 (COVID-19) emerged in December 2019 in Wuhan, a city in the Hubei Province of China, and became a pandemic only in a couple of months. To date, there are 102.1 million confirmed cases and over 2.2 million deaths worldwide (1). The responsible virus is a member of betacoronavirus family and initially it was called "novel coronavirus 2019" (2019-nCoV) while designating severe acute respiratory syndrome – coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (2). Although the RNA sequence is similar to bat coronavirus types, it is unclear whether the transmission is directly from bats or through some other mechanism (3). The disease progression occurs in 3 phases, including early infection phase (viral replication and mild symptoms), pulmonary phase (adaptive immunity and predominance of respiratory symptoms), and hyperinflammation phase (4). During the hyperinflammation phase, an excessive proinflammatory cytokine release causes a destructive state described as a cytokine storm previously observed in SARS-CoV and MERS-CoV infections. In the patients suffering from a cytokine storm, life-threatening complications such as multiple organ failure (MOF), acute respiratory distress syndrome (ARDS), septic shock, hemorrhage/coagulopathy, acute heart/liver/kidney injury, and secondary bacterial infections can develop (4).

[1]Department of Nephrology, University of Health Sciences, Koşuyolu High Specialization Research and Traning Hospital, Istanbul, Turkey, and [2]Department of Infectious Diseases, University of Health Sciences, Koşuyolu High Specialization Research and Traning Hospital, Istanbul, Turkey

Address for correspondence: M. Gucun, University of Health Sciences, Koşuyolu High Specialization Research and Traning Hospital, Istanbul, Turkey. Phone: +90 505 265 44 30

Contrast-induced acute kidney injury (CI-AKI) is an iatrogenic form of kidney injury that develops following contrast media administration. CI-AKI can be defined as an increase in serum creatinine by≥0.3 mg/dL (≥26.5 micromole/L) within 48 hours in the absence of other causes of AKI (5). It is the third common cause of hospital-acquired AKI (6). The clinical course is usually benign, serum creatinine levels peak between 2 and 5 days and typically return to normal in 14 days following the contrast medium administration (7). However, in some cases, CI-AKI remains permanent and in some of them it results in dialysis treatment. Also, CI-AKI has been associated with prolonged hospital stay, morbidity and mortality (8). There are no specific treatment options for CI-AKI. Avoidance of other factors causing potential kidney injury, hemodynamic stabilization and electrolyte management, dose adjustment of medications according to glomerular filtration rate are available strategies to prevent severe kidney injury (9).

AKI has been reported as a common and severe complication of COVID-19 infection with a rate of 20 % of hospitalized patients and 50 % of patients in ICU (10). Mortality rate in these patients is as high as 57 %. Although the underlying mechanisms of AKI development remain unclear, the kidney involvement is thought to be a manifestation of acute tubular necrosis (ATN) resulting from multiple organ failure, sepsis, and shock associated with COVID-19 infection (11). It has also been reported that SARS-CoV-2 renal tropism may be another factor involved in the development of AKI (12). However, the relationship between the contrast medium administration and AKI development in COVID-19 patients has not been evaluated yet. In this study, we aimed to share our experience of contrast-induced nephropathy in COVID-19 patients who underwent emergency percutaneous coronary intervention.

Tab. 1. Clinicopathological features of COVID-19 patients who underwent angiography.

	Total	CI-AKI (+)	CI-AKI (-)	p
Gender (male)	34 (81%)	23 (67.6%)	11 (32.4%)	0.781
Age (years)	63±14.76	67±10	60±16	0.199
Diabetes mellitus (%)	19 (45.2%)	11 (57.9%)	8 (42.1%)	0.273
Ejection fraction (%)	50±11.96	45 (30–65)	55 (30–65)	**0.039**[b]
Time (days)[a]	1 (1–12)	1 (1–12)	2 (1–12)	0.419
Pre-procedure Cr (mg/dl)	0.89 (0.56-4.09)	1.29 (0.56–4.29)	0.86 (0.63–2.22)	0.133
Pre-procedure e-GFR (ml/min/1.73m²)	87 (14–124)	61.50±34.79	83±23.44	**0.028**[c]
Contrast media (cc)	95 (25–336)	136 (55–236)	95 (25–336)	0.153
CRP (mg/L)	17.8 (1.61–353)	45.2 (1.61–179)	16 (3.1–353)	0,257
Albumin (g/L)	35.6±4.88	3.3±0.5	3.7±0.4	**0.021**[c]
Hemoglobin (g/dl)	12.5±2.31	11.7±1.8	12.9±2.4	0,098
Troponin	0.62 (0.22–10)	1.12 (0.03–10)	0.373 (0.02–10)	0.177
NLR	5.35 (1.56–25.6)	6.32 (1.81–25.62)	3.65 (1.56–16.57)	0.088
PLR	191 (72.41–1179)	341.92 (114.29–1179)	159.29 (72.41–578.57)	**0.010**[b]

