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Risk Factors of AKI in Acute Respiratory Distress Syndrome: A Time-Dependent Competing Risk Analysis on Severe COVID-19 Patients

Antoine Marchiset[1], Valerie Serazin[2], Omar Ben Hadj Salem[1], Claire Pichereau[1], Lionel Lima Da Silva[1], Siu-Ming Au[1], Christophe Barbier[1], Yann Loubieres[1], Jan Hayon[1], Julia Gross[1], Herve Outin[1], and Matthieu Jamme[1,3,4]

Abstract

Introduction: Acute kidney injury (AKI) is frequently observed in patients with COVID-19 admitted to intensive care units (ICUs). Observational studies suggest that cardiovascular comorbidities and mechanical ventilation (MV) are the most important risk factors for AKI. However, no studies have investigated the renal impact of longitudinal covariates such as drug treatments, biological variations, and/or MV parameters.

Methods: We performed a monocentric, prospective, longitudinal analysis to identify the dynamic risk factors for AKI in ICU patients with severe COVID-19.

Results: Seventy-seven patients were included in our study (median age: 63 [interquartile range, IQR: 53-73] years; 58 (75%) men). Acute kidney injury was detected in 28 (36.3%) patients and occurred at a median time of 3 [IQR: 2-6] days after ICU admission. Multivariate Cox cause-specific time-dependent analysis identified a history of hypertension (cause-specific hazard (CSH) = 2.46 [95% confidence interval, CI: 1.04-5.84]; $P = .04$), a high hemodynamic Sequential Organ Failure Assessment score (CSH = 1.63 [95% CI: 1.23-2.16]; $P < .001$), and elevated $Paco_2$ (CSH = 1.2 [95%CI: 1.04-1.39] per 5 mm Hg increase in Pco_2; $P = .02$) as independent risk factors for AKI. Concerning the MV parameters, positive end-expiratory pressure (CSH = 1.11 [95% CI: 1.01-1.23] per 1 cm H_2O increase; $P = .04$) and the use of neuromuscular blockade (CSH = 2.96 [95% CI: 1.22-7.18]; $P = .02$) were associated with renal outcome only in univariate analysis but not after adjustment.

Conclusion: Acute kidney injury is frequent in patients with severe COVID-19 and is associated with a history of hypertension, the presence of hemodynamic failure, and increased Pco_2. Further studies are necessary to evaluate the impact of hypercapnia on increasing the effects of ischemia, particularly in the most at-risk vascular situations.

Abrégé

Introduction: L'insuffisance rénale aiguë (IRA) est fréquemment observée chez les patients atteints de COVID-19 admis dans les unités de soins intensifs (USI). Des études observationnelles suggèrent que les comorbidités cardiovasculaires et la ventilation mécanique (VM) seraient les plus importants facteurs de risque de l'IRA. Aucune étude n'a cependant examiné l'impact sur la fonction rénale de covariables longitudinales telles que les traitements médicamenteux, les variations biologiques et/ou les paramètres de la VM.

Méthodologie: Nous avons procédé à une analyse prospective et longitudinale dans un seul centre hospitalier afin d'identifier les facteurs de risque dynamiques de l'IRA chez les patients hospitalisés aux USI en raison d'une forme grave de la COVID-19.

Résultats: Soixante-dix-sept patients ont été inclus dans notre étude (75 % d'hommes [n=58]; âge médian: 63 ans [ÉIQ: 53-73]). L'IRA a été détectée chez 28 patients (36,3 %) et est survenue dans un délai médian de 3 jours (ÉIQ: 2-6 jours) après l'admission à l'USI. Une analyse de Cox multivariée, spécifique à la cause et tenant compte du temps, a permis de dégager les éléments suivants comme étant des facteurs de risque indépendants pour l'IRA: des antécédents d'hypertension (probabilité par cause [PPC]=2,46 [IC 95 %: 1,04-5,84]; p=0,04), un score SOFA hémodynamique élevé (PPC=1,63 [IC 95 %: 1,23-2,16]; p<0,001) et une concentration élevée de PaCO2 (PPC=1,2 [IC 95 %: 1,04-1,39] pour chaque augmentation de 5 mmHg de pCO2; p = 0,02). En ce qui concerne les paramètres de la VM, une pression expiratoire positive (PPC=1,11

[IC 95 %: 1,01-1,23] pour chaque augmentation de 1 cm H2O; p = 0,04) et l'utilisation d'un bloc neuromusculaire (PPC=2,96 [IC 95 %: 1,22-7,18]; p=0,02) ont été associés à l'IRA dans l'analyse univariée seulement, et non après ajustement.
Conclusion: L'IRA est fréquente chez les patients atteints d'une forme grave de COVID-19 et elle est associé à des antécédents d'hypertension, à la présence d'une instabilité hémodynamique et à une augmentation de la pCO2. D'autres études sont nécessaires pour évaluer l'impact de l'hypercapnie sur l'augmentation des effets de l'ischémie, en particulier dans les situations vasculaires les plus à risque.

