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Original Article

ORIGINAL ARTICLE

Acute and chronic kidney disease and risk of hospital mortality during COVID-19 pandemic waves in the pre-vaccination era

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ABSTRACT

Background. Chronic kidney disease (CKD) is a risk factor for death from coronavirus disease 2019 (COVID-19), and COVID-19 may cause acute kidney injury (AKI) which also influences outcomes. There is little information on the independent contribution of CKD and AKI to the risk of death in COVID-19 on different waves, as CKD is a key risk factor for AKI.

Methods. We have studied the epidemiology of CKD and AKI in 2878 patients hospitalized for COVID-19 and their independent association with in-hospital mortality in the two largest pre-vaccination COVID-19 waves in Madrid, Spain. Hospitalized COVID-19 patients were grouped into four mutually exclusive categories: previous-CKD, community-acquired AKI (CA-AKI), hospital-acquired AKI (HA-AKI) and normal renal function throughout hospitalization.

Results. Pre-existent or acquired kidney involvement was observed in 35.5% and 36.8% of COVID-19 patients in the 1st and 3rd waves, respectively. Overall, 13.9% of patients with normal kidney function on arrival developed HA-AKI. In the 3rd wave, CA-AKI was more common than in the 1st wave. Overall, 9%–20% of CKD cases and 22%–40% of AKI cases remained undiagnosed in the discharge report. CKD, CA-AKI and HA-AKI were independently associated with risk of death in multivariate analysis, with HA-AKI, which was usually mild, being the most relevant independent risk factor for in-hospital mortality. A model including kidney involvement category, age, Charlson index, admission lactate dehydrogenase and lymphocytes predicted death with a receiver operating characteristic area under the curve of 0.898.

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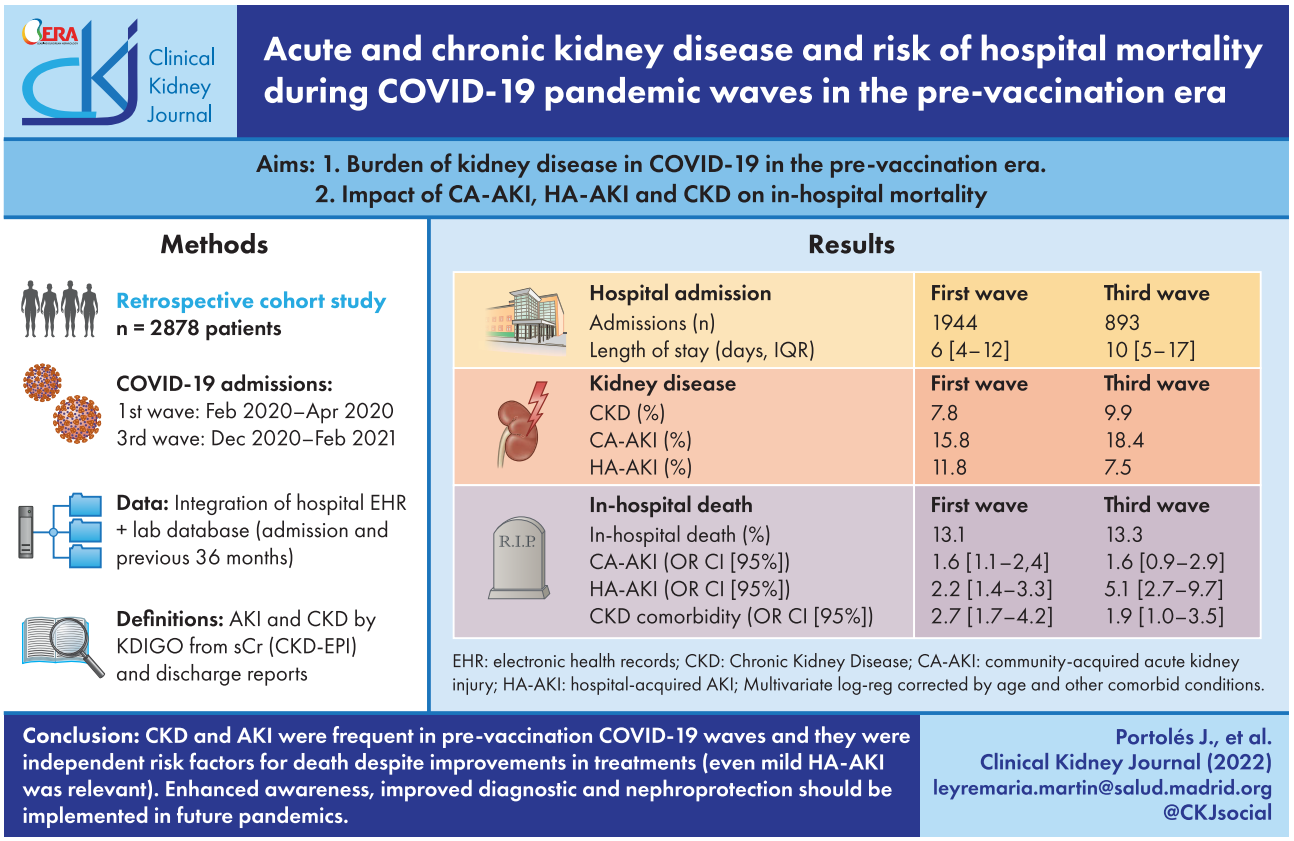
Conclusion. In conclusion, CKD and AKI were common in pre-vaccination waves among hospitalized COVID-19 patients and were independent risk factors for death, even when AKI was mild to moderate, and despite improvements in treatment.

