SARS-COV2 Renal Impairment in Critical Care: A Retrospective Study of 42 Cases - Kid COVID Study

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Research

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Abstract

Background

The new coronavirus (SARS-CoV-2) infection leads to 5% to 16% hospitalization in Intensive Care Units (ICU) and is associated with 23% to 75% of kidney impairments, including acute kidney injury (AKI), as a major prognosis factor. The current work aims to characterize the renal impairment associated to SARS-CoV-2 in ICU patients, to evaluate its risk factors and its relationship with morbidity and mortality.

Methods

Forty-two patients consecutively admitted to the ICU of a university hospital (Paris, France) who tested positive for SARS-CoV-2 between March 25, 2020 and April 29, 2020 were included and classified in categories according to their renal function. Complete renal profiles and their evolution during ICU stay were fully characterized in 34 patients. Factors associated with AKI were identified through univariate analysis.

Results

Thirty-two patients (94,1%) met diagnostic criteria for intrinsic renal injury with a mixed pattern of tubular and glomerular injuries within the first week of ICU admission, that lasted upon discharge. During their ICU stay, 24 patients (57.1%) presented AKI which was associated with increased mortality ($p = 0.007$), hemodynamic failure ($p = 0.022$), and more altered clearance at hospital discharge ($p = 0.001$). AKI occurrence was associated with lower pH ($p = 0.024$), higher $PaCO_2$ ($p = 0.027$), PEEP ($p = 0.027$), procalcitonin ($p = 0.015$), and CRP ($p = 0.045$) on ICU admission.

Conclusions

Critical SARS-CoV-2 is associated with persistent intrinsic renal injury and AKI, which is a risk factor of mortality. Identifying SARS-CoV-2 patients at risk of AKI will help in modifying clinical practice in ICU.

Trial registration

In accordance with the French law on biomedical research, this study obtained the approval of an Institutional Review Board (“Comité d’Éthique de la Recherche en Anesthésie-Réanimation” under the reference IRB 00010254 - 2020 - 106). Patients were all informed of the possible use of their data in researches as well as their right and terms of objection. Data were collected and integrated anonymously into a secure database in accordance with the French CNIL MR-004 methodology (registration number 20200803123416).

Background

About 5% to 16% (1,2) of the patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) required hospitalization in Intensive Care Units (ICU), mainly for respiratory distress associating dyspnea, high respiratory rate, low oxygen saturation, or rapid increase in lung infiltrates (3,4). Mortality associated with ICU hospitalizations ranged from 49% to 67% (5,6). While respiratory symptoms are the cornerstone of the disease, other organs can be affected. Acute kidney injury (AKI) occurred in 23% of SARS-CoV-2 patients during their hospitalization (7), and Renal Replacement Therapy (RRT) was used for 13% of them (8). However, when urine dipstick tests are systematically performed, the incidence of renal impairment on hospital admission can be evaluated as high as 75% (9). The SARS-CoV-2 is thought to have a direct renal toxicity (10) *via* entry into proximal tubular cells and podocytes where angiotensin converting enzyme 2 (ACE2) receptors and transmembrane serine proteases (TMPRSS) are highly expressed (11,12). In critically ill patients, other factors may be implicated, such as cytokine storm, angiotensin II pathway activation, dysregulation of complement, hypercoagulation, and microangiopathy (7). Moreover, 14% of SARS-CoV-2 patients will develop acute respiratory distress syndrome (ARDS) (2) that is, by itself, also independently associated with AKI out of SARS-CoV-2 context (13,14). This specific impairment could be associated with a higher mortality rate in ICU (10).

However, at this time, no study has characterized renal impairment of SARS-CoV-2 in ICU patients. Our work aims to define the intrinsic renal injury induced by SARS-CoV-2 infection in critically ill patients, its consequences in terms of renal function, and its relationship with morbidity and mortality.

Methods

Study design and patients

This data-based, monocentric, observational study was conducted in a university hospital (Hôpital Saint-Antoine, Assistance Publique - Hôpitaux de Paris, France). All patients admitted to the ICU who tested positive for SARS-CoV-2 by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) on nasopharyngeal or tracheal swab between March 25, 2020 and April 29, 2020 were included. Data were selected from electronic medical records (**see additional file 1**).

