ORIGINAL ARTICLE

UDC: 616.98:578.834]:616.61
DOI: https://doi.org/10.2298/VSP230614070K

The use of continuous renal replacement therapy in critically ill patients with COVID-19-related acute kidney injury

Primena kontinuirane terapije zamene funkcije bubrega kod kritično obolelih sa akutnim oštećenjem bubrega povezanim sa COVID-19

Violeta Knežević*†, Tijana Azaševac*†, Bojana Ljubičić*‡, Ana Lazarević*‡, Dragana Milijašević*§, Dušan Božić*†

***University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; University Clinical Center of Vojvodina, †Clinic for Nephrology and Clinical Immunology, ‡Emergency Center, Department of Emergency Internal Medicine, Novi Sad, Serbia; §Institute of Public Health of Vojvodina, Novi Sad, Serbia**

Abstract

Background/Aim. Patients with severe clinical COVID-19 are at higher risk of developing acute kidney injury (AKI). The aim of the study was to analyze the risk factors for AKI/AKI on chronic kidney disease (CKD) and the results of treatment using continuous renal replacement therapy (CRRT) in critically ill COVID-19 patients. **Methods.** The study included 101 COVID-19 patients with AKI treated with CRRT out of a total of 293 patients with AKI. The study was conducted from March 2020 to July 2021 at the University Clinical Center of Vojvodina, Serbia. **Results.** The average age of patients was 64.69 ± 9.71 years. Out of the total number of patients, 82.2% were male, of whom 75.2% suffered from hypertension. On invasive mechanical ventilation (IMV) were 93.7% of patients, and 92.1% were on vasopressor therapy. The average length of IMV until the beginning of CRRT was 4.65 ± 4.57 days. In the first 24 hrs after starting IMV, 60% of patients had to undergo CRRT. Before administering CRRT, the average Simplified Acute Physiology Score II was 39.13 ± 14.45, creatinine 312 μmol/L [Interquartile Range (IQR) 208.0–437.5], procalcitonin 2.70 ng/L (IQR 0.62–7.20), while 10.9% of patients had SpO_2/FiO_2 index > 200 and 41.6% had anuria. The mean number of procedures was 2.01 ± 1.36. The most frequent modality was hemodiafiltration in 67.3% of patients, and 46% used the oXiris® membrane. Using binary logistic regression, including demographic parameters, comorbidities, as well as clinical parameters before CRRT, it was found that patients with previous kidney disease were 3.43 times more susceptible to developing AKI, and patients with SpO_2/FiO_2 index ≥ 200 were 69% less susceptible to developing AKI/AKI on CKD requiring CRRT in the first 24 hrs from the start of IMV. **Conclusion.** Determining the risk factors for AKI/AKI on CKD is important for planning the prevention of these conditions that require the application of CRRT with the correct choice of dialysis modality and dose, membrane/filter type, and anticoagulant dose.

Key words:
acute kidney injury; continuous renal replacement therapy; covid-19; critical illness; risk factors.

Apstrakt

Uvod/Cilj. Bolesnici sa teškom kliničkom slikom COVID-19 imaju viši rizik od razvoja akutnog oštećenja bubrega (AOB). Cilj rada bio je da se analiziraju faktori rizika od AOB/akutizacije bubrežne insuficijencije kod obolelih sa hroničnom bolešću bubrega (HBB), kao i rezultati lečenja primenom kontinuirane terapije zamene funkcije bubrega (KTZFB) kod kritično obolelih od COVID-19. **Metode.** Istraživanjem je obuhvaćen 101 COVID-19 bolesnik sa AOB, od ukupno 293 bolesnika lečenih primenom KTZFB. Istraživanje je sprovedeno od marta 2020. do jula 2021. godine u Univerzitetskom Kliničkom centru Vojvodine, Srbija. **Rezultati.** Prosečna starost bolesnika bila je 64,69 ± 9,71 godina. Od ukupnog broja bolesnika, 82,2% bilo je muškog pola, od kojih je 75,2% bilo obolelih od hipertenzije. Na invanzivnoj mehaničkoj ventilaciji (IMV) bila su 93,7% bolesnika, a 92,1% na vazopresornoj terapiji. Prosečna dužina IMV do početka KTZFB bila je 4,65 ± 4,57 dana. U prva 24 sata od početka IMV, 60% bolesnika je zahtevalo KTZFB. Pre KTZFB, prosečna vrednost *Simplified Acute Physiology Score II* iznosila je 39,13 ± 14,45, kreatinina 312 μmol/L [*Interquartile Range* (IQR) 208,0–437,5], prokalcitonina 2,70 ng/L (IQR 0,62–7,20), dok je 10,9% bolesnika imalo indeks SpO_2/FiO_2 > 200 i njih 41,6% anuriju. Prosečan broj procedura iznosio je 2,01 ± 1,36. Najčešći modalitet bio je hemodijafiltracija kod 67,3% bolesnika, a 46% je