GRAPHICAL ABSTRACT



Keywords: acute kidney injury, chronic kidney disease, COVID-19, epidemiology, mortality, SARS-CoV-2

INTRODUCTION

Clusters of pneumonia cases occurring in the city of Wuhan, Hubei Province, China in December 2019 led to the eventual identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent for coronavirus disease 2019 (COVID-19) [1, 2]. COVID-19 spread rapidly from Wuhan to other regions in China and all over the world. On 11 March 2020, the World Health Organization (WHO) declared COVID-19 to be a global pandemic and more than 525 million infections and over 6.3 million deaths have been reported [1].

Early data from China suggested that the severity of the disease varies among individuals and that the incidence of acute kidney injury (AKI) among patients with COVID-19 was low. For example, in a Chinese cohort of 1099 patients with COVID-19, 91.1% had pneumonia and 5.3% were admitted to the intensive care units (ICU), but only 0.5% developed AKI [2]. However, another 1st wave early report from a reference hospital in Wuhan showed a 5.1% incidence of AKI, 49.3% of proteinuria and 18% of increased serum creatinine (sCr) [3]. Our research group had already reported by May 2020 a high incidence of AKI and a high prevalence of chronic kidney disease (CKD) among patients admitted with SARS-CoV-2 infection, and their association with in-hospital mortality, even after correction by COVID-19 severity index [4].

Six pandemic waves have been defined in Spain. We have selected the 1st and 3rd waves as the most relevant pre-vaccination waves as they had the highest mortality rates, in order to compare the epidemiology of CKD and AKI and their association with outcomes [5]. Different waves of COVID-19 may differ from the first in the characteristics of the virus [2] and the profile of patients affected [6–10]. Although some global epidemiological studies have compared the incidence, patient characteristics, prescription of medications, mortality or burden on the health system, we did not find studies whose main objective was to analyze the incidence of AKI, the prevalence of CKD and their independent impact on in-hospital mortality in different COVID-19 waves.

The aim of this study was to assess the burden of kidney injury in COVID-19 by comparing the frequency of CKD and AKI among patients admitted with COVID-19 in the 1st and 3rd pandemic waves, prior to the availability of vaccines, and to estimate the independent association of AKI and CKD with in-hospital mortality.

MATERIALS AND METHODS

Participants

We defined waves according to public health system reports and local hospital admission rates as: 1st wave from 20 February to 30 April 2020, and 3rd wave as from 1 December 2020 to 28 February 2021 (Fig. 1) [5]. Of the three Spanish COVID-19 waves that occurred in the pre-vaccination era, we have selected the 1st and 3rd as they had the highest incidence and mortality [11]. Adult patients with registered outcomes (in-hospital death or discharge) admitted to University Hospital Puerta de Hierro in the date range of the 1st and 3rd waves were identified in the Minimum Basic Data Set (CMBD is the Spanish acronym) database (Fig. 2). The only exclusion criterion was being on chronic dialysis. Previous hematopoietic and solid organ transplantation recipients (e.g. renal transplant recipients) were included. COVID-19 was diagnosed based on clinical or laboratory criteria. Clinical and tomography scan criteria were according to the WHO's interim guidelines [12]. Laboratory-confirmed cases were identified with nucleic acid detection of SARS-CoV-2 from a throat swab sample using reverse transcription-polymerase chain reaction (RT-PCR) as described by others [13].

This study was approved by the ethics committee of Hospital Universitario Puerta de Hierro (IRB number 2020/32).

Data sources and definitions

Clinicians recorded clinical data and vital signs on electronic medical records (EMR) under routine clinical practice conditions. Laboratory data and drug prescriptions were obtained from EMR and pharmacy electronic worksheets. The information included demographic characteristics, comorbidity, disease severity and vital signs on arrival, laboratory values and treatments during the hospitalization, and outcomes. A common protocol for hospital admission, evaluation of severity, laboratory sampling and drug prescriptions was implemented in the hospital by 28 February 2020. The severity of pneumonia was defined on arrival by the CURB65 index [14]. During both waves, the in-hospital treatment for COVID-19 was categorized as hydroxychloroquine and its analogues, antiretroviral agents (mainly lopinavir/ritonavir) and immunomodulators such as prednisone or humanized anti-interleukin-6 antibody (tocilizumab). Every patient gave oral consent for the off-label use of these drugs for COVID-19. Other commonly used drugs were prescribed for complications, such as anti-thrombotic prophylaxis, antibiotics, antifungals and other antiviral agents for superimposed infections.

Laboratory values on admission and those previously described as relevant for the disease [15] were included: blood count, renal function, inflammatory markers (high sensitivity C-reactive protein, procalcitonin, albumin and ferritin), haemostasis parameters (D-dimer, coagulation times); liver, muscle and cardiac function markers (NT-proBNP, lactate dehydrogenase). We also obtained interleukin-6 levels if tocilizumab prescription was considered. We selected the peak and nadir values during hospital stay of kidney function biomarkers. Every patient has an sCr value on admission and another value within 48 h, with a median of 5 sCr values during their hospital stay; those values were used for AKI definition.