Keywords
acute kidney injury, acute respiratory distress syndrome, COVID-19, time-dependent survival analysis

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Introduction

Acute kidney injury (AKI) is one of the most frequent organ dysfunction encountered in intensive care units (ICUs), particularly in patients admitted for acute respiratory distress syndrome (ARDS).[1,2] Resulting from various mechanisms (inflammatory, hemodynamic, ischemic, etc), the occurrence of AKI affects short-term and long-term outcomes.[3]

Since December 2019, ICUs around the world have faced a significant increase in admissions for a particular form of ARDS: severe COVID-19. It is estimated that AKI is frequently observed in patients with COVID-19. If several risk factors for AKI identified are mainly related to patients' comorbidities (hypertension, diabetes, chronic kidney disease), mechanical ventilation (MV) seems to be the most affected.[4]

The kidney-lung interaction concept is not new, and several animal models had already reported kidney alteration occurring after MV initiation through hemodynamic, immunoinflammatory, and/or neurohormonal mechanisms.[5] In humans, recent data published by Geri et al[6] suggested the relationship between increased positive end-expiratory pressure (PEEP) and the onset of AKI. However, although using an adapted model for longitudinal data, the absence of adjustment on other biomarkers and/or nephrotoxic drugs limited the interpretation.

We aimed to identify risk factors for AKI in a cohort of ICU patients admitted for severe SARS-CoV-2 infection.

Patients and Methods

Patients

All adult patients admitted to our ICU between March 1, 2020, and June 1, 2020, for acute respiratory failure with a positive SARS-CoV2 reverse transcription-polymerase chain reaction (RT-PCR) by nasopharyngeal swab or bronchoalveolar lavage (protocol based on the RdRp gene [nCoV_IP2 and nCoV_IP4] developed by the National Reference Center for Respiratory Viruses, Institut Pasteur, Paris) or SARS-CoV-2 serology were included (Figure 1).

Included patients presented at least several characteristics suggesting onset of an ARDS, with chest radiograph showing bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules; clinical respiratory failure with polypnea or struggle to breath; and need for high levels of oxygen (MV, noninvasive ventilation [NIV], high-flow nasal oxygen [HFNO], or standard oxygen >10 L/min). Baseline characteristics of the patients are listed in Table 1.

RT-PCR Protocol

Because our cohort study is composed of patients admitted during first wave, no commercial RT-PCR kit for SARS-CoV-2 diagnosis was available. We used the protocol based on the RdRp gene (nCoV_IP2 and nCoV_IP4) developed by the National Reference Center for Respiratory Viruses, Institut Pasteur, Paris. This protocol is available on the World Health Organization Web site (https://www.who.int/docs/default-source/coronaviruse/real-time-rt-pcr-assays-for-the-detection-of-sars-cov-2-institut-pasteur-paris.pdf). Real-time RT-PCR was performed with the SuperScript III Platinum One-Step Quantitative RT-PCR System (Invitrogen, Waltham, MA) on the Roche LightCycler 480 Real-Time PCR Detection System. Primers and probes were provided by Eurogentec (Liege, Belgium).

Data Collected

Data collected at admission to the ICU were extracted: medical and surgical history, demographic characteristics, date of symptoms' onset, date of PCR or serology positivity,

[1]Médecine intensive - Réanimation, Centre hospitalier de Poissy - Saint Germain en Laye, Poissy, France
[2]Laboratoire de biologie, Centre hospitalier de Poissy - Saint Germain en Laye, Poissy, France
[3]INSERM U1018, Centre de recherche en épidémiologie et santé des populations, Equipe "Epidémiologie clinique", Université Paris Saclay, Villejuif, France
[4]Réanimation et Unité de Soins Continus, Hôpital privé de l'Ouest Parisien, Ramsay Générale de santé, Trappes, France