Correspondence to: Violeta Kneževic, University of Novi Sad, University Clinical Center of Vojvodina, Clinic for Nephrology and Immunology, Hajduk Veljkova 1–7, 21 000 Novi Sad, Serbia. E-mail: violeta.knezevic@mf.uns.ac.rs

koristilo oXiris® membranu. Korišćenjem binarne logističke regresije, uključujući demografske parametre, komorbiditete i kliničke parametre pre KTZFB, utvrđeno je da su bolesnici sa prethodnim oboljenjem bubrega imali 3,43 puta veće šanse da razviju AOB, a bolesnici sa indeksom $SpO_2/FiO_2 \geq 200$ su imali 69% manje šanse za AOB/akutizaciju bubrežne insuficijencije u miljeu HBB, zavisne od KTZFB, u prva 24 sata od početka IMV. **Zaključak.** Utvrđivanje faktora rizika od AOB/akutizacije bubrežne insuficijencije kod obolelih sa HBB značajno je za planiranje njihove prevencije, koja zahteva i primenu KTZFB uz pravilan izbor modaliteta i doze dijalize, vrste membrane/filtera i doze antikoagulansa.

Ključne reči:
bubreg, akutna insuficijencija; bubreg, zamena funkcije, kontinuirana; covid-19; kritična stanja; faktori rizika.

Introduction

The clinical presentation of coronavirus disease 2019 (COVID-19) varies from asymptomatic to severe, the latter being present in about 5% of patients. The severe clinical presentation was accompanied by the development of acute respiratory distress syndrome (ARDS), multi-organ dysfunction (MODS), and the development of septic shock [1–5]. Patients with a severe clinical presentation of COVID-19 are at a higher risk of developing acute kidney injury (AKI). According to Chinese and American studies, AKI develops on average in 2.5–75.0% of patients [2–9]. Potential risk factors of AKI are the following: direct viral damage to tubular cells, activation of the renin-angiotensin-aldosterone system, inflammatory reaction triggered by the immune system's response to the virus, thromboembolism, and nonspecific factors such as hypotension and hypoxemia [10]. In cases of reduced or absent response to applied conservative treatment methods, renal replacement therapy (RRT) is applied. Application of RRT is necessary in 5–55% of cases [2–9]. In hemodynamically unstable patients, continuous RRT (CRRT) is indicated because this modality ensures better volume control and nutritional balance, which are very important in the treatment of patients with COVID-19 [11]. The aim of the study was to analyze the risk factors for AKI/AKI on chronic kidney disease (CKD) and the results of CRRT treatment in critically ill COVID-19 patients.

Methods

The study included 101 COVID-19 patients with AKI in the MODS who required CRRT from March 2020 to July 2021. They were hospitalized within one institution in the semi-intensive care units (SICU) and intensive care units (ICU). The study was approved by the University Clinical Center Vojvodina, Serbia, Ethics Committee (No 6-00-102, from June 1, 2023).

