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Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak

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ABSTRACT

Background. Novel coronavirus disease 2019 (COVID-19) emerged in Wuhan and rapidly spread, affecting >10 million cases worldwide. Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and primarily manifesting as an acute respiratory failure with interstitial and alveolar pneumonia, it can also affect multiple organs. Kidney involvement was underestimated in early reports and its role remains controversial. The aim of this study was to analyse the role of kidney damage in COVID-19 outcome.

Methods. This is a prospective cohort study of 1603 consecutive patients admitted in a University Reference Hospital in the heart of the European outbreak.

Results. Median age was 64 years, 40.4% were female, 15.2% presented diabetes mellitus, 35.7% hypertension and 20.3% obesity. On admission, the prevalence of elevated serum creatinine (sCr), proteinuria, leucocyturia and haematuria were 21.0, 37.8, 31.8 and 45.6%, respectively. In total, 43.5% of those with an elevated sCr had previous chronic kidney disease (CKD) and 11.4% of those with normal sCr developed an in-hospital acute kidney injury (AKI); 17

patients needed acute haemodialysis; and 197 patients died during hospitalization. Cox proportional hazard regression confirmed that elevated baseline sCr [hazard ratio (95% confidence interval) 2.40 (1.79–3.22)], previous CKD [1.59 (1.06–2.37)], haematuria [1 + 1.68 (0.92–3.06), 2–3 + 2.69 (1.49–4.87)] and in-hospital AKI [1.50 (0.92–2.44)] were independent risk factors for in-hospital death after adjusting for age, sex and comorbidity.

Conclusion. The prevalence of acute and chronic kidney disease on admission and in-hospital AKI is higher than previously reported in Wuhan, and is associated with high in-hospital mortality. We should increase our awareness towards kidney involvement and design specific strategies for management of COVID-19 in these patients.

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

INTRODUCTION

Clusters of pneumonia cases occurring in the city of Wuhan, Hubei Province, China in December 2019 led to the eventual

KEY LEARNING POINTS

What is already known about this subject?

- coronavirus disease 2019 (COVID-19) has a broad clinical presentation. Viral infection of kidney has been histologically demonstrated, though symptomatic kidney disease varies significantly between series and acute kidney injury (AKI) incidence increases from 0.5 to 18%; and
- COVID-19 severity seems to correlate with previous conditions such as hypertension and diabetes mellitus. The role of chronic kidney disease (CKD) in this setting is unknown.

What this study adds?

- in COVID-19 hospitalized patients, we have demonstrated that increase in serum creatinine on arrival is a risk factor for poor outcome, independently of the chronology of this feature: whether previous kidney disease or acute damage; and
- development of AKI during the hospital stay was also associated with poor outcome.

What impact this may have on practice or policy?

- according to these results, previous CKD, acute kidney damage on arrival to the hospital or AKI during admission should be recognized as risk factors for severe COVID-19 and should be used to correctly categorize COVID-19 patients.

identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1, 2]. This is the third epidemic caused by a coronavirus in the 21st century, after SARS and Middle East respiratory syndrome (MERS), and those agents may share some mechanism of damage. The disease has spread rapidly from Wuhan to other regions in China and other countries. On 11 March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be a global pandemic and by 24 April, 2.97 millions of patients have been diagnosed of COVID-19 and more than 200 000 have died all over the world [3–6].

The early data from China suggested that the severity of the disease varies among individuals and the prevalence of acute kidney injury (AKI) among patients with COVID-19 is low. For example, in a Chinese cohort of 1099 patients with COVID-19, 93.6% were hospitalized, 91.1% had pneumonia, 5.3% were admitted to intensive care units (ICUs), 3.4% had acute respiratory distress syndrome and only 0.5% developed AKI [2]. However, recent reports from a high complexity reference hospital in Wuhan analysed 702 patients diagnosed with COVID-19 and found that 18% had increased serum creatinine (sCr), 49.3% proteinuria or urine alterations on arrival at the hospital, and 5.1% developed AKI. They also found that kidney

damage was associated with higher in-hospital mortality [7]. This huge variability in kidney damage associated with COVID-19 among different reports may depend on different patient profiles (age, comorbidity and race), health strategy on diagnostic test, selection criteria for hospital admission or home treatment, and the overload of each health system.