[a] Time between diagnosis of COVID-19 infection and coronary angiography, [b] Mann-Whitney U test, [c] Student's t-test, $p<0.05$. CI-AKI – contrast induced acute kidney injury; Cr – creatinine; e-GFR – estimated glomerular filtration rate; CRP – C-reactive protein; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio

Material and methods

The study was approved by the hospital's local ethics committee and followed the principles of the Declaration of Helsinki.

Patients

A total of 52 consecutive COVID-19 patients who underwent emergency PCI with the diagnosis of acute coronary syndrome between April 2020 and January 2021 were retrospectively enrolled in the study. Patients diagnosed with COVID-19 in our hospital or receiving active treatment at the time of admission were included in the study. Patients who were allergic to contrast media, hemodialysis patients, patients with other causes of AKI, patients with the history of being exposed to contrast media within 10 days, patients with the history of solid organ transplantation, recent surgery or history of trauma within 2 weeks, patients with a diagnosis of malignancy, and patients with chronic inflammatory disease were excluded from the study. Overall, 10 patients were excluded from the study. Seven patients were excluded because of having at least one of the exclusion criteria, and 3 patients were excluded because of missing data. Finally, the study population consisted of 42 patients. Two groups were assigned according to CI-AKI development after coronary angiography. The CI-AKI group included 14 (33.3 %) patients while the non-CI-AKI group included 28 (66.7 %) patients.

All enrolled cases received hydration (0.9 % normal saline at 0.5–1.0 mL/kg/h) for up to 12 h after coronary angiography, depending on the patient's volume status. N-acetylcysteine (>1200 mg/day) was administered starting at admission until the day after coronary angiography. Nonionic, iso-osmolar contrast medium (iohexol) was used during the procedure. CI-AKI was defined as an absolute increase in serum creatinine level by 0.3 mg/dL above baseline within 48 hours of contrast exposure in the absence of an alternative diagnosis. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Data collection

The data on demographic, clinical and laboratory findings were collected from the hospital's medical database retrospectively. Blood samples for the whole blood count and biochemical parameters were obtained from the patients at the time of presentation. Also, serum creatinine levels were measured daily within three consecutive days after the angiography.

Statistical analysis

The Jamovi statistics programme (1.1.9.0 version) was used to compare demographic and clinical variables. For baseline characteristics, the Shapiro-Wilk test was used to determine the normality of distribution. Quantitative variables with normal distribution were specified as mean (standard deviation), variables with nonnormal distribution were shown as median (minimum–maximum). Categorical variables were shown as number and percentage values. For continuous variables with normal distribution, the Students' t-test was used to compare groups, whereas the Mann-Whitney U test was used when the distribution was not normal. For categorical variables, the X^2 test was used. Differences were considered significant at the 2-sided $p<0.05$ level.

Results

In the present study, 42 patients were enrolled to explore contrast nephropathy in COVID-19 patients. Mean age was 63 ± 14.76 and males accounted for 81 % (34/42). Diabetes mellitus was detected in 45.2 % (19/42) of patients. COVID-19 was diagnosed in 83.3 % (35/42) of patients with PCR test and the others (14 %) with radiologic findings. Three patients (7.1 %) died after the CI-AKI diagnosis, and 3 (7.1 %) patients required renal replacement treatment. Baseline demographic and clinical characteristics of the patients categorized according to CIN development are given in Table 1. CI-AKI developed in 33.3 % (14/42) of the patients. While pre-procedure e-GFR, serum albumin levels and ejection fraction were lower in the CI-AKI group, the platelet/lymphocyte ratio (PLR)

was significantly lower in the group without CI-AKI. Gender, age, diabetes mellitus, ejection fraction, time between the diagnosis of COVID-19 and coronary angiography, pre-procedure creatinine, contrast media volume, c-reactive protein, serum albumin level, hemoglobin, pre-procedure troponin level, and neutrophil/lymphocyte ratio (NLR) were similar when compared between two groups.