The following items were analyzed: demographic data; comorbidities; duration of illness, use of antibiotics before admission; first admission to the SICU/ICU; X-ray of the lungs on admission; vaccination status, need for invasive mechanical ventilation (IMV) and vasopressor therapy; AKI/AKI on CKD dependent on CRRT in the first 24 hrs from the start of IMV; duration of IMV until the beginning of CRRT; the beginning of CRRT since the hospital admission; modified index of oxygen saturation to fraction of inspired oxygen ratio (SpO_2/FiO_2), Simplified Acute Physiology Score II (SAPS II) and presence of anuria before CRRT; thromboprophylaxis therapy and dose; length of hospitalization; laboratory parameters before and after CRRT; type of CRRT modality; type of adsorptive membrane/filter; number of procedures; procedure parameters; changes in the dose of unfractionated heparin (UHF) during CRRT and reasons for ending of CRRT. A modified SpO_2/FiO_2 oxygenation index was used. Despite the arterial line being set for optimal monitoring because of a large number of patients, frequent blood sampling for arterial blood gas analysis was unnecessarily numerous during the pandemic. The SpO_2/FiO_2 index is always available as a surrogate P/F ratio [Note: P/F ratio equals the arterial pO_2 ("P") from the arterial blood gas divided by the FiO_2 ("F") – the fraction (percent) of inspired oxygen that the patient is receiving] to assess the severity of ARDS [12]. Severe COVID-19 was defined as the presence of any of the following in each patient's electronic medical record only on admission: first – results of arterial blood gas analyses, followed by sedative drugs, anesthetics, or vasopressor orders, along with diagnostic codes for ARDS and pneumonia associated with mechanical ventilators; second – procedure codes for insertion of an endotracheal tube or IMV in the course of hospitalization [13]. Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury was used to define the AKI, AKI stage, and AKI on CKD [14]. Indications for dialysis were discussed at nephrologist board meetings based on the current guidelines and adjusted individually depending on hypervolemia and/or sepsis.

The choice of CRRT modes depended on the need to remove molecules of different molecular weights and volumes and the clinical status of the patient, and it was based on the availability of resources.

Due to changes in the clinical condition of the patient and specific complications of the procedures, such as systemic coagulation, mode transitions were frequent. CRRT was performed on a Prismaflex standard high-flow Hemofilter (ST150 Gambro) with a high-flow multifiltrate filter (Kit 8 CVVHDF 1000). In septic patients, the following were used: oXiris® membrane (Gambro, membrane based on AN-69, surface treated with polyethyleneimine and heparin-grafted) and EMIC2 hemofilter (Fresenius Medical Care, Bad Homburg, Germany, surface area 1.8 m^2). UFH anticoagulation was used for the most part, whereas regional citrate anticoagulation was used in three patients, and fondaparinux-sodium was administered in one patient.

Results

The average age of the patients was 64.69 ± 9.71 years, and 82.2% of them were men. The most common comorbidity was hypertension in 75.2%, while previous kidney diseases were present in 33.7% of patients. Out of the total number of patients, 61.4% were unvaccinated. Prior to admission to the SICU/ICU, 58% of patients used one, two, or more types of antibiotics, and 66% of them were initially admitted to the ICU with radiographically confirmed pneumonia, bilateral pneumonia in 88.1% of them. On IMV were 93.7% of patients, and 92.1% were on vasopressor therapy. The average length of IMV until the start of CRRT was 4.65 ± 4.57 days. In the first 24 hrs from the start of IMV, 60% of patients had to undergo CRRT, 10.9% of patients had SpO_2/FiO_2 > 200 (Table 1), and 41.6% had anuria.

Table 1

Clinical parameters

Parameter	Values
Gender, male	83 (82.2)
Mean age (years)	64.69 ± 9.71
Comorbidities	
hypertension	76 (75.2)
diabetes mellitus	26 (25.7)
coronary disease	20 (19.8)
chronic obstructive pulmonary disease	9 (8.9)
autoimmune diseases	5 (4.9)
malignancy	5 (4.9)
previous renal disease	34 (33.7)
obesity	24 (22.7)
other	32 (31.7)
without comorbidity	8 (7.9)
Duration of illness before admission (days)	7.2 ± 4.92
Use of antibiotics before admission	
one antibiotic	29 (28.7)
two or more antibiotics	30 (29.7)
without antibiotics	16 (15.8)
unknown	26 (25.8)
Initial admission	
SICU	34 (34.0)
ICU	67 (66.0)
X-ray of the lungs on admission	
unilateral pneumonia	12 (11.9)
bilateral pneumonia	89 (88.1)
Vaccination status	
not vaccinated	62 (61.4)
incompletely vaccinated	36 (35.6)
unknown	3 (3.0)
Noninvasive mechanical ventilation	6 (5.9)
Invasive mechanical ventilation	89 (93.7)
SpO_2/FiO_2 before CRRT	
≥ 200	11 (10.9)
100–199	53 (52.5)
< 100	37 (36.6)
AKI/AKI on CKD day 1 of IMV	57 (60.0)
Duration of IMV until the beginning of CRRT (days)	4.65 ± 4.57
Vasopressors	93 (92.1)
SAPS II before CRRT	39.13 ± 14.45
Anuric patients before CRRT	42 (41.6)
Start of CRRT from admission (days)	11.16 ± 7.61
Therapy	
antivirals	13 (12.9)
steroids	70 (69.3)
tocilizumab	36 (35.6)
Dose of thrombophylaxis (dalteparin-sodium)	
2,500 IU/12 hrs	77 (76.2)
5,000 IU/12 hrs	13 (12.9)
7,500 IU/12 hrs	11 (10.9)
Length of hospital stay (days)	17.03 ± 12.44