Definitions

The diagnosis of ARDS was carried out according to the Berlin criteria (16) (**see additional file 1**). AKI scoring was defined according to the 2012 Kidney Disease: Improving Global Outcome (KDIGO) definitions (17) and AKI as KDIGO ≥ 1. We defined the serum creatinine baseline as the serum value on ICU admission, as previously described (18). In order to characterize the renal impairment of patients, the following standard definitions were used: i/ renal response to hypovolemia – a marker predictive of prerenal acute kidney injury- as a fractional excretion of urea (FeUrea) of less than 35%; ii/ glomerular injury as the excess of high molecular weight proteins in urine: albuminuria >0.03 g/24h accounting for > 50% of total proteinuria or associated with supraphysiologic excretion of immunoglobulin G (IGG) (> 11.3 mg/24h). Samples with macroscopic hematuria were excluded as blood can interfere with the

interpretation of proteinuria; iii/ proximal tubular injury as an increase in urinary low molecular weight proteins: urinary retinol binding protein (RBP) (>1.1 mg/24h) or urinary alpha1-microglobulin (>15.8 mg/24h) in the absence of glomerular injury; iv/ renal tubular acidosis as a positive urinary anion gap in a context of metabolic acidosis; v/ mixed intrinsic kidney injury as the association of glomerular injury and renal tubular acidosis or by the presence of urinary IGG (>11.3 mg/24h) associated with albuminuria < 50% of daily proteinuria; glomerular injury, proximal tubular injury, renal tubular acidosis and mixed intrinsic kidney injury are referred as intrinsic kidney injury. Augmented renal clearance (ARC), was defined as a clearance greater than 120 $ml.min^{-1}$ (19).

Statistical analysis

Mean and standard deviation (SD) or median and interquartile ranges (25th; 75th percentiles) were calculated for continuous variables, while numbers and percentages were calculated for categorical parameters. The normal distribution of each continuous variable was assessed with the use of the Shapiro–Wilk test. For the univariate analysis, categorical variables were compared between independent groups using the exact Fisher test or the Chi-square tests, and continuous variables were compared using the Student's t-test or the Mann-Whitney test. Chord diagrams were used to depict the relationship between organic kidney impairment and kidney function at two different time points of the ICU stay. All statistical analyses were performed on R (version 3.6.2 for Macintosh, licenses GNU GPL, The R foundation for statistical computing, Vienna, Austria). All tests were 2-sided and a p-value < 0.05 was considered for statistical significance.

Results

Characteristics of the study population

During the study period, between March 25, 2020 and April 29, 2020, 42 patients were admitted in ICU for SARS-CoV-2 infection, benefited of urine assessment and were analyzed. The characteristics of the population are summarized in **Table 1**. Patients, median age 61.5 years old (interquartile range (IQR) (54.2;65 years)) were hospitalized in ICU on a median of 8 days (IQR,7;12 days) after their first SARS-CoV-2 symptoms. Among them, 25 patients (59.5%) presented at least one comorbidity, including chronic kidney disease (CKD) in 7 patients (16.7%), and overweight with a median body mass index (BMI) of 27.2 $kg.m^{-2}$ (IQR, 24.3 $kg.m^{-2}$;30 $kg.m^{-2}$). On ICU admission, most of the patients presented a moderate to severe ARDS (41 out of 42) with a median ratio of arterial partial pressure of oxygen and inspired fraction of oxygen (PaO2/FiO2) of 140 (IQR 103.7;172.9). Ten patients (23.8%) presented an altered clearance (< 60 $ml.min^{-1}$) at their ICU admission. **See additional file 2.**

