Acute Kidney Injury in Critical Care COVID-19 Patients on Invasive Mechanical Ventilation: The Potential Preventive Role of Dexamethasone

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Research article

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Abstract

Background.

A high incidence of acute kidney injury (AKI) has been reported in COVID-19 patients in critical care units and those undergoing invasive mechanical ventilation (IMV). The introduction of dexamethasone as treatment for severe COVID-19 has improved mortality, but its effects in other organs remain under study.

Methods.

In this prospective observational cohort study, we evaluated the incidence of AKI in critically ill COVID-19 patients undergoing mechanical ventilation, and the association of dexamethasone treatment with the incidence, severity, and outcomes of AKI. The association between dexamethasone treatment and AKI was evaluated by multivariate logistic regression. The association of the combination of dexamethasone treatment and AKI on mortality was evaluated by Cox-regression analysis.

Results.

We included 552 patients. AKI was diagnosed in 311 (56%), of which 196 (63%) corresponded to severe (stage 2 or 3) AKI, and 46 (14.8%) received renal replacement therapy (RRT). Two hundred and sixty-seven (48%) patients were treated with dexamethasone. This treatment was associated to lower incidence of AKI (OR 0.34, 95%CI 0.22-0.52, $p < 0.001$) after adjusting for age, body mass index, laboratory parameters, SOFA score, and vasopressor use. Dexamethasone treatment significantly reduced mortality in patients with severe AKI (HR 0.63, 95%CI 0.41-0.96, $p = 0.032$).

Conclusions.

The incidence of AKI is high in COVID-19 patients under IMV. Dexamethasone treatment is associated with a lower incidence of AKI and a lower mortality in the group with severe AKI.

Background

Acute kidney injury (AKI) is common in severe coronavirus disease 2019 (COVID-19). The reported incidence of AKI in subjects hospitalized for COVID-19 varies from 20–46% [1–3] with variations between Institutions. At our center, we previously reported that 30% of the population with severe COVID-19 developed AKI during their hospitalization, 19% corresponding to community-acquired AKI, and 11% to hospital-acquired AKI [4]. In critically ill patients, the incidence of AKI is higher, reported between 50% and 90%, with variations in accordance to the population included and the temporality relative to the pandemic evolution [1–3, 5]. In most reports, the critically ill population is composed of patients who are managed in the intensive care unit (ICU) with invasive mechanical ventilation (IMV) as well as patients

managed with non-invasive oxygen delivery devices. When limited to patients under IMV, the incidence of AKI may reach up to 90% [1]. Moreover, a decrement in AKI has been reported as the pandemic evolved and there is better knowledge of the disease [3].

The pathophysiology of AKI in critically ill COVID-19 patients is not fully known. Several mechanisms are possibly involved, including direct parenchymal invasion by the SARS-CoV-2, microthrombosis, an imbalance in the renin-angiotensin-aldosterone system (RAAS), hemodynamic instability, inflammatory cytokines, and the indirect effects of therapeutic maneuvers (nephrotoxic drugs, high positive-pressure IMV), among others [6, 7].

The RECOVERY trial demonstrated that the use of dexamethasone (DXM) 6mg per day for 10 days improved the 28-day mortality and decreased the need for renal replacement therapy (RRT) in severe COVID-19 patients requiring supplementary oxygen [8]. Previous reports have suggested a potential decrease in the incidence and severity of AKI with the use of glucocorticoids [9–12]. Most of these reports preceded the standardized use of glucocorticoids as employed in the RECOVERY trial.

This study aimed to evaluate the incidence of AKI in severe COVID-19 patients who were treated with IMV in the ICU, and to assess the association of the standardized use of DXM in the incidence and severity of AKI in this population.

Methods

This is a single-center, prospective, and observational cohort study performed at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán in Mexico City. The study was approved by the local Human Research and Ethics Boards (reference NMM-3325-20-20-1).

