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ORIGINAL ARTICLE

Acute kidney injury and mortality in patients with critical COVID-19 in Mexico: case–control study

Lesión renal aguda y mortalidad en pacientes con COVID-19 grave en México: estudio de casos y controles

*Ivette Mata-Maqueda[1,2], Juan C. Solís-Sáinz[2], Guadalupe Zaldivar-Lelo de Larrea[2], Ernesto Deloya-Tomas[1,2,3], Jorge López-Fermín[1,2,3], Mª Guadalupe Olvera-Ramos[1,2,3], Gabriela Castillo-Gutiérrez[1,2,3], Jorge D. Carrión-Moya[1,2,3], and Orlando R. Pérez-Nieto[1,2,3]**

[1]Health Services of the State of Queretaro; [2]School of Medicine, Autonomous University of Queretaro; [3]Intensive Care Unit, General Hospital of San Juan del Rio. Queretaro, Mexico

Abstract

Objective: *We aimed to test the association between acute kidney injury (AKI) and mortality in critically ill patients with Coronavirus disease 2019 (COVID-19).* **Method:** *We conducted a single-center case–control study at the intensive care unit (ICU) of a second-level hospital in Mexico. We included 100 patients with critical COVID-19 from January to December 2021, and collected demographic characteristics, comorbidities, APACHE II, SOFA, NEWS2, and CO-RADS scores at admission, incidence of intrahospital complications, length of hospital and ICU stay, and duration of mechanical ventilation, among others.* **Results***: The median survival of deceased patients was 20 days. After multivariable logistic regression, the following variables were significantly associated to mortality: AKI (adjusted odds ratio [AOR] 6.64, 95% confidence intervals [CI] = 2.1-20.6, p = 0.001), age > 55 years (AOR 5.3, 95% CI = 1.5-18.1, p = 0.007), and arrhythmias (AOR 5.15, 95% CI = 1.3-19.2, p = 0.015). Median survival was shorter in patients with AKI (15 vs. 22 days, p = 0.043), as well as in patients with overweight/obesity (15 vs. 25 days, p = 0.026).* **Conclusion:** *Our findings show that the development of AKI was the main risk factor associated with mortality in critical COVID-19 patients, while other factors such as older age and cardiac arrhythmias were also associated with this outcome. The management of patients with COVID-19 should include renal function screening and staging on admission to the Emergency Department.*

Keywords: *Coronavirus disease 2019. Severe acute respiratory syndrome coronavirus 2. Acute kidney injury. Mortality. Risk factors.*

Resumen

Objetivo: *Probar la asociación entre lesión renal aguda y mortalidad en pacientes con COVID-19 grave.* **Método:** *Realizamos un estudio de casos y controles unicéntrico en la unidad de cuidados intensivos (UCI) de un hospital de segundo nivel en México. Incluimos 100 pacientes con COVID-19 grave de enero a diciembre 2021, recolectando características demográficas, comorbilidad, APACHE II, SOFA, NEWS2 y CO-RADS al ingreso, incidencia de complicaciones intrahospitalarias, duración de la estancia hospitalaria y en la UCI, duración de ventilación mecánica, etc.* **Resultados:** *La mediana de supervivencia de los pacientes que fallecieron fue de 20 días. Al realizar el análisis de regresión logística multivariable, las siguientes variables se asociaron significativamente con la mortalidad: lesión renal aguda (odds ratio ajustada [ORa]: 6.64; intervalo de confianza*

***Correspondence:**
Orlando R. Pérez-Nieto
E-mail: orlando_rpn@hotmail.com

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del 95% [IC95%]: 2.1-20.6; p = 0.001), edad > 55 años (ORa: 5.3; IC95%: 1.5-18.1; p = 0.007) y arritmias (ORa: 5.15; IC95%: 1.3-19.2; p = 0.015). La supervivencia fue menor en pacientes con lesión renal aguda (15 vs. 22 días; p = 0,043), así como en pacientes con sobrepeso u obesidad (15 vs. 25 días; p = 0.026). **Conclusiones:** *Nuestros resultados muestran que el desarrollo de lesión renal aguda es el principal factor de riesgo asociado a mortalidad en pacientes con COVID-19 grave, mientras que otros factores, como la edad > 55 años y la presencia de arritmias cardiacas, también se asocian a mortalidad por COVID-19. El manejo de pacientes con COVID-19 debe incluir el tamizaje y la estadificación de la función renal al ingreso a urgencias.*

Palabras clave: *COVID-19. SARS-CoV-2. Lesión renal aguda. Mortalidad. Factores de riesgo.*