Table 1. Baseline and ICU admission patients' characteristics

	Overall (n=42)	Non-AKI (n=18)	AKI (n=24)	p-value
Age (years)	61.50 [54.25, 65.00]	60.50 [49.75, 66.00]	61.50 [55.50, 65.00]	0.684
Male (%)	34 (81.0)	15 (83.3)	19 (79.2)	1.000
BMI (kg.m-2)	27.25 [24.30, 30.00]	25.10 [23.80, 27.10]	29.40 [27.40, 30.90]	0.009
No comorbidities (%)	17 (40.5)	7 (38.9)	10 (41.7)	1.000
CKD (%)	7 (16.7)	2 (11.1)	5 (20.8)	0.679
SOFA score	7.00 [4.00, 9.75]	4.50 [3.00, 8.50]	8.00 [6.00, 11.25]	0.134
CRP (mg.L-1)	246.15 [144.88, 300.20]	167.00 [140.52, 275.75]	274.30 [213.85, 330.12]	0.045
Procalcitonin (ng.mL-1)	1.01 [0.29, 2.50]	0.27 [0.13, 0.91]	1.56 [0.62, 3.70]	0.015
GFR by MDRD (ml.min-1)	87.72 [64.71, 117.29]	91.80 [72.38, 135.85]	82.47 [54.53, 102.27]	0.213
Creatinine (µmol.L-1)	76.50 [61.75, 100.75]	74.50 [54.25, 93.50]	82.00 [69.25, 118.50]	0.208
ARC (%)	10 (23.8)	6 (33.3)	4 (16.7)	0.281
pH	7.41 [7.34, 7.47]	7.44 [7.40, 7.48]	7.35 [7.29, 7.44]	0.024
PEEP (cmH2O)	12.00 [8.25, 12.00]	8.00 [8.00, 12.00]	12.00 [10.00, 14.00]	0.027
PaCO2 (mmHg)	40.00 [34.00, 44.00]	35.00 [32.25, 40.75]	42.00 [35.00, 47.50]	0.027
PaO2/FiO2 Ratio	140.00 [103.75, 172.86]	112.50 [95.75, 148.25]	148.00 [113.12, 182.86]	0.124

**Values are expressed as median (interquartile ranges), absolute value (percentages); ARC (augmented renal clearance),BMI (body mass index), CKD (chronic kidney disease), CRP (C reactive protein), GFR (glomerular filtration rate), PaCO2 (CO2 partial pressure in the arterial blood), PEEP (positive end-expiratory pressure), SOFA (sequential organ failure assessment score)*

First week kidney abnormalities (Table 2)

The first blood analysis including inflammatory cytokines and urinary assessment was performed on a median of 8 days after ICU admission (IQR 6; 10 days), **see additional file 3**. Complete urinary samples

allowing to define intrinsic renal injury were available for 34 patients.

Ten patients (29.4%) had AKI according to KDIGO criteria (4 patients were KDIGO1, 1 were KDIGO2, and 5 were KDIGO3). Augmented renal clearance was documented in 9 patients (31%).

Fifteen patients (48.4%) presented criteria for renal response to hypovolemia and 32 patients (94.1%) met the diagnostic criteria for intrinsic kidney injury. Among the latter, 25 patients (73.5%) had mixed intrinsic kidney injury while 6 (17.6%) had a proximal tubular injury and 1 (2.9%) had glomerular injury. Twenty-three patients had significant albuminuria (defined as albuminuria >0.03 g/24h).

Table 2. First week kidney function and impairment characterization

	Overall (n = 34)	Non-AKI (n = 15)	AKI (n = 19)	p.value
Days from ICU admission	8.00 [6.00, 10.00]	8.00 [6.00, 10.00]	8.00 [5.50, 10.00]	0.958
Creatinine clearance (ml.min^{-1})	96.21 [67.69, 126.41]	126.41 [105.48, 157.48]	68.73 [41.52, 86.17]	<0.001
ARC (%)	9 (31.0)	7 (53.8)	2 (12.5)	0.041
KDIGO (%)				0.002
0	24 (70.6)	15 (100.0)	9 (47.4)	
1	4 (11.8)	0 (0.0)	4 (21.1)	
2	1 (2.9)	0 (0.0)	1 (5.3)	
3	5 (14.7)	0 (0.0)	5 (26.3)	
RENAL IMPAIRMENT				
Hypovolemia (%)	15 (48.4)	8 (57.1)	7 (41.2)	0.479
Intrinsic kidney injury (%)				0.364
Glomerular	1 (2.9)	0 (0.0)	1 (5.3)	
Mixed	25 (73.5)	10 (66.7)	15 (78.9)	
Proximal tubular	6 (17.6)	3 (20.0)	3 (15.8)	
Tubular acidosis	0 (0.0)	0 (0.0)	0 (0.0)	
None	2 (5.9)	2 (13.3)	0 (0.0)	

Values are expressed as median (interquartile ranges), absolute value (percentages); ICU (intensive care unit), ARC (augmented renal clearance).