Discussion

This study included 42 consecutive patients with acute coronary syndrome and concomitant COVID-19 infection. CI-AKI development during the hospitalization was investigated. CI-AKI occurred in 33.3 % of patients. We also found that lower serum albumin levels, lower ejection fraction, lower e-GFR, and higher PLR were associated with CI-AKI development in these patients.

When SARS-CoV-2 enters the human body, it initially binds to the endothelial cell (EC) ACE-2 receptors and releases its RNA content into the EC (13). Intracellular virus replication then occurs, consequently causing the cell to burst. Viruses released into the environment spread from the nasal passage to the lung's alveolar region by infecting other endothelial cells (14). During homeostasis, EC plays a pivotal role by maintaining vascular integrity, preventing inflammation and inhibiting coagulation (15). Thus, EC with SARS-COV-2 can cause localized inflammation, endothelial activation, tissue damage, and irregular cytokine release (13).

Consequently, tissue edema, endotheliitis, activation of coagulation pathways with the potential development of disseminated intravascular coagulation (DIC) and deregulated inflammatory cell infiltration may develop (15). The main clinical presentation of COVID-19 is a spectrum ranging from asymptomatic patients to pneumonia and respiratory failure. The severe form of the disease may show a multisystemic course involving the brain, gastrointestinal system, heart, liver and kidney (11).

The pathogenesis of kidney involvement in COVID-19 is believed to be multifactorial. An autopsy study of 42 patients who died of COVID-19 complications showed that acute tubular injury (ATI) was the main pathological finding associated with the history of AKI (16). Hypercytokinemia-related septic shock, acute respiratory distress syndrome (ARDS)-associated hypoxia, secondary right heart failure, and iatrogenic exposure to nephrotoxins were the main factors in the development of ATI (16). Another potential mechanism of AKI includes direct infection of the kidney with SARS-CoV-2 through an angiotensin-converting enzyme 2 (ACE2) -dependent pathway driving mitochondrial dysfunction, acute tubular necrosis, formation of protein reabsorption vacuoles, collapsing glomerulopathy, and protein leakage in Bowman's capsules (17, 18). However, post-mortem studies are inconsistent to show the presence of viral particles and implying direct infection of the kidney with COVID-19 (10). Finally, soluble urokinase plasminogen activator receptor (suPAR) levels, an immune mediator of the kidney, have shown to be associated with AKI in COVID-19 patients (19). SuPAR is synthesized as a product of membrane-bound uPAR cleavage process in the case of inflammatory stimuli (19). SuPAR has a role in the development of different renal pathologies such as chronic kidney diseases (CKD), focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy (DN) (20). In addition, an increase in suPAR levels is associated with AKI development through a mechanism of modulating mitochondrial respiration and inducing reactive oxygen species generation in proximal tubular cells and makes them susceptible to additional damage (21–23).

CI-AKI is a well-known complication of contrast media administration. The main pathological finding is acute tubular necrosis (ATN) (24–26). ATN is contributed to renal vasoconstriction resulting in medullary hypoxia, possibly mediated by effects of viscosity and by alterations in nitric oxide, endothelin, and/or adenosine, cytotoxic effects of the contrast agents on tubular cells (27–31). Also, emerging data indicate an association between inflammation and acute tubular injury following both ischemic and nephrotoxic injury. It was reported that specific genotype polymorphisms of cytokine in TNF-α and IL-10 were associated with CI-AKI risk and long-term renal outcome after PCI (32). In addition, recent studies demonstrated a relationship between CI-AKI development and inflammatory markers such as CRP, procalcitonin and hematological indexes derived from peripheral inflammatory blood cells (33, 34). Based on these data, the risk of contrast nephropathy in COVID 19 patients who are susceptible to renal tubular damage is anticipated to increase. However, there is no data about CI-AKI in COVID-19 patients in the literature.

CI-AKI incidence was reported between 4.4 % and 22.1 % in a meta-analysis of 29 studies (35). In our study, the rate of CI-AKI was found to be as high as 33.3 %. It can be attributed to the tubular susceptibility to cytokine damage, organ crosstalk and also systemic effects. In the course of COVID-19 infection, right ventricular failure secondary to pneumonia may cause kidney congestion and subsequent AKI. Similarly, left ventricular dysfunction can result in decreased cardiac output, low effective arterial volume, and renal hypoperfusion (36). Therefore, basal cardiac function may be one of the determinative factors in AKI development in COVID-19 patients. In our study, the basal ejection fraction of CI-AKI developed patients was significantly lower than in non-CI-AKI patients.