The local laboratory reference values were used as the normal range. Kidney involvement was estimated by sCr (normal values up to 1.1 mg/dL for men and up to 0.9 mg/dL for women) and estimated glomerular filtration rate (eGFR), which was calculated from serum creatinine with the Chronic Kidney Disease Epidemiology Collaboration equation [16].

AKI was defined as an increase in sCr >0.3 mg/dL within 48 h or a 50% increase in sCr from baseline within 7 days according to the KDIGO guidelines [17]. AKI was classified into three stages of severity based solely on the sCr criteria of the KDIGO definitions of AKI, as precise urine output data were not available. For those case of community-acquired AKI (CA-AKI) without previous sCr values, the sCr normal reference was considered. AKI stage I was defined as 1.5–1.9 times the initial sCr or ≥0.3 mg/dL increase in sCr; AKI Stage II as 2.0–2.9 times baseline sCr; and AKI Stage III as 3 times baseline or sCr ≥4.0 mg/dL.

Hospitalized COVID-19 patients were grouped into four mutually exclusive categories (Fig. 2): (i) previous CKD was diagnosed using laboratory values from the 36 months before hospital admission in the central laboratory system, which included primary care, hospital outpatient and hospital admission values, and defined as eGFR <60 mL/min/1.73 m^2 at admission and additionally in at least one prior laboratory record or a prior diagnosis of CKD in the I; (ii) CA-AKI (i.e. AKI present at arrival to hospital)—we considered patients with an upper normal sCr on arrival and without any sCr values available during the previous 3 years to have CA-AKI and CKD, since the CKD diagnosis cannot be supported by a single serum creatinine value obtained during acute illness (the rationale to extend the time window for 3 years was to minimize the chance of misdiagnosing CKD as CA-AKI); (iii) hospital-acquired AKI (HA-AKI, i.e. normal sCr at admission and later development of AKI); and (iv) normal renal function throughout hospitalization. It was calculated of percentage of patients admitted with AKI or with CKD and are obtained by dividing the number of cases in each category (CA-AKI, HA-AKI or CKD) by the total number of COVID-19 cases. Other comorbidities such as hypertension or obesity were obtained from CMBD. A trained team of nephrologists and statisticians reviewed all the datasets.

Statistical analysis

Continuous variables were presented as the mean ± standard deviation or median [interquartile range (IQR)], and categorical variables were presented as percentages. The number of available values is indicated for every variable. Two sample *t*-test or Wilcoxon rank-sum test was used for continuous variables and chi-square test or Fisher's exact test for categorical variables as appropriate. The associations between kidney disease and in-hospital death were examined using logistic regression and performed separately for each of the waves. Predictive models were examined using uni- and multivariate analysis in a stepwise backward analysis *P*-in .10, *P*-out .20. No missing value imputation method was used. Those who did not have data in any of the included variables were excluded from the analysis. The main variable was kidney disease by category (CA-AKI, HA-AKI or CKD) and other variables were considered as secondary or confounding factors in the multivariate analysis. A confounding factor is the one that generates a change greater than 10% in the main variable.

Explanatory models were examined using a backward and forward stepwise model; the best model in this case is selected among those with higher area under the curve (AUC).

Statistical analyses were performed using Stata software (v14 Stata Corp., TX, USA) with statistical significance set at 2-tailed $P < .05$.