Kidney abnormalities on ICU discharge (Table 3)

The first blood analysis including inflammatory cytokines and urinary assessment was performed on discharge from ICU at a median of 20 days after admission (IQR 15.75;23.25 days), **see additional file 4**. Urinary samples were available for 16 patients who stayed in ICU, eight were dead and ten were transferred to another hospital without any urinary analysis.

On discharge, 4 patients (25%) had AKI according to KDIGO criteria (2 patients were KDIGO 1, 1 patient was KDIGO 2, 1 was KDIGO 3). Conversely, ARC was found in 6 patients (50%).

Five patients (35.7%) presented criteria for renal response to hypovolemia and 16 patients (100%) met the diagnostic criteria for intrinsic kidney injury. Among them, mixed injury was documented in 7 patients (43.8%) while proximal tubular injury was documented in 4 patients (25%) and glomerular injury in 5 patients (31.2%). Seven patients had significant albuminuria.

Relationship between kidney function estimated by KDIGO and intrinsic kidney injury at early and late stages are represented in **Figure 1**.

Table 3. Kidney abnormalities on ICU discharge.

	Overall (n = 16)	Non-AKI (n = 7)	AKI (n = 9)	p.value
Days from ICU admission	20.00 [15.75, 23.25]	20.00 [15.00, 22.50]	20.00 [19.00, 23.00]	0.749
Creatinine clearance (ml.min^{-1})	113.49 [69.30, 142.07]	139.90 [81.20, 143.75]	101.11 [50.37, 133.69]	0.372
ARC (%)	6 (50.0)	3 (60.0)	3 (42.9)	1.000
KDIGO (%)				0.070
0	10 (71.4)	7 (100.0)	3 (42.9)	
1	2 (14.3)	0 (0.0)	2 (28.6)	
2	1 (7.1)	0 (0.0)	1 (14.3)	
3	1 (7.1)	0 (0.0)	1 (14.3)	
RENAL IMPAIRMENT				
Hypovolemia (%)	5 (35.7)	2 (28.6)	3 (42.9)	1.000
Intrinsic kidney injury (%)				0.572
Glomerular	5 (31.2)	3 (42.9)	2 (22.2)	
Mixed	7 (43.8)	2 (28.6)	5 (55.6)	
Proximal tubular	4 (25.0)	2 (28.6)	2 (22.2)	
Tubular acidosis	0 (0.0)	0 (0.0)	0 (0.0)	
None	0 (0.0)	0 (0.0)	0 (0.0)	

Values are expressed as median (interquartile ranges), absolute value (percentages); ARC (acute renal clearance), ICU (intensive care unit)

Prognosis associated with AKI

Twenty-four patients (57.1%) presented AKI during their ICU stay. Mortality (33.3% vs. 0%, respectively in AKI and non-AKI group, p = 0.007) and duration of catecholamine support (7 days vs. 2 days respectively in AKI and non-AKI group, p = 0.022) were higher in AKI patients. Conversely, length of stay in ICU (20 days vs 19.5 days respectively in AKI and non-AKI group, p = 0.507) and mechanical ventilation duration (22 days vs 17 days respectively in AKI and non-AKI group, p = 0.173) were comparable between the two groups. Discharge from hospital occurred at a median of 30 days after admission (IQR 18.5; 46.5 days). At this time, patients with AKI during ICU stay had a lower value of creatinine clearance (37.93 ml.min⁻¹

vs 121.04 ml.min⁻¹ respectively in AKI and non-AKI group, p = 0.005). Creatinine clearance significantly decreased from hospital admission to discharge when AKI occurred during the stay. **(Table 4)**

Augmented Renal Clearance was observed in 23 patients (54.8%) and more frequent in the non-AKI group (29.2% and 88.9% respectively in AKI and non-AKI group, p < 0.001). **See additional file 5.**

Table 4. Prognosis of SARS-COV-2 patients according to the presence of an acute kidney injury during the ICU stay.