Corresponding Author:
Matthieu Jamme, Réanimation et Unité de Soins Continus, Hôpital privé de l'Ouest Parisien, Ramsay Générale de santé, 14 rue Castiglione del lago, Trappes 78190, France.
Email: mat.jamme@gmail.com

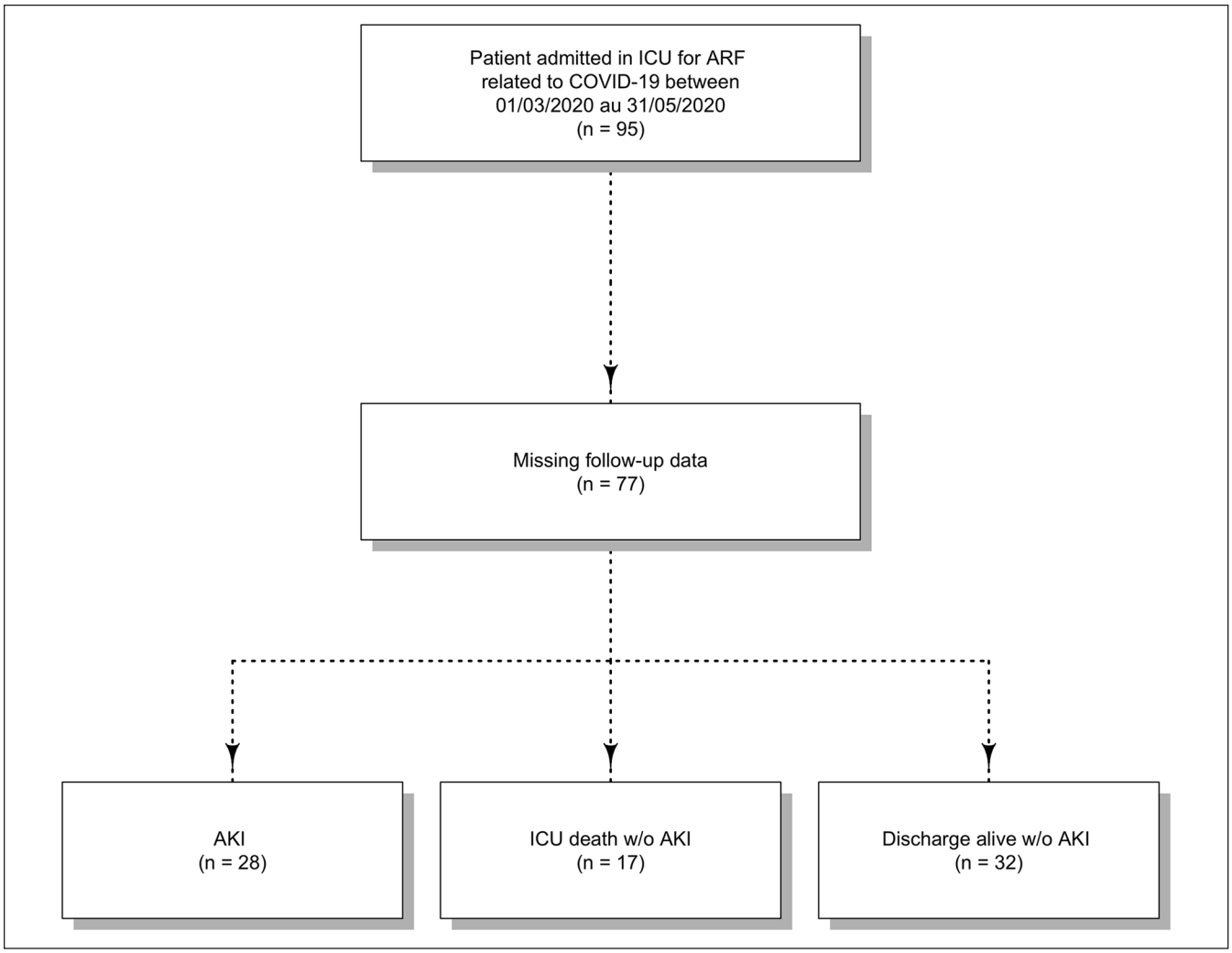

Figure 1. Flowchart.
Note. ICU = intensive care unit; ARF = acute respiratory failure; AKI = acute kidney injury.

and biological results. To these admission data were added the longitudinal follow-up data composed of hemodynamic monitoring with the need for vasoactive support, fluid load and fluid balance, mechanical ventilation parameters including volume and pressure parameters, prone positioning, administration of curare or nitrous oxide, nature and posology of nephrotoxic drugs administered, the need for kidney replacement therapy, all biological values, and the occurrence of ventilator-associated pneumonia and bacteremia over a maximum period of 14 days after admission. Vital status and discharge serum creatinine (SCr) levels were collected. Ethics discussions with decision of therapeutic limitation were also recorded.