Limitations

Our study has several limitations. Firstly, due to the nature of the retrospective study design, we had to exclude ten patients because of missing data. Secondly, the number of patients enrolled to our study was not high enough. Thus, these results may not apply to a more general population of unscreened individuals. Finally, inflammation-associated markers other than CRP, NLR, and PLR were not analyzed.

Conclusion

Results of our study indicated a high possibility of CI-AKI development after the administration of contrast media in COVID-19 patients. It is important to take preventive strategies for CI-AKI and a closer follow up is necessary in high-risk patients after contrast media administration.

References

1. Weekly epidemiological update – 2 February 2021. (n.d.). Retrieved February 08, 2021, from https://www.who.int/publications/m/item/weekly-epidemiological-update---2-february-2021.

2. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, Gorbalenya, AE, Bake, SC et al. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020; 5: 536–544. https://doi.org/10.1038/s41564-020-0695-z

3. Perlman S. Another Decade, Another Coronavirus. N Engl J Med 2020; 382 (8): 760–762. DOI: 10.1056/NEJMe2001126.

4. Tsang HF, Chan LWC, Cho WCS et al. An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies (published online ahead of print, 2020 Dec 29). Expert Rev Anti Infect Ther 2020; 1–12. DOI: 10.1080/14787210.2021.1863146.

5. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdmann EA, Goldstein SL. KDIGO AKI guidelines. Kidney Int 2012; 2 (1). DOI: 10.1038/kisup.2012.1.

6. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Amer J Kidney Dis 2002; 39 (5): 930–936. DOI: 10.1053/ajkd.2002.32766.

7. Contrast-Induced Nephropathy: Practice Essentials etiology, Epidemiology. (n.d.). Retrieved January 31, 2021, from https://emedicine.medscape.com/article/246751-overview.

8. Mohammed NM, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. Heart Views 2013; 14 (3): 106–116. DOI: 10.4103/1995-705X.125926.

9. Shah R, Le FK, Labroo A, Khan MR. Contrast-associated acute kidney injury. Quant Imaging Med Surg 2020; 10 (4): 891–894. DOI: 10.21037/qims.2020.03.20.

10. Nadim MK, Forni LG, Mehta RL et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020; 16: 747–764. https://doi.org/10.1038/s41581-020-00356-5.

11. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and Multiorgan Response. Curr Probl Cardiol 2020; 45 (8): 100618. DOI: 10.1016/j.cpcardiol.2020.100618.

12. Braun F, Lütgehetmann M, Pfefferle S et al. SARS-CoV-2 renal tropism associates with acute kidney injury. Lancet 2020; 396 (10251): 597–598. DOI: 10.1016/S0140-6736 (20)31759-1.

13. Singh SP, Pritam M, Pandey B, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: A comprehensive review (published online ahead of print, 2020 Jul 3). J Med Virol 2020; 10.1002/jmv.26254. DOI: 10.1002/jmv.26254.

14. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J 2020; 55 (4): 2000607. DOI: 10.1183/13993003.00607-2020.

15. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed (published correction appears in Nat Rev Immunol 2020; 20 (7): 389–391. DOI: 10.1038/s41577-020-0343-0.

16. Santoriello D, Khairallah P, Bomback AS et al. Postmortem Kidney Pathology Findings in Patients with COVID-19. J Am Soc Nephrol 2020; 31 (9): 2158–2167. DOI: 10.1681/ASN.2020050744.

17. Su H, Yang M, Wan C et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney Int 2020; 98 (1): 219–227. DOI: 10.1016/j.kint.2020.04.003.

18. Larsen CP, Bourne TD, Wilson JD et al. Collapsing glomerulopathy in a patient with coronavirus disease 2019 (COVID-19). Kidney Int Rep 2020; 5: 935– 939. DOI: 1016/j.ekir.2020.04.002.

19. Azam TU, Shadid HR, Blakely P et al. Soluble Urokinase Receptor (SuPAR) in COVID-19-Related AKI. J Am Soc Nephrol 2020; 31 (11): 2725–2735. DOI: 10.1681/ASN.2020060829.