Introduction

Coronavirus disease 2019 (COVID-19) is an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was declared a global pandemic on March 11, 2020. As of April 19, 2023, more than 6.9 million deaths have been reported worldwide[1]. This virus mainly affects the respiratory system, producing fever, cough, headache, shortness of breath, sore throat, and chest pain[2]. Nevertheless, it may also cause acute respiratory distress syndrome (ARDS) and multiple organ dysfunction among other severe manifestations of disease. In this regard, acute kidney injury (AKI) has been described as a severe complication of COVID-19, with an incidence ranging from 4.5% and 28%, and a higher prevalence in patients hospitalized in the intensive care unit (ICU)[2,3]. The mechanisms that promote kidney disease have been related to damage induced by cytokines, systemic effects related to mechanical ventilation, and ARDS[4].

AKI is known to increase the severity of illness, duration of hospitalization, and mortality in COVID-19 patients[5]. In fact, AKI has been described as an independent risk factor for mortality in COVID-19 patients hospitalized in the ICU[6]. However, information on kidney disease in patients with COVID-19 is still limited, as the majority of published studies in this respect are case reports and case series[5]. Furthermore, little is known concerning the relationship between AKI and COVID-19 in Hispanic populations, in whom risk factors for disease progression, adverse outcomes, and death from COVID-19 are especially prevalent[7-9].

For the above reasons, in this study, we aimed to test the association between AKI and mortality in critically ill patients with COVID-19 in the ICU of a second-level public hospital in Mexico.

Materials and methods

Setting and patients

We conducted a single-center case–control study at the ICU of the Hospital General de San Juan del Río, part of the Health Services of the State of Queretaro, Mexico (SESEQ), from January to December 2021. Inclusion criteria were all patients with critical COVID-19 (according to the World Health Organization severity definitions[10]) admitted to the ICU during the entire study period. Exclusion criteria were incomplete or missing medical records and patients who were transferred to another medical unit. Consecutive convenience sampling of patients was performed.

In this study, the ethical precepts of the Declaration of Helsinki were followed, and the study protocol was approved in July 2020 by the Research Committee of SESEQ, with the registration number *1201/Subdirección de Enseñanza, Programa de Investigación en Salud/31-07-2020*.

The primary outcome was mortality; hence, cases were defined as patients who died in the ICU, while controls as patients who survived until discharge. Exposures were defined as sex, age, history of comorbidities, APACHE II, SOFA, NEWS2, and CO-RADS scores at ICU admission, the incidence of intrahospital complications (AKI, arrhythmias, and secondary infections), length of hospital and ICU stay, duration of mechanical ventilation, patient-ventilator asynchrony, PaO_2 levels, and static pulmonary compliance. Data were collected by Critical Care Medicine resident physicians and attendings through a review of patients' medical records.

Statistical analysis

Sample size calculations were performed based on the mortality risk by AKI in COVID-19 patients.

Assuming a relative risk of 3.08[11], and a mortality rate of 47%[2], we estimated a minimum of 33 individuals, with an 80% power and alpha of 0.05, allowing for a loss of 20%.

Descriptive statistics were used in qualitative variables. Continuous and categorical variables are presented as means, standard deviations, frequencies, and percentages, where applicable. Differences between categorical variables were evaluated by Fisher's exact test and by analysis of variance for continuous variables. Statistical significance was defined as $p < 0.05$. Normality in the distribution of the variables was tested by the Kolmogorov–Smirnov test. The Mann–Whitney and Kruskal–Wallis tests were used to evaluate the difference between medians, as well as Spearman's one-tailed correlation test for all the non-normally distributed data. Kaplan–Meier analyses were performed to assess survival. Both bivariable and multivariable binary logistic regression analyses were used to identify factors associated with the mortality. Variables with a $p < 0.05$ in the bivariable analysis were fitted into the multivariable logistic regression analysis. Both crude odds ratio and adjusted odds ratio with their corresponding 95% Confidence intervals were calculated to show the strength of the association. In multivariable analysis, variables with a $p < 0.05$ were considered as statistically significant. The fitness of the model was checked by using the Hosmer-Lemeshow goodness-of-fit test. All analyses and figures were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, N.Y., USA) and PRISM Software (GraphPad Prism v. 8), respectively.