Outcome

The primary outcome was the occurrence of AKI defined as any AKI ≥2 according to the KDIGO (Kidney Disease Improving Global Outcomes) classification (urine output [UO] and/or SCr). We limited our analysis to KDIGO stage 2 because the impact of KDIGO stage 1 on mortality is still on debate.[2] In case of discordance between UO and SCr, the worst staging was retained.

Baseline SCr is defined using the median value of all SCr measurements recorded in the 6 months to 1 year prior to admission. In the case of prior SCr not available, either a back-calculated value or ICU admission SCr was used as the baseline SCr.[7] Because France public health policies do not allow ethnic record information, back-calculated SCr was performed using the assumption of low-normal estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73m^2 and back-calculation of the associated SCr using the CKD Epidemiology Collaboration (CKD-EPI) without race equation[8] as follows:

$$\mathrm{GFR} = 142 \times m\left(\frac{\mathrm{SCr}}{\kappa},1\right)^{\alpha} \times \max\left(\frac{\mathrm{SCr}}{\kappa},1\right)^{-1200} \times 0.9938^{\mathrm{Age}} \times 1.012\left[\mathrm{Iffemalegender}\right]$$

Table 1. Baseline Characteristics of the Study Population.

	Total (N = 77)
Demographics	
Sex, male (n)	58
Age, y, median [IQR]	63 [53-73]
BMI, kg/m^2, median [IQR]	28.4 [25.9-32.7]
Comorbidities, n (%)	
Alcohol consumer	17 (23.6)
Tobacco smoker	22 (30.6)
Arterial hypertension	36 (47.4)
RAAS blocking drugs	17 (22.4)
Diabetes	20 (26.0)
Dyslipidemia	23 (30.3)
Solid organ malignancy	6 (7.9)
Biological data at ICU admission, median [IQR]	
Lymphocytes, G/L	0.85 [0.61-1.07]
Platelets, G/L	236 [184-262]
Bilirubinemia, µmol/L	11 [9-17]
D dimers, ng/mL	3093 [1732-4235]
C-reactive protein, mg/L	164 [105-280]
Ferritin, ng/mL	1869 [811-2370]
Serum creatininemia, µmol/L	74 [59-96]
pH	7.37 [7.32-7.43]
Pco_2, mm Hg	44 [39-51]
Bicarbonates, mmol/L	25.4 [24.1-27.1]
Lactate, mmol/L	1.2 [1-1.4]
SOFA score at ICU admission, median [IQR]	
SOFA	3 [1-7]
Neurologic SOFA	0 [0-0]
Respiratory SOFA	2 [0-3]
Hemodynamic SOFA	0 [0-3]
Kidney SOFA	0 [0-1]
Hematologic SOFA	0 [0-3]
Hepatic SOFA	0 [0-0]

Note. IQR = interquartile range; BMI = body mass index; ICU = intensive care unit; RASS = rennin-angiotensin-aldosterone system; SOFA = Sequential Organ Failure Assessment; RAAS = RAAS = renin-angiotensin-aldosterone system.

with $\kappa = 0.7$ for women and 0.9 for men and $\alpha = -0.241$ for women and −0.302 for men.

Statistical Analysis

Categorical data were described as absolute numbers (%) and continuous data as medians [IQR]. Given the competing nature of the occurrence of AKI in the ICU with discharge from the ICU (alive or dead), a survival analysis adapted to the situation of competing risks (Cox cause-specific model regression) with a modeling of the cumulative incidence of AKI was performed. Data previously reported in the literature as a risk factor for AKI and those with a $P < .20$ in the univariate analysis were used to create a final multivariate model. A boostrap procedure according Austin et al[9] was used for multivariate selection process. This method uses bootstrap to assess the distribution of an indicator variable denoting the inclusion of a specific variable. Basically, if one covariate is selected frequently in models derived from bootstrap samples using the same selection method, it will be included in the final model. One hundred bootstrap replicates were used, and the choice of the stepwise method was backward stepwise selection. The cutoff for when to include or exclude a variable used was 50%.[10]

Covariates daily collected and subjected to longitudinal variation were analyzed as time-dependent variables. In the case of nonlinearity of the observed continuous variables, a transformation of the continuous variables using Splines function was applied. Proportionality assumption was checked by the Schoenfeld residual analysis. Missing data were imputed using a multiple imputation chained equation methodology.