SICU – semi-intensive care unit; ICU – intensive care unit; CRRT – continuous renal replacement therapy; AKI – acute kidney injury; CKD – chronic kidney disease; IMV – invasive mechanical ventilation; SAPS – Simplified Acute Physiology Score; SpO_2/FiO_2 – oxygen saturation to fraction of inspired oxygen ratio.
All values are expressed as numbers (percentages) or mean ± standard deviation.

The average number of CRRT procedures was 2.01 ± 1.36. The most common mode was hemodiafiltration (HDF) in 67.3% of patients, and 46.5% of patients used the oXiris® membrane (Table 2).

The mean values and differences between laboratory parameters before and after CRRT, obtained using the paired sample test, are shown in Table 3. A significant decrease in hemoglobin, platelet, urea, creatinine, sodium, aPPT, and fibrinogen values was found after CRRT. By using binary logistic regression, including demographic parameters, comorbidities, and clinical parameters before CRRT, the patients with previous kidney disease were found to have 3.43 times

Table 2

Parameters of continuous renal replacement therapy (CRRT) procedures

Parameter	Values
Type of procedure	
CVVH	1 (1.0)
CVVHD	27 (26.7)
CVVHDF	68 (67.3)
CVVHDF/CVVHD	3 (3.0)
CVVHDF + ECMO	2 (2.0)
Type of adsorptive membrane	
oXiris®	47 (46.5)
ST-150	11 (10.9)
EMIC2	27 (26.7)
Kit 8	5.9 (6)
2 membrane	9.9 (10)
Average number of CRRT	2.01 ± 1.36
Treatment parameters	
blood flow rate (mL/h)	200.3 ± 26.44
replacement flow rate (mL/h)	1,986 ± 669.37
dialysate flow rate (mL/h)	1,572 ± 456.37
dose of CRRT (mL/kg/TT)	30.89 ± 6.42
bolus dose of UFH (IU)	3,897 ± 923.52
continuous dose of UFH (IU)	1,460 ± 469.63
ultrafiltration rate (mL)	3,092 ± 2,035.64
Reasons for interruption of the CRRT	
clotting circuit	8 (7.9)
hemodynamic and/or respiratory instability	10 (9.9)
problems with vascular access	4 (3.9)
without interrupting CRRT	79 (78.2)
Change in UFH dose during CRRT	
increased dose by 1/3	40 (39.6)
increased dose by 1/2	14 (13.9)
unchanged dose	25 (24.7)
reduced dose	22 (21.9)

CVVH – continuous venovenous hemofiltration; CVVHD – continuous venovenous hemodialysis; CVVHDF – continuous venovenous hemodiafiltration; ECMO – extracorporeal membrane oxygenation; UFH – unfractionated heparin.
All values are expressed as numbers (percentages) or mean ± standard deviation.