	Overall (n=42)	Non-AKI (n=18)	AKI (n=24)	p-value
KIDNEY FUNCTION DURING ICU STAY				
ARC (%)	23 (54.8)	16 (88.9)	7 (29.2)	<0.001
KDIGO				
KDIGO 0 (%)	18 (42.9)	18 (100.0)	0 (0.0)	<0.001
KDIGO 1 (%)	12 (28.6)	0 (0.0)	12 (50.0)	
KDIGO 2 (%)	3 (7.1)	0 (0.0)	3 (12.5)	
KDIGO 3 (%)	9 (21.4)	0 (0.0)	9 (37.5)	
ORGAN SUPPORT DURING ICU STAY				
Length of mechanical ventilation (days)	19.00 [11.00, 28.00]	17.00 [6.25, 23.75]	22.00 [12.00, 34.00]	0.173
Vasopressors (days)	5.00 [1.00, 10.00]	2.00 [1.00, 5.50]	7.00 [3.50, 14.50]	0.022
Dialysis (%)	9 (21.4)	0 (0.0)	9 (37.5)	0.005
PROGNOSIS				
Creatinine clearance < 60 ml.min^{-1} on ICU discharge (%)	11 (27.5)	0 (0.0)	11 (45.8)	0.001
ICU LOS (days)	19.50 [14.00, 33.25]	20.00 [13.75, 30.75]	19.50 [15.50, 36.25]	0.507
ICU mortality (%)	8 (19.0)	0 (0.0)	8 (33.3)	0.007

**Values are expressed as median (interquartile ranges), absolute value (percentages); ARC (acute renal clearance), LOS (length of stay).*

On univariate analysis, patients of the AKI group had higher creatinine levels on hospital admission (94 µmol.L⁻¹ vs 74 µmol.L ⁻¹, p = 0.037). They also had higher BMI (29.4 kg.m⁻² vs 25.1 kg.m⁻², p = 0.009), higher PaCO2 (42 mmHg vs 35 mmHg, p = 0.027), lower pH (7.35 vs 7.44, p = 0.024), higher positive end-expiratory pressure (PEEP) (12 cmH2O vs 8 cmH2O, p = 0.027), higher procalcitonin (PCT) blood concentration (1.56 ng.ml⁻¹ vs 0.27 ng.ml⁻¹, p = 0.015), higher C-reactive protein (CRP) blood concentration (274.3 mg.L⁻¹ vs 167 mg.L⁻¹, p = 0.045) on ICU admission in comparison to non AKI group (**Table 1 and Suppl. Table E1**)

Other known risk factors such as nephrotoxic agents' infusion (e.g., contrast agents, diuretics, aminosides), negative fluid balance and admission severity scores (SOFA and SAPSII scores) didn't show any statistical association with the occurrence of AKI.

Discussion

The current cohort is representative of critical SARS-COV-2 patients with 80% of overweight men with a median age of 61.5 years, and at least one comorbidity (including hypertension and diabetes mellitus), (20,21). All of the patients had mechanical ventilation because of moderate to severe ARDS onset, which is in line with previous retrospective studies (20). Patients were comparable in terms of severity (median SOFA score of 7) to those usually admitted for ARDS (22).

Within the first week of ICU admission, 94.1% of patients had features of intrinsic kidney injury and all the patients had documented intrinsic kidney injury three weeks after admission. Fifty-seven per cent of patients presented AKI according to KDIGO ranking and one third of them required RRT (**Table 4**). Conversely, 54.8% of patients presented augmented renal clearance (ARC) during their ICU stay including 29.2% patients in the AKI group. The intrinsic renal injury differed according to the time from admission; within the first week, patients presented mainly mixed injury (73.5%) while on discharge injuries were distributed between mixed injury, glomerular injury, and tubular injury (43.8%, 31.2%, and 25% respectively). To our knowledge, this is the first study describing with this level of precision kidney injury during SARS-CoV2 infection leading to ICU care.

In our cohort, 82.5% of critical SARS-CoV-2 patients presented proteinuria, indicating a high rate of intrinsic kidney injury which is in line with Pei et al concerning the Wuhan pandemic (9). In ICU patients, acute tubular necrosis is well documented up to 78% patients in autopsy series (23) whereas this current population of critically ill SARS-CoV-2 patients presented mixed pattern lesions (23,24). The prognostic significance of proteinuria or intrinsic kidney injury is unclear: it might reflect a strong adaptative potential of the kidney, or on the opposite, might be an early symptom of renal impairment. It might also reflect a specific effect of SARS-CoV-2 infection on kidney cells, as suggested by previous descriptions of viral inclusions and by the expression of the ACE2 (the virus' putative receptor for cell invasion) in renal glomerular and tubular cells (7). It has to be noted that all the patients had a urinary catheter that could

induce proteinuria in case of traumatic catheterization, reinforcing the importance of a complete urinary profile to describe the intrinsic kidney injury specific to SARS-CoV2. In another study conducted by Cheng et al. (18), including ICU and non ICU patients, only 9.8% of the patients had a urinary catheter, whereas 43.9% had proteinuria. This supports the idea that SARS-CoV-2 was responsible for the proteinuria that could be as high as 6.6 g/l in the current cohort.