Two sensitive analyses were performed. We first realized the same analysis in the population study using the Fine-Gray model.[11] We next performed analysis in the subgroups of patients intubated and excluded patients treated by only noninvasive ventilation.

All statistical tests were performed with a risk α of 5%. All analyses were performed using R and R Studio software.

Results

Ninety-five patients were admitted to our ICU for severe COVID-19. Of these patients, 11 were excluded due to transfer to another ICU in the first 24 hours and 7 patients were excluded because of missing kidney status.

The median age was 63 [53-73] years, and male sex was predominant with 58 (75%) patients. Arterial hypertension was present in 36 (47%) patients and treated in 17 (47%) of them with a renin-angiotensin system blocker (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker). Diabetes was present in 20 patients (26%) (Table 1). Median length of stay in the ICU was 11 [6-23] days. More than three-quarters of the included patients used MV during treatment (77.9%). Introduction of neuromuscular blockade was present in more than 90% of ventilated patients, and the use of prone positioning was observed in 17% of cases. Initial MV parameters were characterized by PEEP levels of 10 [8-12] cm H_2O, a plateau pressure of 24 [20-26] cm H_2O, and a motor pressure of 14 [11-16] cm H_2O. Intensive care unit admission gas exchange analysis showed a Pao_2/Fio_2 ratio of 143 [103-213] mm Hg and a Pco_2 of 44 [39-51] mm Hg. During ICU, 34 patients (44.1%) required introduction of vasopressor support with noradrenaline at a dose greater than >0.5 µg/kg/min for 31/34 (91%) of them.

Acute kidney injury was observed in 28 (36.3%) (Supplemental Figure 1) patients and occurred at a median time of 3 [2-6] days (Supplemental Table 1).

Univariate analysis showed a significant statistical association between the use of invasive MV and the occurrence of AKI (cause-specific hazard (CSH) = 3.94 [1.18-13.2],

$P = .02$). Concerning MV parameters, the level of PEEP (CSH = 1.11 [1.01-1.23] per 1 cm H_2O increase, $P = .04$) and the use of neuromuscular blockade (CSH = 2.96 [1.22-7.18], $P = .02$) were associated with kidney outcome. No statistical association was observed with plateau pressure (CSH = 1.04 [0.99-1.10] per 1 cm increase in H_2O, $P = .08$) and motor pressure (CSH = 1.04 [0.99-1.08] per 1 cm increase in H_2O, $P = .06$). In multivariate Cox cause-specific time-dependent model, risk factors of AKI identified were a history of hypertension (CSH = 2.46 [1.04-5.84], $P = .04$), a high hemodynamic Sequential Organ Failure Assessment (SOFA) score (CSH = 1.63 [1.23-2.16], $P < .001$) and an elevated $Paco_2$ (CSH = 1.2 [1.04-1.39] per 5 mm Hg increase in Pco_2, $P = .02$). Table 2 resumed the results of analysis. Similar results were observed in the subgroups of intubated patients (n = 60) (Supplemental Table 2).

Several variables were significantly associated with AKI with the Fine-Gray model: Pao_2/Fio_2 ratio, Po_2 value, prone positioning, use of nitrous oxide, respiratory SOFA score, the use of NaCl 0.9%, hepatic SOFA score, bicarbonate value, and serum chloride. However, the same multivariate model was identified with a history of hypertension (sub-distribution hazard ratio (SHR) = 2.12 [1.02-3.65], $P = .04$), a high hemodynamic SOFA score (SHR = 1.41 [1.11-1.79], $P = .004$), and an high $Paco_2$ (SHR = 1.21 [1.06-1.37] per 5mm Hg increase in Pco_2, $P = .005$) (Supplemental Table 3).

Discussion

After respiratory failure, AKI is the second most common organ dysfunction in patients with COVID-19. Although the mechanisms involved are still controversial, ischemia seems to be the most important one, given the high prevalence of acute tubular necrosis in ICU patients.[12]

In our cohort, we observed that severe AKI is frequently observed and associated with 3 risk factors: a history of hypertension, a greater hemodynamic instability, and a more important hypercapnia.