Table 3

Differences in laboratory parameters before and after continuous renal replacement therapy (CRRT)

Parameter (NR)	Before CRRT	After CRRT	*p*
Leukocytes (4.0–10.0 × 10–9 mm^3/L)	26.72 ± 79.65	16.77 ± 8.61	0.845
Hemoglobin (120–160 g/L)	105.44 ± 20.99	98.48 ± 15.60	0.000
Platelets (140–400 × 10–9 mm^3/L)	202.42 ± 94.66	174.42 ± 88.16	0.010
C-reactive protein (< 5.0 mg/L)	155.30 ± 112.70	150.16 ± 143.72	0.709
Procalcitonin (< 2.0 ng/L)	2.70 (0.62–7.20)	1.93 (0.63–4.64)	0.170
Urea (2.5–7.5 mmol/L)	26.8 (19.65–36.50)	18.40 (13.25–25.25)	0.000
Creatinine (50–98 μmol/L)	312 (208–437.5)	233 (163.5–303)	0.000
Potassium (3.5–5.5 mmol/L)	4.8 (4–5.8)	5.4 (4.6–6.0)	0.649
Sodium (136–145 mmol/L)	141 (138–147)	140 (138–142.5)	0.000
aPTT (0.83–1.30 R)	1.07 (0.82–1.28)	1.79 (1.38–3.38)	0.000
Prothrombin time (0.83–1.30 ratio)	1.12 (1.01–1.17)	1.18 (1.06–1.31)	0.114
Fibrinogen (1.86–4.86 g/L)	5.04 (3.75–6.25)	3.90 (2.08–5.00)	0.000
D-dimer (< 0.5 mg/L)	2,145 (1,239–4,727)	3,336 (1,345–6,311)	0.144

NR – normal range; aPTT – activated partial thromboplastin time.
All values are presented as mean ± standard deviation or as mean (interquartile range).

Table 4

Association of AKI/AKI on CKD presenting on day 1 of invasive mechanical ventilation with demographic parameters, comorbidities, and clinical parameters before continuous renal replacement therapy (CRRT)

Parameters	B	Sig	Exp(B)	95% CI for EXP(B)	
				lower	upper
Female[§]	0.855	0.161	2.35	0.71	7.78
Hypertension arterialis [§]	0.007	0.990	1.01	0.33	3.04
Coronary disease[§]	-0.101	0.874	0.90	0.26	3.16
COPD[§]	-0.478	0.579	0.62	0.11	3.35
Anuria before CRRT[§]	-0.009	0.985	0.99	0.38	2.60
Vasoactive therapy[§]	-1.292	0.460	0.27	0.01	8.42
SpO_2/FiO_2 index before CRRT[#]	-1.168	0.025	0.31	0.11	0.87
Age category[¥]	0.195	0.725	1.22	0.41	3.61
Previous renal disease[§]	1.233	0.036	3.43	1.08	10.84
Diabetes mellitus[§]	-0.193	0.722	0.82	0.28	2.39

[§]Reference value for "yes"; [#]Reference value for SpO_2/FiO_2 < 100 before CRRT; [¥] Reference value for 35–59 age category.

CI – confidence interval; COPD – chronic obstructive pulmonary disease. For other abbreviations, see Table 1.

higher risks [odds ratio (OR) = 3.43; 95% confidence interval (CI) = 1.08–10.84; p = 0.036] and patients with index $SpO_2/FiO_2 \geq 200$ had a 69% lower risk (OR = 0.31; 95%CI = 0.11–0.87; p = 0.025) of developing AKI/AKI on CKD which required CRRT in the first 24 hrs from the start of IMV (Table 4). The average hospital admission was on the seventh day, IMV to CRRT on the third day, the start of CRRT was on the tenth day from admission, and 60% of patients developed AKI/AKI on CKD which required CRRT on the first day of IMV.