Results

One hundred and twenty-two potentially eligible patients were screened. After the application of inclusion and exclusion criteria, 100 patients were included in the final analyses (Fig. 1). Table 1 shows the general characteristics of our study population. Fifty patients were male and the mean age was 49 years. Obesity was the most frequent comorbidity (n = 44, 44%). Median APACHE II, SOFA, NEWS2 and CO-RADS scores at admission were 15, 9, 9, and 5, respectively. The incidence of intrahospital complications such as AKI, arrhythmia, ventilator-associated pneumonia, and catheter-related urinary tract infections were 56%, 70%, 67%, and 10%, respectively.

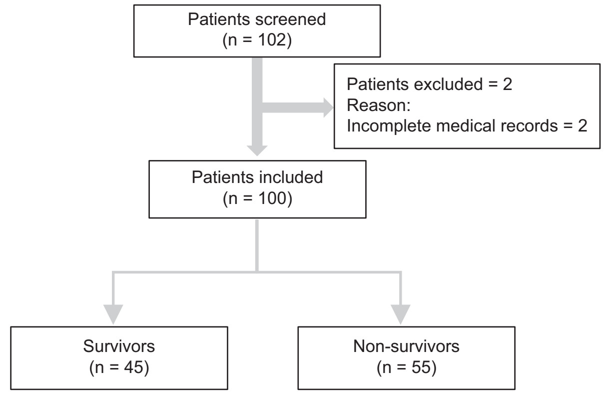

Figure 1. *Patient inclusion flowchart and reasons for exclusion.*

Table 1. General characteristics of our population

Variable	Total sample (n = 100)
Sex*	
Male	50 (50)
Female	50 (50)
Age** (years)	
Male	49.1 (12.2)
Female	49.4 (14.4)
Comorbidities*	
None	22 (22)
Obesity	44 (44)
Overweight	11 (11)
Hypertension	38 (38)
Diabetes mellitus	30 (30)
Patients with two or more comorbidities	35 (35)
Scores***	
APACHE II	15 (12-20)
SOFA	9 (7-11)
NEWS2	9 (7-11)
CORADS	5 (5-5)
Intrahospital complications*	
Acute kidney injury	56 (56)
Arrhythmias (all ventricular extrasystoles)	70 (70)
Ventilator-associated pneumonia	67 (67)
Catheter-related UTI	10 (10)
Days of hospital stay***	14 (10.75-23.25)
Days in ICU***	11 (6-20)
Days on mechanical ventilation***	9 (5-17)
Patient-ventilator asynchrony*	49 (49)
PaO_2 (mmHg)**	63.4 (11.4)
Static pulmonary compliance***	23 (18-26)
Mortality*	55 (55)

*Frequency, (percentage). **Mean, (standard deviation). ***Median, (25^{th}-75^{th} percentiles). ICU: intensive care unit; PaO_2: arterial partial pressure of oxygen; UTI: urinary tract infection.

The median ICU stay was 11 days (interquartile range [IQR] ± 14), while the median days on mechanical ventilation were 9 (IQR ± 12). The mortality rate in our population was 55% (n = 55).

In the bivariable logistic regression, the variables AKI, APACHE score > 25, age > 55, arrhythmias, overweight and obesity, and male sex were positively associated with mortality. However, when the multivariable logistic regression was employed only AKI (AOR 6.64, 95% CI 2.14-20.62, p = 0.001), age >55 years (AOR 5.3, 95% CI 1.57-18.15, p = 0.007), and arrhythmia (AOR 5.15, 95% CI 1.37-19.27, p = 0.015) were significantly associated with mortality (Table 2).

On the other hand, age was significantly higher in deceased patients, compared to survivors (52.9 vs. 44.9 years, using Student's t-test, p = 0.0014; data not shown). Similarly, APACHE II scores were also higher in the non-survivor group, compared to survivors (16 vs. 14, using Mann–Whitney test, p = 0.032; data not shown). In addition, the length of mechanical ventilation was also higher in deceased patients, compared to non-deceased (11 vs. 8 days, using the Mann–Whitney test, p = 0.032; data not shown).

There were no significant differences in the SOFA and NEWS2 scores, length of hospital and ICU stay, number of comorbidities, PaO_2 levels, and static pulmonary compliance between survivors and non-survivors (data not shown). Similarly, there was no correlation between age and length of ICU stay (p = 0.18, Spearman's correlation test; data not shown).

Concerning the deceased patients, the global median survival was 20 days. When comparing the survival of deceased patients with and without overweight and obesity, median survival was 15 and 25 days, respectively (p = 0.026, Fig. 2). Likewise, when comparing the survival of deceased patients with and without AKI, median survival values were 15 and 22 days, respectively (p = 0.043, Fig. 3).