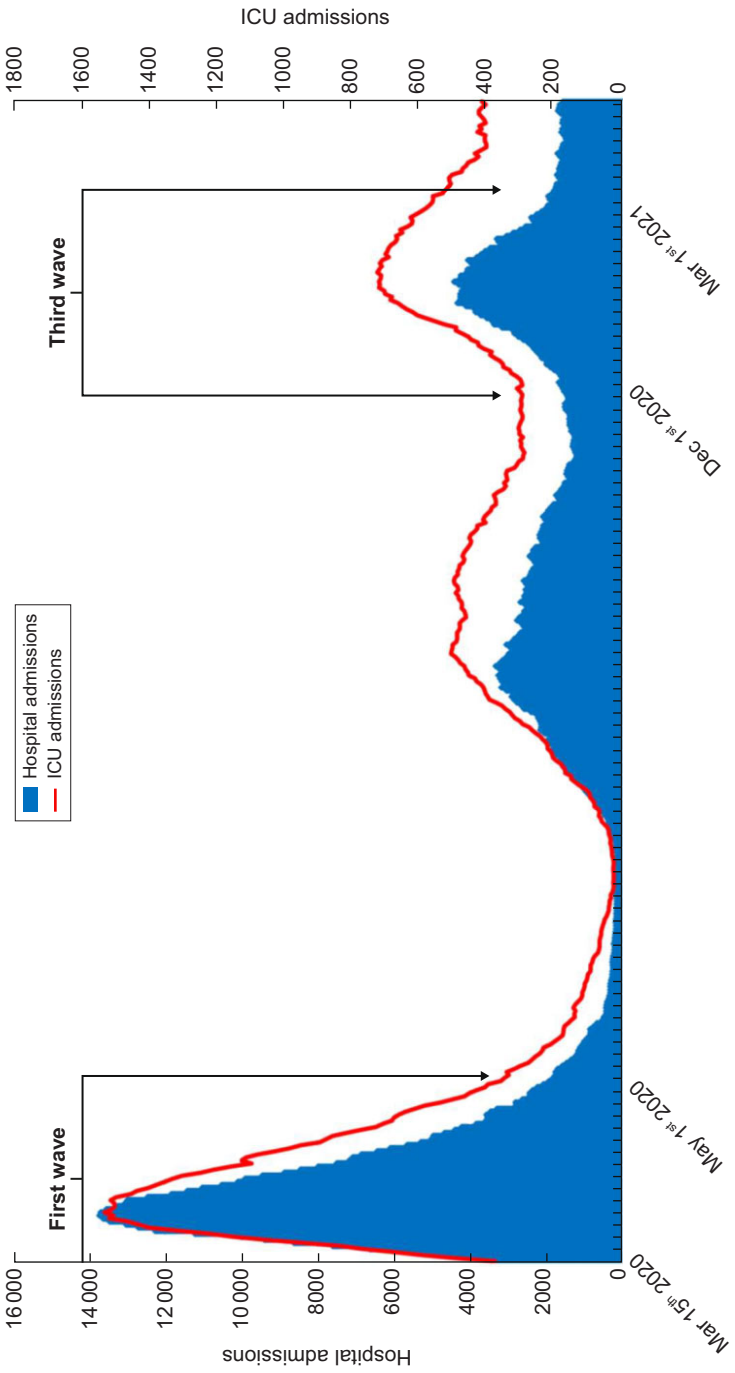


Figure 1: Daily hospital and ICU admissions during the first three COVID-19 waves in the Madrid regional health system. Note: adapted from Covid report from Health Regional system for 2021 March. https://www.comunidad.madrid/sites/default/files/aud/sanidad/210401_cam_covid19.pdf (accessed on 7 July 2022).

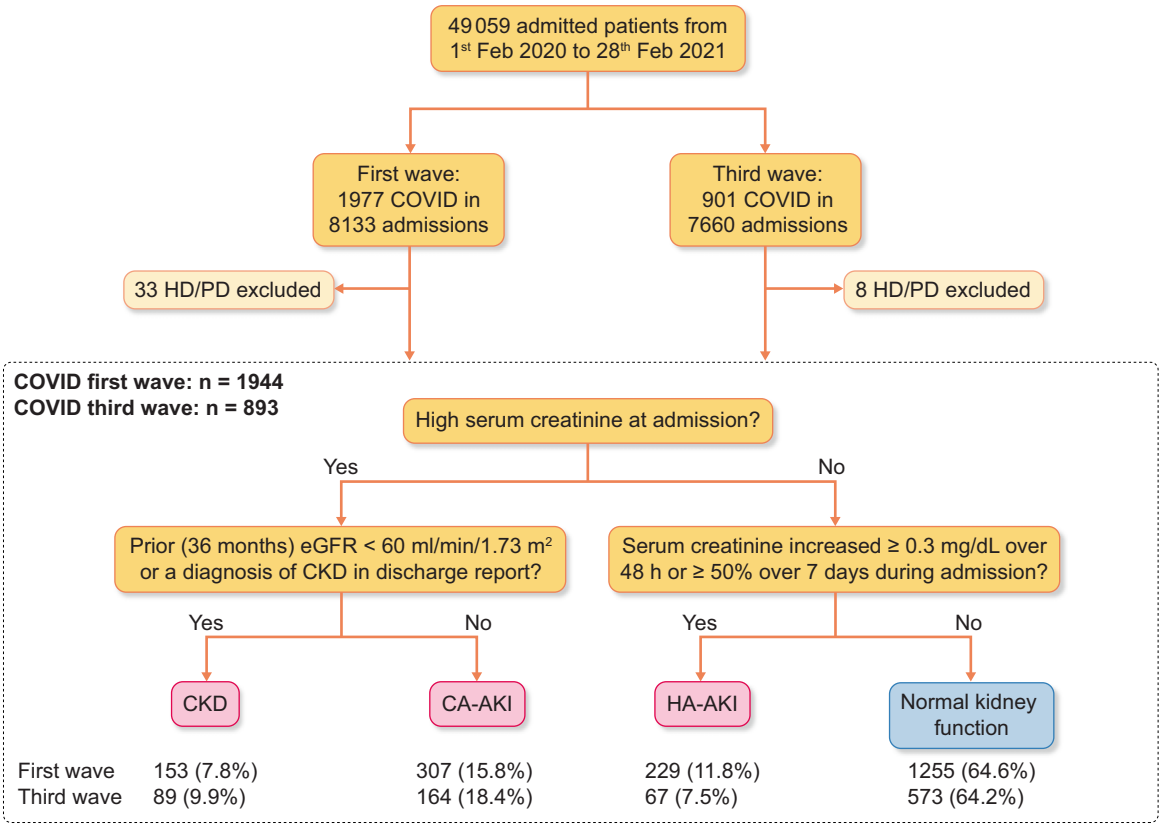


Figure 2: Patient flow chart. Note: 1st wave 20 February to 30 April 2020; 3rd wave from 1 December 2020 to 28 February 2021.