Several specific potential mechanisms of kidney involvement during COVID-19 disease have been identified to date, such as virus tropism by angiotensin-converting enzyme 2 (ACE2) receptor in renal cells, cytokine damage and organ crosstalk, but also common causes of acute kidney damage such as drug toxicity, pre-renal factors or other causes of AKI [8]. In this setting, rhabdomyolysis, metabolic acidosis and hyperkalaemia are not rare in severe COVID-19 and are almost always associated with haemodynamic instability. Superimposed infections are also frequent in patients with long hospitalizations, and septic AKI may occur in such patients and act synergistically with other mechanisms of kidney damage. Therefore, renal involvement during COVID-19 disease is multifactorial and may have a broad clinical spectrum, and mild kidney injury can easily go unnoticed. On the other hand, kidney disease may constitute to be a risk factor for SARS-CoV-2 infection [5].

The aim of this study is to define globally the burden of kidney injury in the COVID-19 from a double perspective; namely the incidence of COVID-19-associated AKI and its characteristics and the relevance of acute or chronic kidney disease in the outcome of hospitalized COVID-19 patients in the European scenario of the pandemic.

MATERIALS AND METHODS

Participants

All patients with a confirmed COVID-19 infection admitted to Puerta de Hierro University Hospital from 25 February to 24 April were included. Diagnosis of COVID-19 disease was based on a positive lab detection of SARS-CoV-2 or by clinical and tomography scan criteria, according to the WHO's interim guidelines [9]. Laboratory confirmed cases were identified with nucleic acid detection of SARS-CoV-2 from throat swab samples using reverse transcription-polymerase chain reaction as described by others [10]. Only adult patients with final outcome (in-hospital death or discharged) were included. Previous haemopoietic and solid organ transplantation including renal transplant recipients were included but end-stage renal disease patients on chronic dialysis were excluded.

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

Data sources and definitions

Clinicians recorded clinical data and vital signs on electronic medical record (EMR) during daily work. Laboratory data and drug prescriptions were obtained from EMR. Information included demographic characteristics, comorbidity, disease severity and vital signs on arrival of all laboratory values and treatments during the hospitalization and final outcomes. Comorbidities comprised hypertension or cardiovascular

disease, diabetes mellitus, obesity [defined as body mass index (BMI) ≥ 30 kg/m²], previous immunosuppressive treatment and chronic kidney disease (CKD) defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m². A common protocol for hospital admission, evaluation of severity, laboratory sampling and drug prescriptions was implemented in-hospital by 28 February. The severity of pneumonia was defined on arrival by CURB65 index [11]. The in-hospital treatment for COVID-19 was categorized as hydroxychloroquine (HCQ) and its analogues, antiretroviral agents (mainly lopinavir–ritonavir) and immunomodulators such as prednisone or humanized interleukin-6 (IL)-6 antibody (tocilizumab). Every patient gave oral consent for the off-label use of these drugs in COVID-19. Other commonly used drugs were prescribed to control some of the disease 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 [12] were selected: 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, creatinine kinase, lactate dehydrogenase (LDH)]. We also obtained IL-6 if tocilizumab prescription was considered (443 cases). We have also included the peak and nadir values during hospital stay of all kidney function biomarkers. Every patient has a sCr value on admission and another value within 48 h with a mean of 3.6 during the first 5 days in hospital.

Our laboratory reference values were used as normal values. Kidney involvement was estimated by sCr (normal upper values 1.1 mg/dL for men and 0.9 mg/dL for women) and urea (normal upper values < 50 mg/dL), and also by proteinuria, haematuria and leucocyturia. eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [13].