In the current cohort, 94.12% patients presented with either AKI (KDIGO≥1) or intrinsic renal impairment (tubular or glomerular or mixed injury with KDIGO=0). Lower molecular weight proteins excretion (such as alpha1-microglobulin) in the non-AKI group in comparison to the AKI group suggests a continuum from intrinsic kidney injury to AKI. On the other hand, we assessed the contribution of prerenal mechanisms to AKI in these patients using the fractional excretion of urea (FeUrea). FeUrea is a robust marker of the renal response to hypovolemia more relevant than other markers like fractional excretion of sodium or urine to plasma ratio of creatinine, especially in case of diuretic use. According to FeUrea values hypovolemia is frequent among COVID-19 patients in ICU but the lack of association between AKI and low FeUrea values strengthens the role of intrinsic kidney injury associated to SARS-CoV2 infection in AKI occurrence.

Although the small number of patients did not allow to perform a multivariate analysis, univariate analysis highlighted several predictive factors of AKI during SARS-CoV-2 infection. Firstly, pre-hospital kidney function, defined as renal functional reserve (25), might be critical in renal prognosis with higher creatinine level on hospital admission in patients who will develop AKI (94 μmol.l^{-1} in AKI group vs 74 μmol.l^{-1}in non-AKI group). This creatinine value depends on patient's prior renal function but also on many other factors: hypovolemia induced by prolonged fever, infection-induced digestive disorders (26) and chronic hypertension, especially if treated by ACE inhibitors (27,28). However, hypovolemia may, at least partly, play a role as up to 50% of SARS-COV-2 patients had modified fractional excretion of urea during their ICU stay related to ARDS management, that requires avoidance of excess fluid infusion (29).

Secondly, in the current cohort, all the patients presented high inflammatory response to SARS-CoV-2 infection, including high levels of IL6 plasma concentrations, as documented in previous studies (30) and morevover those who developed AKI had significantly higher CRP and PCT values on ICU admission.

Thirdly, mechanical respiratory support including the level of PEEP is critical in developing AKI in SARS-COV-2. As described by Hirsch et al., SARS-CoV-2 ventilated patients are at greater risk of developing AKI than non-ventilated ones (89.7% vs. 21.7%), especially during the first 24 hours following intubation (31). Elevation of central venous pressure due to high intrathoracic pressures may result in an increased kidney hydrostatic pressure, which leads to glomerular filtration impairment (32,33). Patients in both groups (AKI or non-AKI) presented similar PaO2/FiO2 ratios, indicating that the severity of the lung impairment is independent of kidney injury and, thus, reinforcing the importance of a tight controlled and tailored PEEP level. Finally, even if univariate analysis did not show any association between the type of organic impairment and AKI, all of critical patients presented intrinsic kidney injury 3 weeks after admission, which should contribute to the loss of renal functional reserve.

Renal prognosis is also a key issue for SARS-CoV-2 patients, considering the incidence of intrinsic kidney injury and the proportion of AKI. In a study including 5,273 non-SARS-COV-2 patients with no preexisting CKD, who developed AKI during an ICU stay, de novo AKI was associated with increased short and long-term risk of death at one and five years (34). At one year, AKI acquired in ICU was also independently associated with increased risk of CKD (6%) and end stage renal disease (2%). In our study, among the 42 patients, 24 patients (57.1%) presented AKI during their ICU stay. When discharged from the hospital, 45.8% of the patients who developed AKI had impaired renal function with a creatinine clearance < 60 ml.min^{-1}. Given the facts that patients had several known risk factors for developing chronic kidney disease (sepsis, ARDS, mechanical ventilation, and inflammatory and procoagulant responses) and that direct viral injury on kidney cells is still not yet fully characterized, long-term nephrological follow-up may be required for all those who have developed AKI, especially if they have other comorbidities or still have proteinuria.