We included all consecutive adult patients, with a positive polymerase chain reaction (PCR) test for SARS-CoV-2, who were admitted to the ICU and managed with IMV from March 2020 to January 2021. We excluded patients who were transferred to another hospital, those with advanced chronic kidney disease (eGFR below 30mL/min/1.73m²), prior kidney transplantation, patients who already had severe (see *ahead*) AKI at admission, and patients who remained hospitalized by January 31th, 2021. All data was obtained from a local database that prospectively collected data from the first COVID-19 patient admission to the present date. All patients are followed up to their discharge. Those patients who required RRT during their hospitalization were contacted to define if they recovered their kidney function by January 31th, 2021.

The collected variables included demographic data, comorbidities, home medications, clinical findings at presentation, the laboratory parameters at presentation and at the start of the IMV in the ICU, chest CT-scan findings, use of vasopressors, AKI development, medications administered during the ICU stay, and patient outcomes. Dexamethasone administration was standardized at 6mg intravenously per day for a total of 10 days, and started from the first day of patient admission.

Variable Definitions

Acute kidney injury was defined and staged according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines by the serum creatinine criteria, urine output was not registered [13]. Patients were staged according to the highest AKI degree attained during their hospitalization. Baseline serum creatinine (SCr) was defined as the mean SCr value in the 6 months before hospitalization, or the minimum SCr value obtained during hospitalization if the previous values were unavailable [14]. As potential factors contributing to AKI we registered the strategy of ventilation in prone position, the use and dose of vasopressors, concomitant antibiotic and antifungal therapy, and exposure to intravenous contrast. The Charlson Comorbidity Index was calculated to synthesize comorbidities information [15].

Outcomes

The primary outcome was the incidence of severe AKI, defined as KDIGO stage 2 or 3 AKI [13]. As secondary outcome, we explored the association of DXM treatment on patient mortality, length of hospitalization, and AKI recovery. With the available number of patients, the study had 80% of potency to detect a difference >12% on patient mortality between patients treated and untreated with DXM. The length of hospitalization and AKI recovery is reported for surviving patients. Recovery from AKI was operationally defined as a reduction in peak AKI stage to a SCr level below 1.5 times the baseline [16].

Statistical analysis

For continuous variables, their distribution was assessed by the Kolmogorov-Smirnov test. Descriptive statistics are expressed as number (percentage) and median (interquartile range) as appropriate. Baseline patient characteristics between those with or without AKI, and within AKI stages were analyzed using the U-Mann-Whitney or Kruskal Wallis test, respectively. Chi-square or Fisher's exact test was used for categorical variables.

The factors associated with severe AKI development including DXM treatment were evaluated by univariate logistic regression. All variables with a p-value <0.05 and all factors previously reported to be associated with AKI were selected for the multivariate analysis. The factors associated with patient survival were evaluated by a multivariate Cox regression analysis. The effect of the interaction between DXM treatment and severe AKI development in mortality was evaluated by an adjusted Cox-regression analysis. For all variables, there were less than 1% missing values, and for missing data, variables were imputed by using multiple imputations.

All statistical tests were two-sided, and a p-value below 0.05 was considered statistically significant. All analyses were performed using SPSS 24.0 (IBM, Armonk, NY, USA) and GraphPad Prism 6.0 (GraphPad Software, San Diego, CA, USA).

Results

From March 1st, 2020, to January 31st, 2021 a total of 3604 patients were admitted to our Institution for severe COVID-19. Among them, 552 patients were admitted to the ICU and managed with IMV (Figure 1). The baseline characteristics of all the patients included in this study are provided in **Table S1**. A total of 371 patients (67%) were treated with IMV in a prone position at some time during their hospitalization, 472 (86%) received vasopressor support, and in 176 (32%) the peak dose of norepinephrine was >0.1mg/kg/min. The median PaO₂/FiO₂ (P/F) ratio at admission was 107 (82-147). Among the 552 patients included in this study, 267 (48%) received treatment with a standardized DXM regimen.