The first 2 risk factors identified are widely described in the literature and can be linked to kidney hemodynamics. Hemodynamic management and optimal mean arterial pressure target have been advocated in the literature to prevent AKI. Our findings are consistent with the Acute Kidney Injury-Epidemiologic Prospective Investigation (AKI-EPI) study which observed arterial hypertension and/or shock at ICU admission as AKI risk factors.[2] These results are also consistent with the Sepsis and Mean Arterial Pressure (SEPSISPAM) trial that evidenced a significantly lower proportion of severe AKI and rate of kidney replacement therapy in patients with chronic hypertension when a higher blood pressure was targeted in ICU.[13]

Our work highlights the impact of $Paco_2$ on kidney function (Figure 2). In contrast to pressure regimes, which are suspected of influencing kidney hemodynamics, the relationship between $Paco_2$ variations and kidney function is poorly described. However, the rise in Pco_2 had been proven to induce an alteration in cardiac output and could alter kidney blood flow.[14] Rose et al[15] demonstrated in a canine model that a $Paco_2 > 50$ mm Hg induced a decrease in kidney blood flow. Several animal and human models have suggested that hypercapnia can lead to a decrease in systemic vascular resistance associated with a decrease in cardiac contractility.[16,17] The use of tromethamine, a buffer that does not generate CO_2 (unlike bicarbonate), has been shown to increase myocardial contractility and mean arterial pressure in patients with hypercapnia.[18] However, these data should be treated with caution as the impact on cardiac output appears to be quite moderate.[17,18] Another hypothesis described is that hypercapnia causes an increase in pulmonary vascular resistance, leading to right ventricular dysfunction.[19] Edwards et al[20] demonstrated an increase in oxygen consumption at the level of the proximal tubule in rats placed in respiratory acidosis, suggesting a synergistic effect of hypercapnia when occurred in hypoxemic context. These data highlight a potential aggravating role for hypercapnia, promoting low kidney flow and increasing ischemia, which may favor the occurrence of acute tubular necrosis. Nevertheless, to date the data in the literature on the impact of hypercapnia remain controversial. Some authors even report a direct benefit from hypercapnic acidosis.[21] Among the mechanisms proposed, the rightward shift of the oxygen-hemoglobin dissociation curve allows an improvement in oxygen delivery to the tissues and an anti-inflammatory activity.[22,23]

This study has several strengths, the first being the statistical methodology used. Study of complications in the ICU being by its nature dependent on the occurrence of competing events, failure to take this competition into account, as is the case with classical regression models, may be at the origin of a major bias. Furthermore, due to the longitudinal design of our study, it was important to be able to assess all the information occurring over time. Application of a cause-specific survival model with time-dependent covariates allows these 2 major features to be considered.

However, this study also has several limitations. The monocentric nature and relatively small size limit the statistical power and external validity of our results. Among our population, 17 patients (22 %) did not require invasive MV during their ICU stay and only 1 developed AKI. Sensitive analysis realized in the subgroup of invasive MV patients found similar results. Finally, we have chosen a particular ARDS study population: the severe forms of COVID-19. This could be limiting the extrapolation of our results. However, the hypothesis of a direct kidney involvement of SARS-CoV-2 is still debated. Moreover, the similarity of the incidences of kidney damage found in patients with ARDS or severe forms of COVID-19 pleads in the direction of an indirect physiopathological pathway of kidney lesions.[1,4] Finally, an important limitation for the validation of our results is the absence of a control group (due to the retrospective design and the impossibility of matching because of the small size of our cohort).

Table 2. Time-Dependent Cox Cause-Specific Analysis of Acute Kidney Injury.