20. Hayek SS, Sever S, Ko YA et al. Soluble Urokinase Receptor and Chronic Kidney Disease. N Engl J Med 2015; 373 (20): 1916–1925. DOI: 10.1056/NEJMoa1506362.

21. Hayek SS, Leaf DE, Samman Tahhan A et al. Soluble Urokinase Receptor and Acute Kidney Injury. N Engl J Med 2020; 382 (5): 416–426. DOI: 10.1056/NEJMoa1911481.

22. Iversen E, Houlind MB, Eugen-Olsen J. Soluble urokinase receptor and acute kidney injury. N Engl J Med 382: 2166–2167: 2020.

23. Mossanen JC, Pracht J, Jansen TU et al. Elevated Soluble Urokinase Plasminogen Activator Receptor and Proenkephalin Serum Levels Predict the Development of Acute Kidney Injury after Cardiac Surgery. Int J Mol Sci 2017; 18 (8): 1662. DOI: 10.3390/ijms18081662.

24. Detrenis S, Meschi M, Musini S, Savazzi G. Lights and shadows on the pathogenesis of contrast-induced nephropathy: state of the art. Nephrol Dial Transplant 2005; 20 (8): 1542–1550. DOI: 10.1093/ndt/gfh868.

25. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. Kidney Int 2005; 68 (1): 14–22. DOI: 10.1111/j.1523-1755.2005.00377.x.

26. Heyman SN, Rosenberger C, Rosen S. Regional Alterations in Renal Haemodynamics and Oxygenation: A Role in Contrast Medium-Induced Nephropathy. Nephrol Dial Transplant 2005; 20 (Suppl. S1): i6–i11.

27. Agmon Y, Peleg H, Greenfeld Z, Rosen S, Brezis M. Nitric oxide and prostanoids protect the renal outer medulla from radiocontrast toxicity in the rat. J Clin Invest 1994; 94 (3): 1069–1075. DOI: 10.1172/JCI117421.

28. Pflueger A, Larson TS, Nath KA, King BF, Gross JM, Knox FG. Role of adenosine in contrast media-induced acute renal failure in diabetes mellitus. Mayo Clin Proc 2000; 75 (12): 1275–1283. DOI: 10.4065/75.12.1275.

29. Katholi RE, Taylor GJ, McCann WP et al. Nephrotoxicity from contrast media: attenuation with theophylline. Radiology 1995; 195 (1): 17–22. DOI: 10.1148/radiology.195.1.7892462.

30. Cantley LG, Spokes K, Clark B et al. Role of endothelin and prostaglandins in radiocontrast-induced renal artery constriction. Kidney Int 1993; 44: 1217–1223. DOI: 10.2214/ajr.183.6.01831673.

31. Weisberg LS, Kurnik PB, Kurnik BR. Radiocontrast-induced nephropathy in humans: role of renal vasoconstriction. Kidney Int 1992; 41 (5): 1408–1415. DOI: 10.1038/ki.1992.206.

32. Chang CF, Lu TM, Yang WC, Lin SJ, Lin CC, Chung MY. Gene polymorphisms of interleukin-10 and tumor necrosis factor-α are associated with contrast-induced nephropathy. Am J Nephrol 2013; 37 (2): 110–117. DOI: 10.1159/000346528.

33. Gu G, Yuan X, Zhou Y, Liu D, Cui W. Elevated high-sensitivity C-reactive protein combined with procalcitonin predicts high risk of contrast-induced nephropathy after percutaneous coronary intervention. BMC Cardiovasc Disord 2019; 19 (1): 152. DOI: 10.1186/s12872-019-1137-9.

34. Zorlu C, Koseoglu C. Comparison of the Relationship Between Inflammatory Markers and Contrast-Induced Nephropathy in Patients With Acute Coronary Syndrome After Coronary Angiography. Angiology 2020; 71 (3): 249–255. DOI: 10.1177/0003319719892160.

35. Eng J, Wilson RF, Subramaniam RM et al. Comparative Effect of Contrast Media Type on the Incidence of Contrast-Induced Nephropathy: A Systematic Review and Meta-analysis. Ann Intern Med 2016; 164 (6): 417–424. DOI: 10.7326/M15-1402.

36. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nature reviews. Nephrology 2020; 16 (6): 308–310. DOI: 10.1038/s41581-020-0284-7.

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