Acute Kidney Injury in Critical Care COVID-19 patients

Acute kidney injury was diagnosed in 311 (57%) patients. The AKI stage was stage 1 AKI in 115 (37%), stage 2 AKI in 75 (24%), and stage 3 AKI in 121 (39%) (Table 1). Most AKI developed early during the admission to the ICU and the start of the IMV, with a median 1 day (IQR 0-4) within admission to the ICU and IMV initiation. The laboratory studies at IMV initiation are also shown in Table 1. The therapeutic interventions and exposures in the ICU and the outcomes including mortality are shown in Table 2.

Table 1

Clinical characteristics of the patients included in this study by AKI development and AKI staging.

	No AKI n=241	AKI n=311	p- Value (AKI vs no AKI)	Stage 1 AKI N=115	Stage 2 AKI N=75	Stage 3 AKI N=121	p-Value (among AKI stages)
Age, years	53 (41-62)	54 (45-68)	0.069	54 (47-62)	52 (40-66)	55 (46-64)	0.667
Male, n (%)	167 (69)	230 (74)	0.227	92 (80)	51 (68)	87 (72)	0.148
Body mass index, kg/m ²	29.4 (26.6-33.2)	30.5 (27.6-34.6)	0.017	30.2 (27.9-33.2)	30.9 (27.6-35.1)	31.2 (27.3-36.5)	0.348
Charlson index, n (%)	1 (0-2)	1 (0-2)	0.012	1 (0-2)	1 (0-2)	1 (0-3)	0.233
Comorbidities, n (%)	181 (75)	256 (82)	0.039	92 (80)	58 (77)	106 (88)	0.134
Diabetes, n (%)	58 (24)	93 (30)	0.127	35 (30)	17 (23)	41 (34)	0.246
Hypertension, n (%)	58 (24)	94 (30)	0.108	32 (28)	20 (27)	42 (35)	0.383
Obesity, n (%)	113 (47)	169 (54)	0.082	55 (48)	41 (55)	73 (60)	0.156
Chronic kidney disease, n (%)	3 (1)	10 (3)	0.130	1 (1)	4 (5)	5 (4)	0.179
Cancer, n (%)	3 (1)	5 (2)	0.723	3 (3)	1 (1)	1 (1)	0.540
Rheumatologic disease, n (%)	10 (4)	10 (3)	0.560	2 (2)	4 (5)	4 (3)	0.389
Cardiovascular disease, n (%)	5 (2)	16 (5)	0.061	5 (4)	4 (5)	7 (6)	0.879
Days for the start of symptoms	8 (6-11)	7 (5-10)	0.144	8 (6-11)	7 (5-10)	7 (6-10)	0.610
Days from hospital admission to ICU admission	2 (1-3)	1 (0-3)	0.075	2 (1-3)	1 (0-4)	1 (0-2)	0.169
SOFA score at ICU admission	4 (4-6)	5 (4-6)	0.024	4 (4-5)	5 (4-6)	6 (4-7)	0.002

Note. All continuous variables are expressed as median (interquartile range).

Abbreviations. AKI, acute kidney injury; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; SCr, serum creatinine; N/L, neutrophil to lymphocyte ratio; TnI, troponin I.