	Univariate analysis			Multivariate analysis		
	CSH	95% CI	*P* value	CSH	95% CI	*P* value
Demographic data						
Male sex	1.25	0.47-3.31	.64			
Age (per 10 y)	1.02	0.76-1.36	.91			
BMI (per kg/m^2)	0.97	0.92-1.02	.25			
Comorbidities						
Tobacco use	0.46	0.17-1.24	.12			
Hypertension	1.76	0.82-3.78	.15	2.46	1.04-5.84	.04
RAAS blocking drugs	1.55	0.71-3.45	.28			
Dyslipidemia	0.72	0.31-1.64	.43			
Statins	0.87	0.35-2.15	.76			
Diabetes	0.95	0.40-2.24	.90			
Neoplasia	1.41	0.43-4.69	.57			
Longitudinal covariates[a]						
Ventilation						
Ventilatory mode						
No mechanical ventilation	Ref.	Ref.	Ref.			
Mechanical ventilation	3.94	1.18-13.2	.02			
PEEP (per cm H_2O)	1.11	1.01-1.23	.04			
Calculated pulmonary compliance (per mL/cm H_2O)	1.03	1.00-1.07	.04			
Driving pressure (per cm H_2O)	1.05	0.99-1.10	.08			
Pao_2/Fio_2 (per 0.1 unit)	0.98	0.94-1.03	.56			
Curare use	2.96	1.22-7.18	.02			
Prone positioning	2.08	0.81-5.33	.13			
Nitrous oxide	2.84	0.80-10.12	.10			
Respiratory SOFA	1.30	0.96-1.78	.09			
Hemodynamic						
Hemodynamic SOFA	1.72	1.32-2.26	<.001	1.63	1.23-2.16	<.001
Noradrenaline	5.32	2.20-12.82	<.001			
Dobutamine	8.69	1.10-69.05	.04			
Fluid balance (per 100 mL)	0.84	0.46-1.53	.57			
NaCl 0.9%	2.66	1.14-6.22	.02			
Volume (per 500 mL)	1.49	1.03-2.16	.03			
Balanced crystalloids	1.70	0.78-3.71	.18			
Volume (per 500 mL)	1.14	0.92-1.41	.24			
Glucose 5% exposure	0.99	0.95-1.04	.89			
Volume (per 500 mL)	0.98	0.68-1.43	.93			
Nephrotoxic drugs						
Aminoside	7.4	0.89-62.1	.06			
Iodine contrast media	Not converged	—	—			
Diuretics	2.35	0.78-7.12	.13			
Other organ failure						
Neurological SOFA						
Hepatic SOFA	1.68	1.03-2.74	.04			
Hematologic SOFA	1.78	0.90-3.54	.09			
Biological data						
Arterial pH (per 0.1)	0.42	0.29-0.59	<.001			
Arterial lactate (per mmol/L)	1.12	0.62-2.03	.70			
Po_2 (per 10 mm Hg)	0.99	0.92-1.07	.81			
Pco_2 (per 5 mm Hg)	1.25	1.08-1.44	.002	1.2	1.04-1.39	.02
Bicarbonates (per mmol/L)	0.91	0.84-0.98	.01			
Base excess (per unit)	0.88	0.82-0.94	<.001			
Ionized calcemia (per 0.1 mmol/L)	0.30	0.15-0.61	<.001			

(Continued)

Table 2. (Continued)

	Univariate analysis			Multivariate analysis		
	CSH	95% CI	*P* value	CSH	95% CI	*P* value
Serum sodium (per mmol/L)	0.88	0.81-0.97	.01			
Serum chloride (per mmol/L)	0.87	0.80-0.95	<.001			
Serum potassium (per mmol/L)	2.65	1.52-4.63	<.001			
Proteinemia (per g/L)	0.99	0.94-1.04	.72			
Fibrinogen (per g/L)	1.24	0.85-1.81	.27			
Procalcitonin (per mg/mL)	1.05	1.01-1.08	.006			
Prothrombin time ratio (per %)	0.98	0.95-1.01	.20			
Hemoglobin (per g/dL)	0.87	0.69-1.09	.22			
Leukocyte count (per G/L)	1.04	0.97-1.12	.31			
Lymphocytes (per G/L)	1.09	0.53-2.23	.82			
Platelets (per 50 G/L)	0.91	0.71-1.14	.39			

Note. BMI = body mass index; RAAS = renin-angiotensin-aldosterone system; PEEP = positive expiratory end pressure; SOFA = Sequential Organ Failure Assessment; CSH = cause-specific hazard.
[a]All covariates are considered time-dependent.