Previous CKD was obtained as a comorbidity from records on EMR and confirmed when available using laboratory values from 36 months' previous to hospital admission in the central laboratory system. 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 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [14]. For the main analysis, patients were classified as normal or elevated sCr on arrival, and for secondary analysis we consider also previous CKD, AKI on admission or AKI during hospital stay for those with normal sCr on arrival (Figure 1). A trained team of nephrologists and statisticians reviewed all the data sets.

Statistical analysis

Continuous variables were expressed as the mean [standard deviation (SD)] or median with interquartile range and categorical variables were presented as percentages. 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-

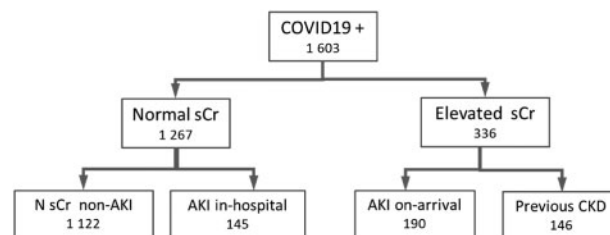


FIGURE 1: Patient flow chart. Normal values for sCr adjusted by sex. CKD defined as eGFR by CKD-EPI < 60 mL/min/1.73 m². AKI definition according to KDIGO.

hospital death were examined using Cox proportional hazard regression analysis. No violations of the Cox proportional hazards assumptions were detected.

The multivariate analysis includes kidney disease indicators adjusted by age, sex and comorbidities in a Cox proportional hazard model. Severity index CURB65 was not included in the models because it is a composite score that includes renal function [as blood urea nitrogen (BUN)] and age among other factors. Patients with missing values in proteinuria and haematuria were excluded when the association with in-hospital death was assessed. In order to dissect the impact of different status in terms of kidney function, we also have prepared four multivariate submodels by groups: previous CKD versus AKI on arrival; AKI on arrival versus normal sCr; in-hospital AKI versus normal sCr without AKI; and AKI anytime versus normal sCr without AKI (Figure 1). Statistical analyses were performed by Stata software (v14 StataCorp., College Station, TX, USA) with statistical significance set at two-tailed $P < 0.05$.

RESULTS

Patients characteristics and laboratory values

At the time of closing the database, 24 April 2020, 1821 patients have been admitted to our hospital because of COVID-19 disease. Two hundred and two remained in hospital wards, 51 of them in the critical care unit, and 16 were in chronic dialysis programmes. Therefore, 1603 patients with final hospital outcome were included in the analysis. Median age was 64 years (25.8% were > 75 years) and 59.6% of patients were male. The main comorbid conditions on admission were hypertension (35.7%), obesity (20.3%), diabetes (15.2%) and previous immunosuppressive treatment (2.9%). In our overall study population, 49.5% have at least one comorbidity. Most patients developed fever during hospitalization and 28.6% had it on arrival. Other clinical characteristics are summarized in Table 1.

A high proportion of patients showed increase of inflammatory markers (increased high-sensitivity C-reactive protein and ferritin), altered coagulation (elevated D-dimer and prolonged thrombin times) and 10.3% of them presented leucopenia. Most relevant laboratory values are shown in Table 2 for all patients and for those with normal or elevated sCr on arrival and for CKD and non-CKD patients.

Final outcome was in-hospital death in 12.3% of the patients. Those that had completed treatment course and were in good

Table 1. Demography, vital signs, disease severity, comorbidity and renal disease by sCr values on arrival and by previous CKD