	No AKI n=241	AKI n=311	p- Value (AKI vs no AKI)	Stage 1 AKI N=115	Stage 2 AKI N=75	Stage 3 AKI N=121	p-Value (among AKI stages)
Kidney function							
Baseline SCr, mmol/L	61 (53-74)	71 (53-84)	<0.001	65 (53-79)	69 (53-82)	79 (58-99)	<0.001
SCr at IMV initiation, mmol/L	66 (57-78)	99 (76-128)	<0.001	89 (68-111)	99 (72-131)	117 (86-165)	<0.001
Peak SCr, mmol/L	74 (66-90)	170 (122-287)	<0.001	118 (104-136)	159 (126-209)	349 (249-510)	<0.001
Laboratory at ICU admission							
Leukocytes, x 1000/mm ³	10.5 (8.4-13.5)	11.4 (8.5-15.2)	0.049	11.4 (8.5-14.7)	11.3 (8.9-15.9)	11.4 (8.6-15.4)	0.864
Lymphocytes, x 1000/mm ³	5.9 (3.7-9.3)	6.6 (3.8-9.5)	0.314	6.2 (3.6-9.9)	6.8 (4.0-10.6)	6.7 (4.0-9.2)	0.673
N/L ratio	15.1 (9.0-25.1)	13.2 (8.9-24.0)	0.273	13.9 (8.2-25.7)	13.0 (8.1-23.7)	12.9 (9.3-21.9)	0.644
Serum glucose, mmol/L	7.44 (5.99-9.66)	8.32 (6.55-11.4)	<0.001	8.49 (6.72-11.1)	8.05 (6.11-11.4)	8.49 (6.61-11.7)	0.803
Serum albumin, mmol/L	45 (41-51)	45 (41-50)	0.684	44 (41-50)	45 (44-50)	45 (41-48)	0.291
C-reactive protein, nmol/L	168 (103-244)	194 (131-285)	0.001	185 (126-274)	180 (93-274)	218 (163-297)	0.010
Creatine kinase, U/L	88 (46-160)	107 (55-283)	0.002	128 (49-303)	91 (50-276)	99 (67-243)	0.869
Lactate dehydrogenase, U/L	416 (313-557)	488 (383-650)	<0.001	430 (344-615)	497 (411-660)	542 (421-682)	0.008

Note. All continuous variables are expressed as median (interquartile range).

Abbreviations. AKI, acute kidney injury; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; SCr, serum creatinine; N/L, neutrophil to lymphocyte ratio; TnI, troponin I.

	No AKI n=241	AKI n=311	p- Value (AKI vs no AKI)	Stage 1 AKI N=115	Stage 2 AKI N=75	Stage 3 AKI N=121	p-Value (among AKI stages)
Ferritin, nmol/L	1.50 (0.92- 2.63)	1.91 (1.13- 3.02)	0.020	2.05 (1.20- 3.10)	1.71 (1.04- 2.91)	1.95 (1.08- 3.16)	0.564
D-dimer, mg/L	1333 (713- 4049)	1615 (914- 4674)	0.103	1535 (856- 3515)	1604 (1047- 4426)	1952 (919- 5203)	0.470
Troponin I, pg/mL	8.0 (4.3- 23.2)	25.8 (7.0- 123.5)	<0.001	11.8 (5.1- 50.5)	34.7 (7.6- 158)	44.2 (11.0- 157)	0.027
Abnormal TnI, n (%)	72 (30)	165 (53)	<0.001	46 (40)	41 (55)	79 (65)	<0.001
PaO ₂ /FiO ₂ ratio	103 (82- 145)	107 (81- 147)	0.812	109 (89- 150)	107 (77- 146)	107 (74- 145)	0.309
Note. All continuous variables are expressed as median (interquartile range).							
Abbreviations. AKI, acute kidney injury; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment score; SCr, serum creatinine; N/L, neutrophil to lymphocyte ratio; TnI, troponin I.							

Table 2
Management in the ICU and patient outcomes by AKI development and AKI staging.