Discussion

This study included 34% of critically ill COVID-19 patients who required the ICU out of a total of 293 with AKI treated with conservative therapy. Namely, the incidence of AKI in COVID-19 patients varies in different studies, as well as mortality from AKI, which ranges from 35–89%, the prevalence of RRT was 5–55%, and mortality from RRT was 70–90% [2–9]. The global record covered 168 hospitals from 16 countries, with 20,608 patients, from February to November 2020, and reported an incidence of AKI in the ICU of 42.4%, mortality of 40.8% in patients on IMV alone, and 71.68% on IMV, vasopressor therapy, and RRT [8]. The same incidence of AKI of 75% was shown in two other studies: the first included 575 patients, of whom 63% required vasopressors; the second included a total of 300 patients and the need for IMV was determined in as many as 97% of patients with moderate to severe ARDS. These authors also reported the same mortality of 70% [3, 4]. It should also be noted that the need for IMV increases by ≥ 90% in critically ill patients with sepsis in KDIGO stage 3 on vasopressor therapy [15]. Our study patients were predominantly men, with an average age of 64.69 ± 9.71 years. The relation of age to unfavorable outcomes has been reported in previous studies [16–18]. The most prevalent comorbidities were hypertension 75.2% and previous stage 1–4 of CKD 33.7%, which are also mentioned in other studies [14, 19]. Namely, it has already been established that patients with existing kidney damage have a higher chance of dialysis-dependent AKI [20]. About two-thirds of the patients were initially admitted to the ICU with pneumonia, predominantly bilateral pneumonia, which was probably the reason for seeking medical help later at the healthcare facility, given that the average duration of illness until admission was 7.2 ± 4.92 days, similar to the average duration published by Doher et al. [21]. Moreover, during that period, about two-thirds of the patients were not vaccinated, and they used one or two or more antibiotics at home. Unlike other studies, all our patients were in the ICU with multiorgan failure, and 93% of them were on IMV and vasopressor therapy. A similar high percentage of patients with IMV requiring RRT was also shown by some authors [5, 14]. In other words, AKI in COVID-19 can indirectly affect other organs, such as the kidney, as part of lung-kidney cross-talk [22]. There are several reasons for the development of AKI as a consequence of respiratory insufficiency: 1) systemic hypoxia, 2) hypercapnia, 3) AKI leading to a severe inflammatory response syndrome, and 4) IMV [23]. Previous studies have shown that IMV is associated with a threefold increased risk of AKI in critically ill patients [24]. After the start of IMV, 60% of our patients already had to undergo CRRT in the first 24 hrs. Similar results have already been shown, namely that AKI/AKI on CKD requiring CRRT usually occurs at the time of intubation, which indicates the role of hemodynamic changes as a potentially important mechanism for AKI in COVID-19, as vasopressors are often initiated at the time of intubation [9, 17, 21]. Considering that previous kidney diseases were behind hypertension in terms of the representation of comorbidities with 33%, we tried to determine the number of patients undergoing CRRT on the first day of IMV and determined that it was over 50%. We compared our results with the results of an American multicenter study, which included 3,099 critically ill patients. In both studies, previous kidney disease was present in a similar percentage. However, in a multicenter study, 74% of them were dialysis dependent with median values on the third day from IMV and the onset of CRRT on the fourth day, in contrast to our patients who underwent IMV on the first day, and the median start of CRRT was on the tenth day of admission [9].