Clinical description	All	Normal Cr	Elevated Cr ^a	P-value ^b	Non-CKD	CKD	P-value ^b
Patients, n (%)	1603	1267 (79)	336 (21)		1457 (90.9)	146 (9.1)	
Age (years)	64.2 (15.6)	61.4 (15.2)	74.5 (12.4)	<0.001	62.8 (15.3)	77.5 (11.4)	<0.001
Male (%)	59.6	57.8	66.4	0.004	58.9	65.8	0.1
Length of stay (days)	7.74 (5.8)	7.48 (5.6)	8.70 (6.4)	0.002	7.7 (5.7)	8.1 (6.4)	0.5
BMI (kg/m ²)	27.2 (4.5)	27.2 (4.6)	27.3 (4.0)	0.9	27.2	26.8	0.5
SBP (mmHg)	138.4 (24.5)	139.7 (24.0)	133.6 (25.9)	0.001	138.8 (24.0)	134.1 (26.9)	0.03
DBP (mmHg)	79.2 (15.4)	80.9 (14.7)	72.8 (16.2)	<0.001	80.1 (14.9)	71.1 (16.2)	<0.001
Hypotensive (MBP <80 mmHg)	12.3	11.9	13.5	0.4	11.5	28.8	<0.001
Fever anytime (%)	66.5	68.2	66.8	0.5	68.0	66.5	0.5
SpO ₂ ≤92% (%) ^c	82.7	84.3	76.6	0.001	83.0	80.0	0.4
Severity CURB65: low/high (%)	76.3/23.7	86.5/13.5	31.1/68.9	<0.001	18.2	77.2	<0.001
Diabetes (%)	15.2	10.5	33.0	<0.001	12.6	40.7	<0.001
Hypertension or CV disease (%)	35.7	30.5	55.3	<0.001	32.7	64.8	<0.001
Immunosuppression (%)	2.9	1.6	7.8	<0.001	1.7	15.2	<0.001
Obesity (%)	20.3	20	21.4	0.76	19.8	24.1	0.5
Pre-existing CKD (%)							
CKD Stage 3 ^d	5.4	0.6	23.8	<0.001	0	54.8	<0.001
CKD Stage 4 ^d	2.4	0	11.3		0	26.1	
CKD Stage 5 ^d	1.7	0	8.3		0	19.1	

Data shown as mean (SD) or percentage (%).

^asCr >1.1 g/dL in males and >0.9 mg/dL in females.

^bt-test or chi-squared test or Wilcoxon rank sum test as appropriate.

^cOxygen saturation.

^dCKD as eGFR <60 mL/min/1.73 m². eGFR was calculated with the CKD-EPI formula.

SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure.