	No AKI n=241	AKI n=311	p-Value (AKI vs no AKI)	Stage 1 AKI n=115	Stage 2 AKI n=75	Stage 3 AKI n=121	p-Value (among AKI stages)
Mechanical ventilation	241 (100)	311 (100)	1.000	115 (100)	75 (100)	121 (100)	1.000
Prone position	165 (69)	206 (66)	0.580	70 (61)	48 (64)	88 (73)	0.140
Vasopressor	205 (85)	267 (86)	0.794	91 (79)	64 (85)	112 (93)	0.012
Norepinephrine >0.1µg/kg/min	83 (34)	93 (30)	0.257	24 (21)	20 (27)	49 (41)	0.003
Dexamethasone	149 (62)	118 (38)	<0.001	52 (45)	26 (35)	40 (33)	0.128
Antibiotics	136 (56)	131 (42)	0.001	51 (44)	24 (32)	57 (47)	0.083
Antifungal therapy	28 (12)	24 (8)	0.120	10 (9)	6 (8)	8 (7)	0.831
Intravenous contrast	28 (12)	22 (7)	0.065	8 (7)	5 (7)	9 (7)	0.977
OUTCOMES							
Length of ICU stay (days)	13 (9- 19)	15 (11- 21)	0.042	12 (10- 18)	12 (10- 20)	20 (15- 27)	<0.001
Length of hospitalization* (days)	22 (16- 31)	25 (19- 36)	0.003	23 (17- 32)	22 (18- 31)	34 (24- 43)	<0.001
Creatinine at discharge, mmol/L	53 (44- 62)	62 (53- 80)	<0.001	62 (44- 71)	62 (54- 81)	63 (45- 142)	0.466
Mortality	67 (28)	148 (48)	<0.001	40 (35)	40 (53)	68 (56)	0.002
* In patients who were discharged alive after improvement							

Note. Categorical variables are expressed as number of patients (percentage). Continuous variables are expressed as median (interquartile range)

Forty-six (8.3% of all patients, and 15% of those with AKI) of the 311 patients with AKI received dialytic support at some point during their ICU stay. Renal replacement therapy was administered as prolonged

intermittent RRT (PIRRT) in 22 (47.8%) subjects, as intermittent hemodialysis (IHD) in 15 (32.6%), and as continuous RRT (CRRT) in 9 (19.6%). The median days from the AKI diagnosis to dialysis initiation were 2 (IQR 1-4). Of those patients who developed AKI and survived to hospital discharge, the median peak serum creatinine was 1.9mg/dL (IQR 1.4-3.3), with a median serum creatinine at hospital discharge of 0.7mg/dL (IQR 0.6-0.9).

Factors associated with AKI in critical care COVID-19 patients

The factors associated with severe AKI development (stage 2 or 3) were evaluated by logistic regression (Table 3). Age, body mass index (BMI), the Charlson comorbidity index, a previous history of chronic kidney disease, blood glucose and lactate dehydrogenase at the start of IMV, the SOFA score at IMV initiation, and the need for vasopressor support were associated with the occurrence of severe AKI in the univariate analysis. Treatment with DXM was associated with a reduced risk of AKI development. Time to AKI in the group that received DXM was a median 4 days (IQR 0-4) compared to the group that did not receive DXM was a median 1 day (IQR 0-5). In the multivariate analysis, age (OR 1.03, 95% CI 1.00-1.05), BMI (OR 1.08, 95%CI 1.04-1.12), glucose at IMV initiation (OR 1.05, 1.01-1.10), SOFA score at IMV initiation (OR 1.20, 95%CI 1.08-1.33), use of any vasopressor (OR 1.76, 1.01-3.20), and DXM treatment (OR 0.34, 0.22-0.52) were associated with the occurrence of severe AKI. The incidence of severe AKI was 34% in patients treated with DXM and 66% in those without DXM. As shown in Figure 2, DXM treatment significantly decreased the risk for each stage of AKI.

Table 3
Univariate and multivariate logistic regression analysis for severe AKI development.