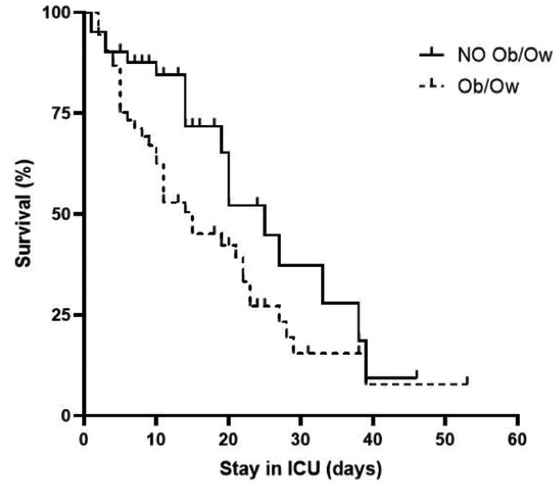

Figure 2. *Kaplan–Meier survival plots in patients with (dashed line) and without (solid line) obesity and overweight (Ob/Ow). Median survival was 15 and 25 days for the group with and without Ob/Ow, respectively. When comparing both curves a significant p = 0.026 was calculated using the Gehan-Breslow-Wilcoxon test.*

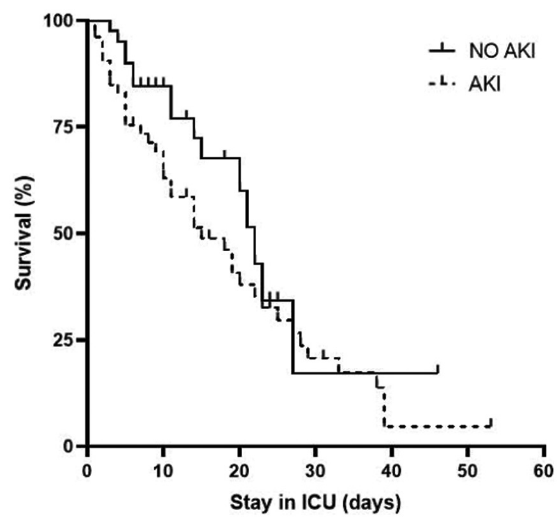

Figure 3. *Kaplan–Meier survival plots in patients with (dashed line) and without (solid line) acute kidney injury (AKI). Median survival was 15 and 22 days for the group with and without AKI, respectively. When comparing both curves a significant p = 0.043 was calculated using the Gehan-Breslow-Wilcoxon test.*

Discussion

In this case–control study conducted in a second-level hospital in Mexico, in accordance with the literature, we found that AKI is an independent risk factor for mortality in critically ill patients with COVID-19, even after adjustment for age and sex. We also found that patients with AKI died earlier than patients without this complication. It has been reported that patients with COVID-19 who develop AKI have a mortality risk 4.5 times higher compared with those who do not[12]. In our study, the incidence of AKI as an intra-hospital complication was 56%, and the patients who developed it showed a 6.6-fold higher risk of dying. The kidney has been identified as a target organ for virus proliferation in patients with severe SARS-CoV-2 infection[13], since a direct SARS-CoV-2 invasion into renal parenchyma has been demonstrated, in addition to microthrombosis, acute tubular necrosis, mitochondrial dysfunction, and arterial occlusion[14]. In addition to direct pathophysiological mechanisms, renal dysfunction in the context of COVID-19 may also occur through the systemic

Table 2. Association of risk factors and mortality in critical COVID-19 patients

Variable	Value n (%)	COR (95% CI; p-value)	AOR (95% CI; p-value)
Acute kidney injury	41 (74.5)	6.2 (2.2-17.6; 0.001)	**6.64 (2.14-20.62; 0.001)**
Age > 55 years	23 (41.8)	4.4 (1.6-12.3; 0.004)	**5.3 (1.57-18.15; 0.007)**
Arrhythmia	46 (83.6)	2.9 (1-8.6; 0.048)	**5.15 (1.37-19.27; 0.015)**
APACHE II score > 25	12 (21.8)	4.9 (1.2-20.1; 0.024)	2.6 (0.47-14.34; 0.271)
Overweight and obesity	37 (67.2)	2.6 (1.15-5.9; 0.021)	2.12 (0.7-6.44; 0.183)
Male sex	34 (61.8)	2.1 (1.2-6.3; 0.013)	0.494 (0.16-1.46; 0.203)
SOFA score > 10	25 (45.4)	1.2 (0.3-1.8; 0.381)	-
NEWS2 score > 10	25 (45.4)	1.31 (0.5-2.9; 0.329)	-
Patient-ventilator asynchrony	17 (30.9)	1.7 (0.6-4.9; 0.177)	-