The later onset of CRRT can be explained by the absence of end-stage CKD. It should also be taken into account that before CRRT, there was a slightly higher percentage of patients on IMV and almost twice the percentage of patients on vasopressor therapy with an SpO_2/FiO_2 index of 100–199, which made our patients more hemodynamical and more unstable in terms of respiration, which indirectly indicates conclusion on the potential delayed onset of CRRT. Similar results were shown in a study by Doher et al. [21] in which AKI-RRT was predominantly present on the first day of IMV in 72% of patients, 17% of whom required RRT on day ten, i.e., three days after IMV. Strategies for initiating RRT in critically ill patients have been described in many studies [25, 26]. Some authors believe that the decision to start CRRT in COVID-19 patients with AKI should be individualized and according to the clinical context (e.g., starting CRRT due to hypervolemia in patients with severe hypoxemia) and not based only on the stage of AKI [14, 27]. The most common modality was HDF in 67.3% of our patients, and 46% of them used the oXiris® membrane. The advantages of a specific CRRT modality are not yet known, so the choice of modality depends on hospital availability and available resources [11, 14]. It is recommended that the dose of dialysis be adjusted according to the KDIGO guide and in accordance with changes in the clinical and/or metabolic state of the patient [14]. Coagulopathy in COVID-19 patients may be the cause of clot formation in the circuit of the CRRT modality and the subsequent interruption of the procedure. The aforementioned process will affect the initially applied dose of RRT, which must then be adapted to the new situation [11]. About 50% of our patients had to be administered an increase in the dose of UFH by 1/2 or 1/3, and in 7.9% of patients, CRRT was discontinued due to clotting in the circuit of the CRRT modality. In our previous work, the use of pre-diluted HDF with an antithrombin membrane (oXiris®) with doses of UFH 1/3 to 1/2 higher than recommended in patients with COVID-19, resulted in prolonged life of filters in the treatment of patients with high inflammatory parameters and D-dimer and estimated risk for the development of deep vein thrombosis [28]. On average, only two CRRT procedures were performed *per* patient due to hemodynamic instability and other complications, as reported by Bezerra et al. [15]. The need for a unique diagnostic strategy and optimization of the treatment of AKI in COVID-19 patients would contribute to determining the optimal approach to CRRT in these patients. The relation between specific laboratory values with adverse outcomes has been demonstrated in many studies [16–18]. In order to determine which parameters had the greatest influence on AKI/AKI on CKD requiring CRRT on the first day of IMV, we used a binary logistic regression model, which included demographic parameters, comorbidities, and clinical parameters before CRRT. It was found that patients with previous kidney disease had 3.36 times higher risks and 64% lower risks if the SpO_2/FiO_2 index was $\geq$ 200, and these results were comparable to the previously mentioned multicenter study [9]. By comparing studies with a similar design, it was determined that the obtained data were the following: 1) different significant predictors of AKI-RRT; 2) different modalities of RRT, anticoagulation, and other procedure parameters; 3) different testing periods which were included (in relation to the representation of vaccines and drugs); 4) the timing of the development of the AKI-RRT, which depends on the type and size of the sample, the availability of the RRT, and the organization capabilities. For these three years, we learned that the priority is the correct selection of patients for RRT, which included: age; the time period from onset of illness to admission to hospital; time from admission to presenting the patient to a nephrologist; presence of comorbidities; existence of previous kidney disease and rhabdomyolysis; the influence of nephrotoxins.

It should be emphasized that the key connection between the nephrologist and the intensivist lies in the presentation of the patient, which includes: SAPS II within 24 hrs, SpO_2/FiO_2 index, vasopressor dose, volemia state, diuresis with or without diuretic stimulation, values of nitrogenous substances, electrolytes and the presence of secondary infections.

The limitations of our study were: retrospective experience of a single center, absence of a control group, and having no complete data on volemia status and outcomes. Most patients were treated before recent clinical trials, which showed other drugs to be more effective.

Conclusion

Determining the risk factors for AKI/AKI on CKD is important for planning the prevention of these conditions that require the application of CRRT with the correct choice of dialysis modality and dose, membrane/filter type, and anticoagulant dose.

Acknowledgement

We would like to thank Dr. Dragana Milijašević for her assistance with statistical analysis.

REFERENCES

1. *Ronco C, Reis T, Husain-Syed F.* Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020; 8(7): 738–42.
2. *Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Baweja M,* et al. Acute Kidney Injury in Hospitalized Patients with COVID-19. medRxiv [Preprint] 2020. Update in: J Am Soc Nephrol 2021; 32(1): 151–60.
3. *Mohamed MMB, Lukitsch I, Torres-Ortiz AE, Walker JB, Varghese V, Hernandez-Arroyo CF,* et al. Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. Kidney360 2020; 1(7): 614–22.
4. *Thakkar J, Chand S, Aboodi MS, Gone AR, Alahiri E, Schecter DE*, et al. Characteristics, Outcomes and 60-Day Hospital Mortality of ICU Patients with COVID-19 and Acute Kidney Injury. Kidney360 2020; 1(12): 1339–44.
5. *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; 98(1): 209–18.