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Age, per year	1.019	1.005-1.033	0.007	1.026	1.003-1.049	0.029
Male, vs female	0.891	0.606-1.310	0.558	0.834	0.530-1.311	0.431
BMI, per kg/m ²	1.065	1.033-1.097	<0.001	1.078	1.040-1.116	<0.001
Charlson index, per point	1.228	1.086-1.388	0.001	1.107	0.907-1.350	0.318
History of CKD, vs not	4.235	1.287-13.93	0.018	3.260	0.843-12.60	0.087
Glucose at ICU admission, per mmol/L	1.050	1.014-1.087	0.006	1.051	1.008-1.095	0.019
LDH at ICU admission, per 100 UI/dL	1.239	1.128-1.361	<0.001	1.335	1.202-1.481	<0.001
SOFA at ICU admission, per point	1.220	1.115-1.335	<0.001	1.198	1.083-1.326	<0.001
Vasopressor, vs not	1.784	1.040-3.059	0.035	1.762	1.014-3.201	0.043
Dexamethasone, vs not	0.392	0.272-0.563	<0.001	0.341	0.224-0.522	<0.001
Abbreviations. OR, odds ratio; 95%CI, confidence interval at 95%; BMI, body mass index; CKD, chronic kidney disease; ICU, intensive care unit; LDH, lactate dehydrogenase; SOFA, Sequential Organ Failure Assessment score.						

Factors associated with survival in critically-ill COVID-19 patients

A total of 215 (39%) patients died during the study (Table 2). Of them, 148 (69%) developed AKI during their hospitalization (40 [27%] stage 1 AKI, 40 [27%] stage 2 AKI, and 68 [46%] stage 3 AKI). Among the 46 patients who were managed with RRT, 21 (46%) patients died.

The factors associated with mortality were evaluated by Cox regression analysis. Age, male gender, laboratory parameters at IMV initiation (including serum glucose, albumin, lactate dehydrogenase, and C-reactive protein), the PaO₂/FiO₂ ratio at IMV initiation, AKI development, use of vasopressor medications, and treatment with DXM were significantly associated with mortality in the univariate analysis. After adjustment in the multivariate analysis, the occurrence of severe AKI was associated with increased

mortality (HR 1.52, 95%CI 1.14-2.02, $p=0.004$), while treatment with DXM was associated with lower mortality (HR 0.63, 95%CI 0.48-0.83, $p=0.008$).

The effects of severe AKI development and no DXM treatment in patient mortality were independent and additive in the adjusted survival analysis (Figure 3). The highest mortality was observed in patients with severe AKI and no DXM treatment. In patients with severe AKI treated with DXM, mortality was significantly reduced and equivalent to the group without severe AKI and no dexamethasone treatment. The lowest mortality was observed in patients without severe AKI treated with DXM.

Length of hospitalization and recovery of kidney function

In survivor patients, the total days of hospitalization and ICU stay were significantly greater ($p<0.001$) in those who developed severe AKI (median 28 days [IQR 20-41] and 16 days [IQR 11-25], respectively) than in those without AKI (median 22 days [IQR 16-31] and 13 days [IQR 9-19], respectively). There was no difference ($p=0.265$) in the length of hospitalization between those survivors treated with DXM (23 days, IQR 17-32) and those without DXM (25 days, IQR 18-35).

Among 46 patients who were managed with RRT, 21 (45.7%) died. From the 25 patients who survived, 24 recovered their kidney function by 28 days and 1 by 90 days after hospital discharge. Recovery was observed in patients with and without DXM treatment.

Discussion

The occurrence of AKI in critically ill COVID-19 patients is high. In this study, we observed an incidence of 56% in COVID-19 patients undergoing IMV, 36% corresponding to severe AKI, and 8.3% of patients requiring RRT. As previously reported, AKI was associated with higher mortality. The factors associated with AKI development were increasing age and body mass index, laboratory parameters at the initiation of IMV, and vasopressor use. Interestingly, treatment with a standardized DXM regimen reduced the incidence, severity, and mortality of severe AKI after adjusting for other factors. This is one of the first large cohorts of COVID-19 patients on IMV to show this significant reduction in AKI episodes and their severity with the use of DXM.