RESULTS

Patient characteristics and COVID-19 admissions in pandemic waves

There were 49 059 hospital admissions from 1 February 2020 to 28 February 2021 (Fig. 2). During the 1st wave (from 20 February to 30 April 2020), 1977 COVID-19 admissions out of a total of 8133 admissions for any cause were included. During the 3rd wave (from 1 December 2020 to 28 February 2021), 901 COVID-19 admissions out of 7660 admissions were included. Therefore, 2878 patients with data on hospital outcome were selected, but finally we analyzed 2837 patients since 41 were excluded due to having a renal replacement therapy (Fig. 2). The healthcare system overload because of COVID-19 was higher in the 1st wave (24.3% vs 11.8% of admissions were due to COVID-19, respectively).

Patient characteristics in both waves are detailed in Table 1. Patients in the 3rd wave were older and more comorbid but had similar renal disease prevalence.

During the 3rd wave, the hospital stay was longer [median (IQR)]: 10 days (5–17) vs 6 (4–12) days] and the admission rate in the critical care unit was higher (3.5% vs 1.5%), but mortality was similar in both waves.

The most relevant laboratory values are shown in Supplementary data, Table S1 for all patients and classified by waves. Increased levels of inflammatory markers (elevated high sensitivity C-reactive protein, erythrocyte sedimentation rate and ferritin) and altered coagulation parameters (elevated D-dimer and thrombin times) were common.

During the 3rd wave, the prescription of off-label treatments based on early preliminary reports or opinions (hydroxychloroquine, lopinavir/ritonavir, interferon, immunoglobulins and antibiotics) was lower and the prescription of prednisone, tocilizumab, remdesivir, anticoagulation and renin–angiotensin system blockade was higher than during the 1st wave (Table 2).

Kidney disease

Pre-existent or acquired kidney involvement was observed in 35.5% and 36.8% of COVID-19 patients in the 1st and 3rd waves, respectively. Overall, 13.9% of patients with normal kidney function in the emergency room developed AKI during admission. However, there were differences in the specific types of kidney involvement between COVID-19 waves. The distribution of kidney involvement was different among waves ($P < .001$ for all categories distribution; Table 1). The distribution of kidney involvement was different among waves (Table 1, $P < .001$). In the 3rd wave, CKD was numerically more frequent (9.9% vs 7.8%, $P = .09$) and CA-AKI was more common (18.4% vs 15.8%, $P = .001$) while HA-AKI was numerically less common (8.1% vs 11.8%, $P = .06$) than in the 1st wave (Table 1).

The severity of AKI was similar in both waves, when assessed as peak sCr (1.7 ± 1.8 mg/dL in the 1st wave and 1.6 ± 1.1 mg/dL in the 3rd wave), AKI stage (AKI-1 73.0% vs 67.1%; AKI-2 17.2% vs 19.7% and AKI-3 9.8% vs 13.2% ($P = .2$) or the need for acute dialysis (2.5% vs 2.3%). Only two patients remained on haemodialysis at discharge.

The prevalence of CKD as a comorbid diagnosis in the discharge report was lower than the prevalence obtained from current and historical laboratory data (7.3% vs 7.8% in 1st wave and 8.6% vs 9.9% in 3rd wave $P = .05$). Likewise, the frequency of

Table 1: Main outcomes, patient and admission characteristics during the 1st and 3rd waves.

	n	1st wave	3rd wave	*P*-value
COVID-19 admitted patients (*n*)		1944	893	
Age (years)[a]	1944/893	64.9 ± 16.1	66.7 ± 16.0	<.001
Patients aged >65 years at admission (%)	1944/893	50.3	55.4	.01
Male (%)	1944/893	59.8	58.2	.4
Charlson index (without age)[a]	1944/893	1.1 ± 1.8	1.3 ± 2.0	<.001
Renal diagnosis (%)		7.3	8.6	.35
Cardiovascular diagnosis (%)		17.7	20.2	.05
Acute myocardial infarction (%)		4.1	4.2	.9
Stroke (%)		4.5	4.8	.7
Congestive heart failure (%)		9.2	10	.5
Peripheral vascular disease (%)		4.3	5.1	.34
Diabetes mellitus (%)		17.7	20.1	.13
Hypertension (%)	1944/893	32.2	31.5	.7
Obesity (%)	1944/893	7.7	12.3	<.001
Kidney disease (%)				
sCr normal throughout admission[d]	1255/573	64.6	64.2	
CA-AKI	307/164	15.8	18.4	
HA-AKI	229/67	11.8	7.5	<.001
CKD	153/89	7.8	9.9	
Need of dialysis during admission (%)[b]	1944/893	2.5	2.3	.75
Length of stay (days)[c]	1944/893	6 (4–12)	10 (5–17)	<.001
Death (%)	1944/893	13.1	13.3	<.9
Discharge department (%)	1944/893			
Internal medicine		79.3	66.5	<.001
Respiratory medicine		11.0	18.9	
ICU		1.5	4.9	
Obstetrics		2.2		
Geriatrics			1.9	

[a]Mean (standard deviation).
[b]Need of dialysis includes hemodialysis and continuous veno-venous hemofiltration.
[c]Median (interquartile range).
[d]serum creatinine normal throughout admission.