6. *Zhou S, Xu J, Xue C, Yang B, Mao Z, Ong ACM*. Coronavirus-associated kidney outcomes in COVID-19, SARS, and MERS: a meta-analysis and systematic review. Ren Fail 2020; 43(1): 1–15.
7. *Robbins-Juarez SY, Qian L, King KL, Stevens JS, Husain SA, Radhakrishnan J*, et al. Outcomes for Patients With COVID-19 and Acute Kidney Injury: A Systematic Review and Meta-Analysis. Kidney Int Rep 2020; 5(8): 1149–60.
8. *Domecq JP, Lal A, Sheldrick CR, Kumar VK, Boman K, Bolesta S,* et al. Outcomes of Patients with Coronavirus Disease 2019 Receiving Organ Support Therapies: The International Viral Infection and Respiratory Illness Universal Study Registry. Crit Care Med 2021; 49(3): 437–48. Erratum in: Crit Care Med 2021; 49(5): e562.
9. *Gupta S, Coca SG, Chan L, Melamed ML, Brenner SK, Hayek SS*, et al. AKI Treated with Renal Replacement Therapy in Critically Ill Patients with COVID-19. J Am Soc Nephrol 2021; 32(1): 161–76.
10. *Kooman JP, van der Sande FM*. COVID-19 in ESRD and Acute Kidney Injury. Blood Purif 2021; 50(4–5): 610–20.
11. *Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M*, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020; 16(12): 747–64. Erratum in: Nat Rev Nephrol 2020; 16(12): 765.
12. *Bilan N, Dastranji A, Ghalehgolab Behbahani A*. Comparison of the spo2/fio2 ratio and the pao2/fio2 ratio in patients with acute lung injury or acute respiratory distress syndrome. J Cardiovasc Thorac Res 2015; 7(1): 28–31.
13. *Tan BWL, Tan BWQ, Tan ALM, Schriver ER, Gutiérrez-Sacristán A, Das P,* et al. Long-term kidney function recovery and mortality after COVID-19-associated acute kidney injury: an international multi-centre observational cohort study. EClinicalMedicine 2022; 55: 101724.
14. *Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group*. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2(1): 1–138.
15. *Bezerra R, Teles F, Mendonca PB, Damte T, Likaka A, Ferrer-Miranda E,* et al. Outcomes of critically ill patients with acute kidney injury in COVID-19 infection: an observational study. Ren Fail 2021; 43(1): 911–8.
16. *Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A,* et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020; 323(16): 1574–81. Erratum in: JAMA 2021; 325(20): 2120.
17. *Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK*, et al. Covid-19 in critically ill patients in the Seattle region - case series. N Engl J Med 2020; 382(21): 2012–22.
18. *Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG,* et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective case series. BMJ 2020; 369: m1996.
19. *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(20): 2052–9. Erratum in: JAMA 2020; 323(20): 2098.
20. *Chan L, Chaudhary K, Saha A, Chauhan K, Vaid A, Zhao S,* et al. AKI in Hospitalized Patients with COVID-19. J Am Soc Nephrol 2021; 32(1): 151–60.
21. *Doher MP, Torres de Carvalho FR, Scherer PF, Matsui TN, Ammirati AL, Caldin da Silva B,* et al. Acute Kidney Injury and Renal Replacement Therapy in Critically Ill COVID-19 Patients: Risk Factors and Outcomes: A Single-Center Experience in Brazil. Blood Purif 2021; 50(4–5): 520–30.
22. *Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J*, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci 2020; 63(3): 364–74.
23. *Husain-Syed F, Slutsky AS, Ronco C*. Lung−kidney cross-talk in the critically ill patient. Am J Respir Crit Care Med 2016; 194(4): 402–14.
24. *Van den Akker JP, Egal M, Groeneveld AB*. Invasive mechanical ventilation as a risk factor for acute kidney injury in the critically ill: a systematic review and meta-analysis. Crit Care 2013; 17(3): R98.
25. *Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R,* et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med 2018; 379(15): 1431–42.
26. *Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A,* et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet 2020; 395(10235): 1506–15.
27. *Ostermann M, Joannidis M, Pani A, Floris M, De Rosa S, Kellum JA,* et al. Patient Selection and Timing of Continuous Renal Replacement Therapy. Blood Purif 2016; 42(3): 224–37.
28. *Knežević V, Azaševac T, Stražmešter Majstorović G, Marković M, Ružić M, Turkulov V,* et al. The importance of anticoagulation in COVID-19-related acute kidney injury requiring continuous renal replacement therapy. Srp Arh Celok Lek 2022; 150(1–2): 29–34.

Received on June 14, 2023
Revised on August 5, 2023
Revised on October 22, 2023
Revised on November 26, 2023
Accepted on December 5, 2023
Online First December 2023