Several studies from multiple centers have reported an elevated incidence of AKI in COVID-19 patients admitted to the ICU, ranging from 30 to 75% for AKI of any stage, 21 to 56% for severe AKI (stages 2 or 3), and 6 to 39% for AKI requiring RRT [17–22]. In this study, AKI incidence was well between these ranges: 56% AKI of any stage, 36% severe AKI, and 8% for AKI requiring RRT. The high variability in these numbers is explained by the well-reported variation between hospitals [21], the different criteria for ICU admission, the timing of the study relative to the pandemic waves [5, 17], and characteristics of the population admitted to the ICU, among other factors.

An important factor that has been associated with AKI development is the use of IMV [20, 23, 24]. For example, in previous reports from critically ill COVID-19 patients were all patients received IMV [5, 19], the

incidence of AKI was 52 to 75%, and 18 to 20% for AKI with the need for RRT. In our study encompassing mechanically-ventilated COVID-19 patients, we observed an equivalent incidence of AKI, although the percentage of patients who received RRT was lower. The latter may be partially explained by the exclusion of patients with advanced CKD and those with a kidney transplant. Acute kidney injury in COVID-19 has been associated with the use of high positive pressure ventilation [25], although it is not known if this observation is explained by a direct effect of positive pressure ventilation (which can reduce kidney perfusion and glomerular filtration [26]), or the fact that high-pressure ventilation may be a marker for sicker patients.

Several other risk factors are associated with AKI in COVID-19, including age, laboratory parameters, interventions such as vasopressors and IMV, and severity scores (SOFA, APACHE-II) [20, 21, 23, 27–29]. Consistent with the previous reports, we observed an association between increasing age and body mass index, laboratory parameters as glucose and LDH, and vasopressor use with the development of severe AKI.

Noteworthy, we observed that a protocolized dexamethasone regimen was associated with lower development of AKI in mechanically-ventilated COVID-19 patients after adjustment for the risk factors described above. Previous small reports suggested an effect of glucocorticoid treatment on AKI in COVID-19. Lowe *et al* [9], described a lower incidence of AKI in a cohort of 81 critically ill COVID-19 patients treated with glucocorticoids. Moreover, Lumlertgul *et al* [10] observed less AKI progression in subjects treated with glucocorticoids in adjusted analyses. Pineiro *et al* [11] reported less AKI with RRT requirement in those treated with glucocorticoids. These initial reports suggested a potential beneficial effect of glucocorticoid treatment in AKI development; however, they were limited by the small number of patients included and the non-protocolized use of glucocorticoids. In the RECOVERY trial [8], the number of patients who received RRT was lower in those treated with a protocolized dexamethasone regimen. A recent report from France [12] included 100 critically ill COVID-19 patients and where DXM was administered to all patients during the second COVID-19 wave, DXM use was associated with less AKI in the adjusted analysis (OR=0.31, 95%CI 0.09-0.99). Here, in a larger population and a protocolized DXM regimen, we ascertained that DXM treatment is associated with a 66% (95%CI 48-88%) lower incidence of severe AKI.

Acute kidney injury is a well-recognized factor associated with mortality in critically-ill COVID-19 patients [5, 21, 27, 30], therefore, any intervention that decreases AKI incidence would be expected to also decrease patient mortality. As previously demonstrated in the RECOVERY trial and verified in subsequent studies [8, 31, 32], DXM treatment reduces mortality in COVID-19 patients with oxygen requirement, including those undergoing IMV. In this study, we showed that DXM treatment is associated with a reduced mortality in patients with severe AKI, as well as in the group of patients without severe AKI, after adjustment for other risk factors.