Table 2: Drugs prescription (% of patients) during hospital stay on 1st and 3rd waves.

	1st wave	3rd wave	*P*-value
N	1599	796	
ACEI or ARB	19.0	25.3	<.001
Interferon	24.3	0.0	<.001
Hydroxychloroquine	79.5	0.6	<.001
Lopinavir/ritonavir	47.4	0.1	<.001
Azithromycin	42.6	12.2	<.001
Any antibiotic	73.8	52.8	<.001
Any antifungal	2.8	3.9	.1
Anakinra	3.0	3.9	.2
Other antiviral (except remdesivir)	2.5	1.9	.4
Remdesivir	0.0	2.4	<.001
Prednisone	58.3	87.6	<.001
Tocilizumab	17.0	35.1	<.001
Prednisone and/or tocilizumab	59.5	88.1	<.001
Oral anticoagulant therapy (any)	5.8	7.9	.04
Low molecular weight heparin	54.7	83.3	.03

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

AKI diagnosed in the discharge report underestimated the occurrence of AKI diagnosed according to the KDIGO definitions applied to laboratory values (9.4% vs 15.8% in 1st wave and 14.3% vs 18.4% in 3rd wave, $P = .01$). Overall, 9%–20% of CKD cases and 22%–40% of AKI cases remained undiagnosed in the discharge report.

Association of kidney involvement with in-hospital death

The main outcome, in-hospital death, occurred in 13.2% of the patients: 13.1% in the 1st wave and 13.3% in the 3rd wave.

The raw in-hospital mortality rate during both waves was higher in patients with previous CKD (34.7%), CA-AKI (14.0%) or HA-AKI (23.7%) than in those with normal renal function throughout the stay (8.0%). In univariate logistic regression analysis, age, Charlson index, previous CKD, cancer and AKI were associated with higher mortality risk in both waves (Table 3).

In the multivariate logistic regression predictive model, the risk attributable to HA-AKI was 2.2 (1.4–3.3) in the 1st wave vs 5.1 (2.7–9.7) in the 3rd wave after correction for age, gender and Charlson index. The risk attributable to CKD was, by contrast, 2.7 (1.7–4.2) in the 1st wave and 1.9 (1.0–3.5) in the 3rd wave when corrected for age, AKI, gender and Charlson index (Table 3).

We also developed an explicative model including laboratory values during the follow-up with a high predictive value (Table 4). The receiver operating characteristic (ROC) AUC was 0.89 for prediction of death, the positive predictive value was 62.9% and the negative predictive value was 90.9% (Fig. 3).

DISCUSSION

Our main finding is that despite the changing demographics of patients admitted for COVID-19 and the availability of more evidence-based therapy, the risk of AKI and death remained high, and both pre-existent and acquired renal involvement

Table 3: Multivariate and univariate logistic regression for in-hospital death during 1st and 3rd waves (Backward stepwise, predictive model).

	Univariate		Multivariate	
	1st wave OR (95% CI)	3rd wave OR (95% CI)	1st wave OR (95% CI)	3rd wave OR (95% CI)
CA-AKI[a]	1.9 (1.3–2.8)	1.8 (1.1–3.1)	1.6 (1.1–2.4)	1.6 (0.9–2.9)
HA-AKI[a]	2.9 (2.0–4.3)	6.1 (3.4–11.1)	2.2 (1.4–3.3)	5.1 (2.7–9.7)
Previous CKD[a]	7.2 (4.9–10.5)	4.6 (2.6–8.0)	2.7 (1.8–4.2)	1.9 (1.0–3.5)
Age 65–75 years[b]	5.0 (3.1–7.9)	4.1 (2.0–8.4)	3.9 (2.4–6.3)	2.9 (1.3–6.1)
Age >75 years[b]	14.8 (9.8–22.3)	13.0 (6.9–24.4)	10.8 (7.0–16.6)	9.7 (5.0–18.5)
Charlson index (without years)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Female	1.0 (0.8–1.3)	0.9 (0.6–1.3)		
Cancer	2.5 (1.6–3.8)	2.0 (1.0–3.8)		
Hypertension	1.4 (1.1–1.8)	1.0 (0.6–1.5)		
Obesity	0.7 (0.4–1.3)	1.4 (08–2.4)		

[a]Versus patient reference (serum creatinine normal).
[b]Versus age >65 years. COVID severity index out of model.

Table 4: Multivariate logistic regression for in-hospital death during 1st and 3rd waves (backward and forward stepwise, explicative model).