The current study also revealed ARC in more than 50% of patients, especially in those who did not present AKI during their ICU stay (88.9%). In a systematic review, 20 to 65% of critically ill patients presented ARC with a higher prevalence in trauma patients (35). Two main mechanisms have been suggested to explain ARC: i/ the release of pro-inflammatory cytokines that would lead to a decrease in resistance and an increase in glomerular filtration rate thanks to an increase in cardiac output and ii/ the efficacy of the physiological renal reserve allowing an increased glomerular filtration rate to cope with certain pathological situations such as ICU care. However, we did not find an increase in albuminuria in patients with ARC, suggesting that it more likely reflect just a hemodynamic adaptation. According to some authors, ARC is a good prognostic factor, which is confirmed by our study (36). This ARC highlights a potential issue in critical patients because the use of regular doses of renally cleared drugs might induce underdosage (37). This is of most importance considering antimicrobial treatment such as beta-lactam antibiotics, vancomycin or aminoglycosides where ARC may condition clinical failure or emergence of resistance if higher dosage is not used.

Eventually, another point highlighted by the current study is the significant association between kidney failure and mortality, as 33.3% of AKI patients died, in comparison to 0% in the non-AKI patients. This relationship was suggested in previous studies in the pandemic context (18) with a 3.5 fold higher mortality in case of AKI KDIGO stage 2 or more (38).

This study has several limitations. First, it includes only a limited number of patients (42 patients) in one university hospital, making it impossible to rule out residual confusion and bias. In addition, some clinical and biological data from the admission to discharge from ICU were missing. Also, we used the baseline creatinine level at hospital entry as the baseline creatinine level for some patients, which could lead to an underestimation of AKI.

Conclusions

The prevalence of SARS-CoV-2 intrinsic kidney injury in critical care patients is high. A mixed injury is noticed early and persists during hospital stay. AKI is associated with mortality in excess in ICU patients and poor renal outcome. Detecting intrinsic renal injuries by analyzing complete urinary profiles on ICU admission might be recommended to adapt the clinical management of critical SARS-COV-2 patients.

List Of Abbreviations

ACE2: angiotensin converting enzyme 2

AKI: acute kidney injury

ARC: augmented renal clearance

ARDS: acute respiratory distress syndrome

BMI: body mass index

CKD: chronic kidney disease

CNIL: centre national informatique et liberté

CRP: C-reactive protein

FeUrea: fractional excretion of urea

FiO2: inspired fraction of oxygen

GFR: glomerular filtration rate

ICU: intensive care unit

IGG: immunoglobulin G

IL6: interleukine 6

IQR: interquartile range

KDIGO: Kidney Disease: Improving Global Outcome

LOS: length of stay

PaCO2: CO2 partial pressure in the arterial blood

PaO2/FiO2: arterial partial pressure of oxygen and inspired fraction of oxygen

PCT: procalcitonin

PEEP: positive end-expiratory pressure

RBP: retinol binding protein

RRT: renal replacement therapy

RT-PCR: reverse Transcription-Polymerase Chain Reaction

SAPSII: new simplified acute physiology score

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SD: standard deviation

SOFA: sepsis-related organ failure assessment

TMPRSS: receptors and transmembrane serine proteases

Declarations

Ethics and approval

In accordance with the French law on biomedical research, this study obtained the approval of an Institutional Review Board (“Comité d’Éthique de la Recherche en Anesthésie-Réanimation” under the reference IRB 00010254 - 2020 - 106). **See additional file 1.**

Consent for publication

Patients were all informed of the possible use of their data in researches and publications as well as their right and terms of objection In order to guarantee the security of personal data, the investigators integrated the data anonymously into a secure database in accordance with the French Commission Nationale de l’Informatique et des Libertés (CNIL) reference methodology (MR) - 004 and registered it under the number 20200803123416. **See additional file 1.**

Availability of data and materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

All the authors declared no competing interests.

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Author contributions

FF and FV designed the study. ACG, AMB, FF, LD and NH collected the data. EP contributed analytical tools and prepared the figures and tables. AMB, EP, ET, FF, FV, and PG wrote the paper. MG, FB, and FV conceived the project and supervised and coordinated all the work.