Glucocorticoids have been widely used in septic shock and ARDS, given the central role of the inflammatory cascade in the pathogenesis of these diseases. They have also been used in other viral

diseases, such as MERS, SARS, and influenza [33–35]. Nonetheless, the evidence for their efficacy in the management of these diseases has been inconclusive, without a clear definition for dosing, the timing of implementation, and a lack of randomized controlled trials. In the RECOVERY trial [8], DXM was started during the second week of the clinical course of COVID-19, a stage where inflammation plays a determinant role and where the SARS-CoV-2 viral replication may be less relevant. Several cytokines have been associated with AKI in COVID-19, including interleukin (IL) -1, IL-6, interferon-gamma, tumor necrosis factor-alpha; and inflammatory pathways such as the complement pathway have been linked to kidney damage [36]. Therefore, a direct effect of glucocorticoids on inflammation and the consequent improvement in kidney microcirculatory function may aid prevent the development of AKI in COVID-19. Of course, several other mechanisms may be involved, as the effect of DXM in reducing disease severity and other organic failures may be directly associated with less kidney injury.

Finally, it has also been reported that DXM treatment reduces the length of days under IMV and the length of hospitalization [11, 18, 19, 37]. We also observed a reduction in these parameters consistent with these studies, although they were not affected by DXM treatment. Renal recovery was observed in most surviving patients after RRT, with or without DXM treatment. This high percentage is higher than that observed in other series [21, 37, 38] and possibly influenced by the exclusion of patients with advanced previous kidney damage. Still, the serum creatinine-based definition for recovery of kidney function does not account for the loss of the renal reserve and should be taken cautiously as it has been reported that COVID-19 survivors have a higher risk of eGFR decline, end-stage kidney disease, and major adverse kidney events [39].

There are limitations to this study. As an observational study, some factors associated with AKI development may have not been registered. Therefore, the association between DXM treatment and AKI prevention may be overestimated and it is not possible to establish a causal role. The study did not account for differences in AKI incidence and mortality according to the COVID-19 pandemic waves at our center and the time from the start of the pandemic.

Conclusions

The incidence of AKI is high in critically-ill COVID-19 patients undergoing mechanical ventilation. Dexamethasone treatment is associated with a lower incidence of severe AKI and lower mortality in patients with severe AKI. The mechanisms underlying the protective role of DXM in the kidneys remain to be established.

Abbreviations

COVID-19, Coronavirus Disease-19; AKI, acute kidney injury; ICU, intensive care unit; IMV, invasive mechanical ventilation; DXM, dexamethasone; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; RRT, renal replacement therapy; eGFR, estimated glomerular

filtration rate; SCr, serum creatinine; P/F ratio, PaO₂ to FiO₂ ratio; IQR, interquartile range; BMI, body mass index; OR, odds ratio; HR, hazard ratio; LDH, lactate dehydrogenase.

Declarations

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None.

AUTHORS' CONTRIBUTIONS

JMMV, NTC, and OVV designed the study. Patient data was obtained by NTC, ACI, AMR, JHF, JPZ, VSR, DFC, RCB, MNG, RCR. Statistical analysis was performed by JMMV, NTC, OVV. Manuscript drafting was done by JMMV, NTC, RCR, and OVV. All authors have read and approved the final manuscript.

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AVAILABILITY OF DATA AND MATERIALS

All data generated or analysed during this study are included in this manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All the procedures of this study followed the ethical standards of our Institution and our National Research Committee, and the 1964 Helsinki declaration. The study was approved by the local Human Research and Ethics Boards (reference NMM-3325-20-20-1).

CONSENT FOR PUBLICATION.

Not applicable

COMPETING INTERESTS

The authors declare no conflict of interest.

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Figures

Figure 1

Consort diagram of the studied population.

Figure 2

Incidence of acute kidney injury in subjects treated with and without dexamethasone.

Figure 3

Combined effect of severe AKI and dexamethasone treatment in mortality.

Cox regression analysis adjusted for age, PaO₂/FiO₂ ratio, SOFA at IMV initiation, and use of vasopressors.

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