COR: crude OR (from bivariate regression analysis); AOR: adjusted OR (from multivariable regression analysis). Significant values from multivariable regression are shown in bold. Hosmer-Lemeshow test p = 0.253.

effects of SARS-CoV-2 infection and critical illness[15]. In our study, 74.5% of the deceased patients had AKI, and this was the risk factor with the greatest association with mortality, which is consistent with previously reported data, given that AKI has been pointed out as a marker of severe disease, multiple organ dysfunction, and death from COVID-19[16].

Importantly, 78% of our population had a least one comorbidity, including obesity/overweight, diabetes mellitus, and hypertension. These comorbidities have been identified as significant risk factors for COVID-19-associated AKI[2]. They are characterized by low-grade inflammation and increased immune senescence, although how these specifically impact the kidney in the setting of COVID-19 is still unknown[15]. Of these comorbidities, obesity has been recognized as one of the most important risk factors for disease severity, use of invasive mechanical ventilation, and death, especially in those under 65 years of age[17]. Several mechanisms have been proposed to explain this relationship, including increased angiotensin-converting enzyme 2 (ACE2) expression. Therefore, a greater presence of ACE2 could be a mechanism that increases the risk of disease and death in COVID-19 patients with obesity[18,19]. In our population, mortality was twice as high in patients with overweight and obesity, which is consistent with the literature[20-22]. However, this association was not significant when the multivariable logistic regression was performed.

Increasing age has also been identified as an independent risk factor associated with mortality in COVID-19 patients, and this is certainly the case with the Mexican population[23-25]. Furthermore, increasing age has been associated with an increased risk of presenting with symptoms of severity[26]. In our study, age > 55 years was associated with a 5.3-fold risk of mortality, and age tended to be significantly higher in deceased patients compared to survivors.

In contrast to what has been reported in the literature, in our study, 70% of the patients had ventricular extrasystoles. The cardiac manifestations of COVID-19 include arrhythmias, focal or global myocarditis, necrosis, ventricular dysfunction, heart failure, and thrombosis[27-29]. Atrial arrhythmias are the most frequently observed arrhythmias in patients with severe COVID-19. It has been reported that the overall incidence of atrial fibrillation (AF) ranges from 6.6 to 13% in hospitalized COVID-19 patients without a history of atrial arrhythmia[30,31]. Notably, 83% of our deceased patients presented arrhythmias during their ICU stay, whose presence was associated with a 5.15-fold higher risk of dying.

Finally, we would like to highlight that in our study, the length of mechanical ventilation was higher in non-survivors compared to survivors, which is in line with previously published studies[32].

Limitations of our study include its retrospective nature, as well as potential sampling bias due to convenience sampling, which limits the generalizability of results. In addition, given that this study was conducted in a resource-constrained hospital in Mexico, acute renal replacement therapy strategies (when indicated) were very limited. For instance, slow-continuous renal replacement therapy, the most recommended therapy for hemodynamically unstable critically ill patients, has no coverage from the state health services, and could therefore not be implemented in our population. Another limitation of our study includes not having the body mass index of the patients due to the impossibility of objectively measuring weight, since hospitalization and ICU beds do not count with digital scales, and therefore, obesity/overweight was ascertained through medical history. Strengths of our study include its sample size, which was adequately powered to detect differences according to the primary outcome. In addition, this study is one of the few to assess the association between AKI and COVID-19 in a Mexican population, along with Casas-Aparicio and colleagues' 2021 study[33]. Esponda-Prado and colleagues also reported on the incidence of AKI among COVID-19 patients, but theirs was a small observational study consisting of solely 22 patients[34].

Conclusion

Our findings show that the development of AKI was the main risk factor associated with mortality in critical COVID-19 patients, while other factors such as age > 55 years and cardiac arrhythmias were also associated with this outcome. The kidney is one of the target organs for SARS-CoV-2 proliferation, and other indirect pathophysiological mechanisms may also cause kidney dysfunction; hence, physicians who evaluate COVID-19 patients at hospital admission should integrate the Kidney Disease: Improving Global Outcomes (KDIGO) classification to determine the kidney function and timely identify the presence of acute or chronic kidney damage. This would allow for early management and avoidance of complications where feasible. The management of patients with COVID-19 should categorically include renal function screening and staging on admission to the Emergency Department.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

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