	Univariate		Multivariate	
	1st wave OR (95% CI)	3rd wave OR (95% CI)	1st wave OR (95% CI)	3rd wave OR (95% CI)
CA-AKI[a]	1.9 (1.3–2.8)	1.8 (1.1–3.1)	1.6 (1.0–2.7)	1.8 (0.9–3.7)
HA-AKI[a]	2.9 (2.0–4.3)	6.0 (3.4–11.1)	1.6 (1.0–2.5)	2.4 (1.1–5.2)
Previous CKD[a]	7.2 (4.9–10.5)	4.6 (2.7–8.0)	2.5 (1.5–4.2)	1.7 (0.8–3.5)
Age (years)	1.1 (1.1–1.1)	1.1 (1.1–1.1)	1.1 (1.1–1.1)	1.1 (1.1–1.1)
Charlson index (without years)	1.3 (1.2–1.4)	1.3 (1.2–1.4)	1.1 (1.0–1.2)	1.2 (1.1–1.3)
LDH (2nd tertile)[b]	1.4 (0.8–2.4)	1.8 (0.9–3.7)	1.0 (0.5–1.8)	1.7 (0.8–3.6)
LDH (3rd tertile)[b]	7.4 (4.6–11.8)	11.2 (6.1–20.5)	4.9 (2.9–8.4)	6.9 (3.5–13.8)
Lymphocytes (2nd tertile)[b]	4.1 (2.9–5.9)	5.4 (1.8–15.9)	2.5 (0.2–3.3)	2.5 (1.4–5.0)
Lymphocytes (3rd tertile)[b]	9.4 (5.9–15.2)	23.8 [(8.6–66.2)	3.3 (2–10.0)	8.3 (2.5–25.0)
Hypertension	1.4 (1.1–1.8)	1.0 (0.6–1.5)		
Obesity	0.7 (0.4–1.3)	1.4 (08–2.4)		

[a]Versus patient reference (serum creatinine normal).
[b]Versus 1st tertile.
LDH, lactate dehydrogenase. LDH tertiles low to high and lymphocytes high to low were assessed at admission.

continue to be independently associated with a higher risk of death, yet they remain underrecognized by treating physicians.

HA-AKI developed in 14% of patients admitted with COVID-19 and normal kidney function. Even non-severe AKI was associated with an increased risk of mortality. HA-AKI was less common than CA-AKI in the 3rd wave, but the attributable risk of death was greater for HA-AKI during this 3rd wave.

We can only speculate about the reasons underlying the differences in CA-AKI and length of stay between the 1st and 3rd waves. These may range from different population characteristics (older in the 3rd wave) to differences in the duration of the pre-hospital phase of the disease. Unfortunately, we do not have information on the course of prehospital disease. We have generated a model that predicts mortality from a simple set of laboratory variables obtained during hospital stay (lactate dehydrogenase, lymphocytes), age, comorbidities and kidney disease status that achieves a relevant predictive value in ROC curves for both waves. This model can serve as a basis for comparison to analyze new factors or treatments.

Some prior studies have addressed AKI, CKD and mortality across waves, but none has analyzed CKD and AKI as independent, non-overlapping categories, thus removing any potential confounding resulting from the fact that patients with CKD are at an increased risk of AKI and are diagnosed of AKI with even lower decrements in kidney function that those with prior normal kidney function. In fact, a strength of the present study is that the risk attributable to CA-AKI is clearly separated from the risk from a CKD diagnosis, since both categories are mutually exclusive.

In other publications, AKI and CKD may coincide in the same patient, as CKD is a key risk factor for AKI. As an example, a recent report describes a 40% incidence of combined CA-AKI and HA-AKI, but 38% of them had previous CKD. Both pre-renal AKI (hazard ratio 3.2; 95% CI 1.7–5.9) and intrinsic AKI [hazard ratio (HR) 7.7; 95% confidence interval (CI) 3.6–16.3] were associated with higher mortality, but this effect disappeared in the multivariate model when CKD was added [18].

A nationwide Danish study [19] compared a more recent period (June 2020 to June 2021) that included the vaccination era with the 1st wave and found a lower ICU admission rate and a shorter mean hospital stay but a similar mortality. The multivariate risk model for in-hospital mortality included CKD [odds ratio (OR) 2.10 (1.46–3.01)], but AKI was not analyzed. In a recent Swiss study of over 953 admissions the mortality of the 1st wave was higher than in the 3rd wave (9.2% compared with 5.4%). However, this was associated to a lower age and

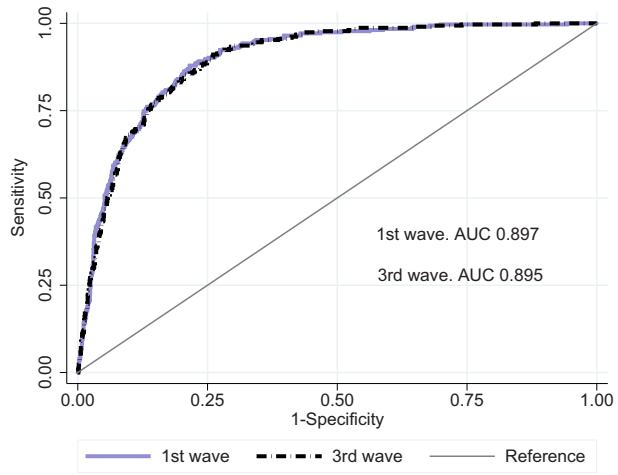


Figure 3: ROC for multivariate regression logistic explicative model for prediction of death. The model incorporated the following variables: kidney involvement category, age, Charlson index and admission lactate dehydrogenase and lymphocytes.

comorbidity burden of admitted patients. They also found that CKD was a risk factor for in-hospital mortality [OR 2.25 (1.35–3.76)] in the multivariate model [20]. CKD was also one of seven relevant comorbidities in a score for predicting infection in a retrospective case–control study on a region of Italy [21], the SARS-CoV-2 Infection Score (SIS).