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Figures

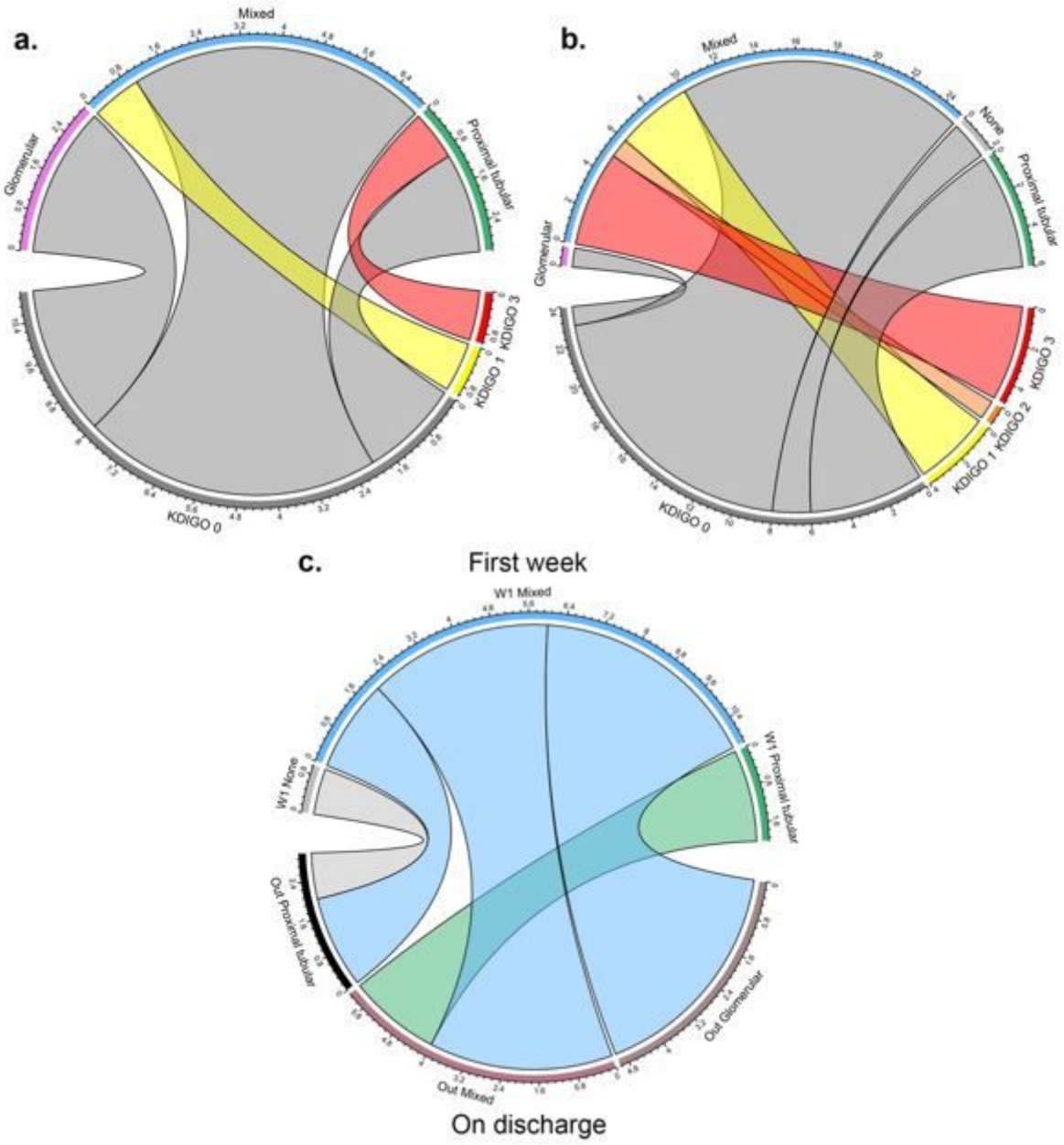

Figure 1

Chord diagrams representing characteristics of kidney injury during the ICU stay. a. Relationship between kidney function estimated by KDIGO and intrinsic kidney injury within the first week after ICU admission. b. Relationship between kidney function estimated by KDIGO and intrinsic kidney injury on ICU discharge. c. Evolution of the intrinsic kidney injury between the first week after ICU admission and ICU discharge. The bottom part of the diagram represents patients sorted by their KDIGO classification, and the top part

represents the same patients ranked according to the intrinsic kidney injury diagnosis made by profiling urinary analysis. Ribbons show for every patient the connection between kidney injury and function.

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