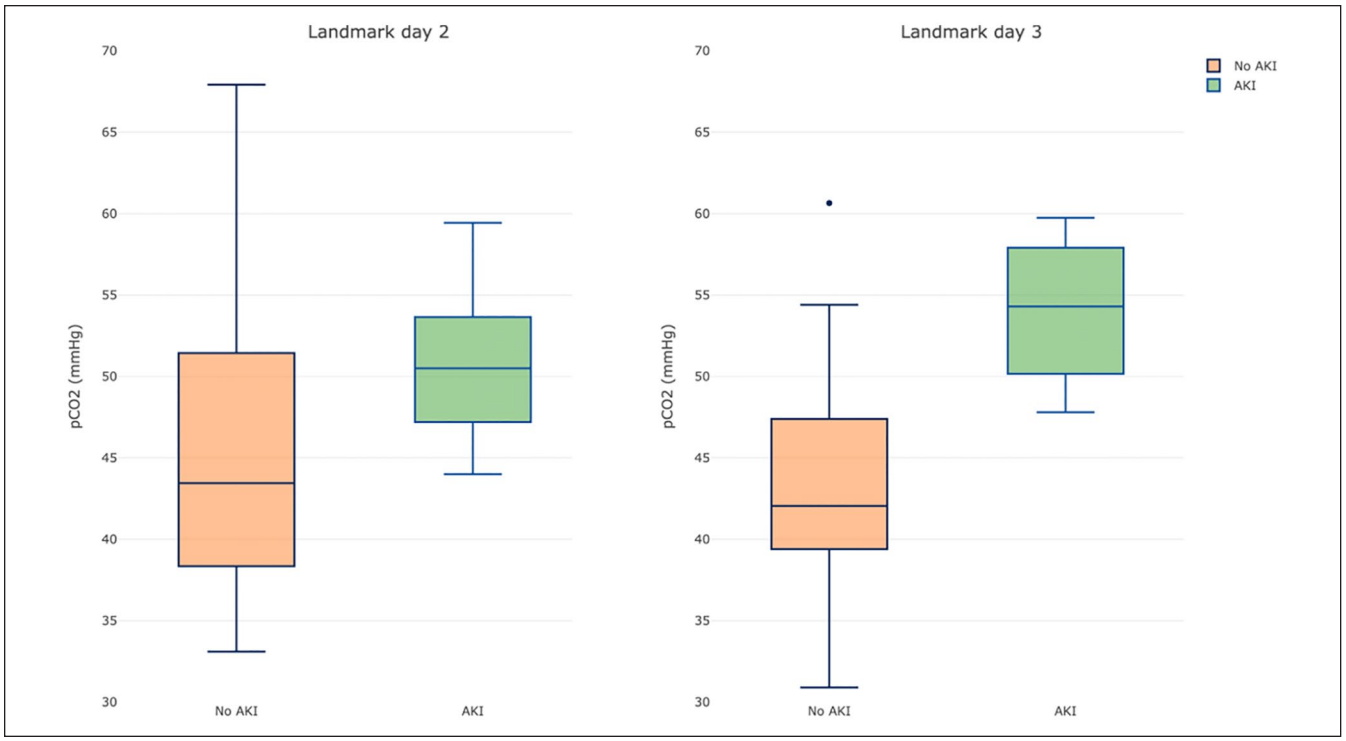

Figure 2. Boxplots of mean Pco_2 (expressed in mm Hg) of patients still at risk at day 2 (landmark day 2, n = 64) and day 3 (landmark day 3, n = 54).
Note. Green box represented the subgroups of patients with AKI. Orange box represented the subgroups of patients without AKI. At landmark day 2, patients with AKI had a mean Pco_2 of 50 [48-54] mm Hg, and no AKI patients had a mean Pco_2 of 43 [38-51] (*P* value for Wilcoxon test <.001). At landmark day 3, patients with AKI had a mean Pco_2 of 54 [50-57] mm Hg, and no AKI patients had a mean Pco_2 of 42 [39-47] (*P* value for Wilcoxon test <.001). AKI = acute kidney injury.

Conclusion

Acute kidney injury in patients admitted to the ICU for COVID-19 is frequent and associated with the presence of 3 risk factors: a history of hypertension, the presence of hemodynamic failure, and increased Pco_2. Further studies seem necessary to evaluate the impact of hypercapnia in terms of increasing the effects of ischemia, particularly in the most at-risk vascular situations.

Ethics Approval and Consent to Participate

This study was approved by the ethic committee of the french society of anesthesia and intensive care (Comission d'éthique pour la recherche en anesthésie et réanimation - CERAR) (IRB number : 00010254 - 2022 - 022).

Consent for Publication

All authors agreed to the publication of this manuscript.

Availability of Data and Materials

The data for this study is publicly available and the models used for the analysis are available upon request.

Authors' Note

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Author Contributions

AM designed the study, collected the data, and drafted the manuscript. VZ, OBHS, CP, LLDS, SMA, CB, YL, JH, HO, and JG collected the data; contributed to data interpretation and analysis; and revised the manuscript for important intellectual content. MJ designed the study, performed the statistical analysis, contributed to data interpretation and analysis, and revised the manuscript for important intellectual content.

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ORCID iD

Antoine Marchiset https://orcid.org/0000-0001-5929-9228

Supplemental Material

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