In the present study, the prevalence of CKD was more common in the 3rd wave, but the risk of death associated with it was similar in both waves. While awareness of CKD is a pivotal strategy to implement kidney protection measures, such as adequate hydration or drug selection and dose adjustment, the discrepancy between the prevalence of CKD diagnoses based on retrospective review of eGFR value and the prevalence of CKD diagnoses in discharge records indicate that further measures should be implemented. EMR automatic systems may help non-nephrologist doctors.

In a retrospective study of pre-vaccine pandemic waves (concurrent with our study), the ICU mortality was lower in the most recent wave and serum creatinine at admission predicted mortality and hospital stay [22]. In the present study, ICU mortality was also lower in the more recent wave.

While a retrospective Japanese study estimated a relative risk reduction of 22%–60% in mortality in the 3rd wave as compared with the 1st wave [23] and ascribed the improved outcomes to improved treatment and general procedures, in the present report, the mean stay was longer and mortality similar in the 3rd than the 1st wave. This may be related to the more severe comorbidities of hospitalized patients in the 3rd wave.

During the 1st pandemic wave, some off-label treatments were widely used based on early small reports, such as some antiviral agents (lopinavir/ritonavir), azithromycin or hydroxychloroquine [24]. Azithromycin has anti-inflammatory and antiviral properties and reduces *in vitro* replication of numerous viruses (including endemic coronaviruses), suppresses some cytokines secretion and inhibits T cells and neutrophils. However, randomized trials failed to demonstrate these positive effects on hard endpoints and they progressively disappeared from protocols [25–27]. Clinical guidelines advise against routine off-label use of azithromycin for all COVID-19 patients and recommend limiting its use to coexistent bacterial infections [25]. A recent systematic review estimates the incidence of co-infections as bacterial (15.9%), fungal (3.7%) or other respiratory viruses (6.6%) in patients diagnosed with COVID-19 (most likely hospitalized) [28]. On the other hand, the use of prednisone and other immunosuppressant agents increased progressively. These changes are reflected in our description of the treatment prescribed in both waves.

Although the present study included only non-vaccinated patients, since vaccines were unavailable, vaccines reduce the severity of COVID-19 but do not completely prevent infection. Hospitalized vaccinated patients with severe COVID-19 had significantly higher rates of most known risk factors for COVID-19 adverse outcomes, including CKD. Despite this, disease outcomes were similar or better than in non-vaccinated patients, although the incidence of AKI was similar [29].

Some limitations should be acknowledged. The retrospective nature of the study prevents the analysis of causality and being unicentric, extrapolation to other healthcare settings may be limited. Moreover, the health burden of different wave patterns differed among countries depending on health system overload, local isolation measures, virus variants, specific treatment protocols and, most recently, vaccine rollout, among other factors [30]. The 1st and 3rd waves in Madrid had a similar impact to the 1st and 2nd waves in Japan and other countries in terms of timing and relationship to vaccine programs [31]. This should be considered when extrapolating the present findings to other scenarios. The external validity of this study depends on several factors such as national/local epidemiology, health system, hospital admission policies and type of hospital, among others. Our hospital can be considered representative of a tertiary referral hospital in our country, but it probably could not be extrapolated to a low-complexity hospital. However, the key point is that renal involvement and deleterious effect on survival are maintained in COVID-19 patients despite the improvement in management and treatment in successive waves. Additionally, CA-AKI may have been overestimated for patients that had undiagnosed preexistent CKD because there no serum creatinine values available in the prior 3 years. However, it is a comprehensive and well-defined study with systematic inclusion and careful data curation and analysis focused on previously unexplored populations, i.e. patients with HA-AKI that have no preexistent CKD.

In conclusion, CKD and AKI were common in pre-vaccination waves among hospitalized COVID-19 patients and were independent risk factors for death despite improvements in treatment. HA-AKI was the most relevant independent risk factor for in-hospital mortality, even when AKI was mild to moderate in severity. However, awareness of AKI remained low among treating physicians. Enhanced awareness, and improved detection, diagnostic and nephroprotection protocols should be implemented in future waves of COVID-19 and likely in future pandemics.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

J.P. and P.L.-S. contributed conceptualization and design; J.P., L.M.-R., M.M. and P.L.-S. carried out data acquisition; J.P., L.M.-R., M.M. and A.O. carried out data analysis/interpretation; P.L.-S., J.P. performed statistical analysis; J.P. and A.O. provided supervision or mentorship. All authors have added relevant content during manuscript drafting or revision, accept personal accountability for the author's own contributions, and agree to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

ETHICS APPROVAL

The ethics committee of the Hospital Universitario Puerta approved the project with reference IRB number 2020/32.

DATA AVAILABILITY STATEMENT

Data will be available after a formal request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

A.O. has received grants from Sanofi and consultancy or speaker fees or travel support from Advicciene, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Kyowa Kirin, Alexion, Idorsia, Chiesi, Otsuka, Novo-Nordisk and Vifor Fresenius Medical Care Renal Pharma, and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes. A.O. is the former Editor-in-Chief of *CKJ*. The rest of the authors declare no conflict of interest in the scope of this study. These results have not been presented previously in whole or part.

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