Table 2. First laboratory values of patients with COVID-19 disease on admission

	All	Normal Cr 1267	Elevated Cr ^a (N = 336)	p value ^b	Non-CKD (N = 1457)	CKD (N = 146)	P-value ^b
sCr (mg/dL)	1.0 (0.9)	0.7 (0.2)	1.9 (1.7)	<0.001	0.8 (0.6)	2.4 (1.9)	<0.001
Peak sCr (mg/dL)	1.2 (1.2)	0.9 (0.4)	2.3 (2.1)	<0.001	1.0 (0.7)	3.0 (2.4)	<0.001
CKD-EPI ^c (mL/min/1.73 m ²)	86.1 (28.3)	97.6 (17.1)	42.8 (18.5)	<0.001	91.4 (23.5)	33.9 (17.2)	<0.001
Urea (mg/dL)	45.14 (37.7)	33.5 (14.0)	89.2 (60.1)	<0.001	39.4 (28.0)	102.9 (64.8)	<0.001
Serum potassium (mEq/L)	4.3 (0.6)	4.3(0.5)	4.5 (0.7)	<0.001	4.3 (0.5)	4.6 (0.7)	<0.001
Urinary proteins (mg/dL)	0.8 (3.7)	0.5 (0.8)	1.3 (6.0)	<0.001	0.7 (4.0)	1.1 (1.9)	0.4
Leucocyturia: Neg/ 1+/2 + 3+; (%)	68.2/12.0/19.8	69.5/11.0/19.5	66.1/13.6/20.3	0.26	68.9/11.9/19.2	65.5/12.1/22.4	0.09
Haematuria: Neg/ 1+/2 + 3+; (%)	54.4/26.4/19.2	61.5 /25.5/13.0	42.3/28.0/29.7	<0.001	55.8/27.3/16.9	48.3/22.4/29.3	0.19
Proteinuria >0.3 g/L (%)	37.8	32.0	47.5	0.005	35.9	46.6	0.13
D-dimer >1.7 mg/dL (%)	36.7	31.7	55.6	<0.001	34.7	56.5	<0.001
Fibrinogen (mg/dL)	601.7 (156.2)	596.8 (152.2)	316.9 (169.1)	0.02	60.1.9 (155.4)	597.2 (163.4)	0.7
Activated partial thromboplastin time (s)	39.2 (15.7)	37.9 (11.5)	43.8 (25.5)	<0.001	38.5 (14.5)	46.1 (23.2)	<0.001
Haemoglobin (g/L)	14.0 (1.9)	14.0 (1.7)	13.2 (2.4)	<0.01	14.1 (1.8)	12.4 (2.5)	<0.001
Leucocytes × 1000/mm ³	7.9 (4.50)	7.6 (3.93)	9.1 (6.0)	<0.001	7.8 (3.9)	9.2 (7.6)	0.02
Lymphocytes × 1000/mm ³	1.20 (1.80)	1.20 (1.20)	1.18(3.17)	0.8	1.18 (1.15)	1.39 (0.61)	0.6
Platelets × 1000/mm ³	219.6 (96.5)	223.6 (96.0)	204.4 (96.8)	0.001	221.8(96.2)	194.5 (96.2)	0.001
Albumin (mg/dL)	3.7 (0.4)	3.8(0.4)	3.5 (0.4)	<0.001	3.7 (0.4)	3.5 (0.4)	<0.001
Procalcitonin (ng/mL)	0.95 (5.91)	0.34 (1.42)	3.0 (11.9)	<0.001	0.7 (5.0)	2.5(10.6)	0.4
CRP (mg/L)	97.4 (74.8)	90.7 (72.4)	122.6 (78.5)	<0.001	95.6 (73.9)	113.7 (79.9)	0.009
Ferritin (ng/mL)	895.0 (999.2)	839.9 (960.1)	1096.8 (1112.5)	<0.001	872.1 (964.2)	1132.5 (1286.5)	0.04
IL-6 (pg/mL)	78.6 (267.5)	71.2 (263.6)	102.6 (279.8)	0.3	75.6 (264.6)	98.8 (288.2)	0.6
Total bilirubin (mg/dL)	0.64 (0.58)	0.63 (0.57)	0.70 (0.63)	0.93	0.64 (0.56)	0.71 (0.78)	0.3
LDH (U/L)	329.9 (187.6)	322.8 (190.3)	356.7 (174.5)	0.004	329.6 (190.8)	335.5 (155.1)	0.7
Lactate (mmol/L)	1.63 (0.88)	1.50 (0.78)	1.97 (1.03)	<0.001	1.59 (0.86)	1.88 (1.02)	0.02
Troponin (g/L)	0.28 (6.0)	0.27 (6.7)	0.30 (2.0)	<0.001	0.27 (6.3)	0.37 (2.3)	0.7
NT-proBNP (pg/ml)	2791.2 (11005.4)	847.9 (2317.7)	7835.6 (19684.4)	<0.001	1244.4 (3273.2)	13 446.4 (27 542.4)	<0.001
Creatinine kinase (mg/dL)	192.8 (814.0)	142.2 (211.6)	391.0 (1743.2)	<0.001	194.8 (849.1)	174.7 (240.8)	0.5
SpO ₂ (%) ^d	89.2 (14.1)	89.6 (13.2)	87.6 (16.8)	0.05	89.3 (13.8)	87.6 (17.1)	0.3

Data shown as mean (SD) or percentage (%).

^asCr >1.1 g/dL in males and >0.9 mg/dL in females.

^bt-test or chi-squared test or Wilcoxon rank sum test as appropriate.

^ceGFR was calculated with the CKD-EPI formula.

^dOxygen saturation.

CRP, C-reactive protein.

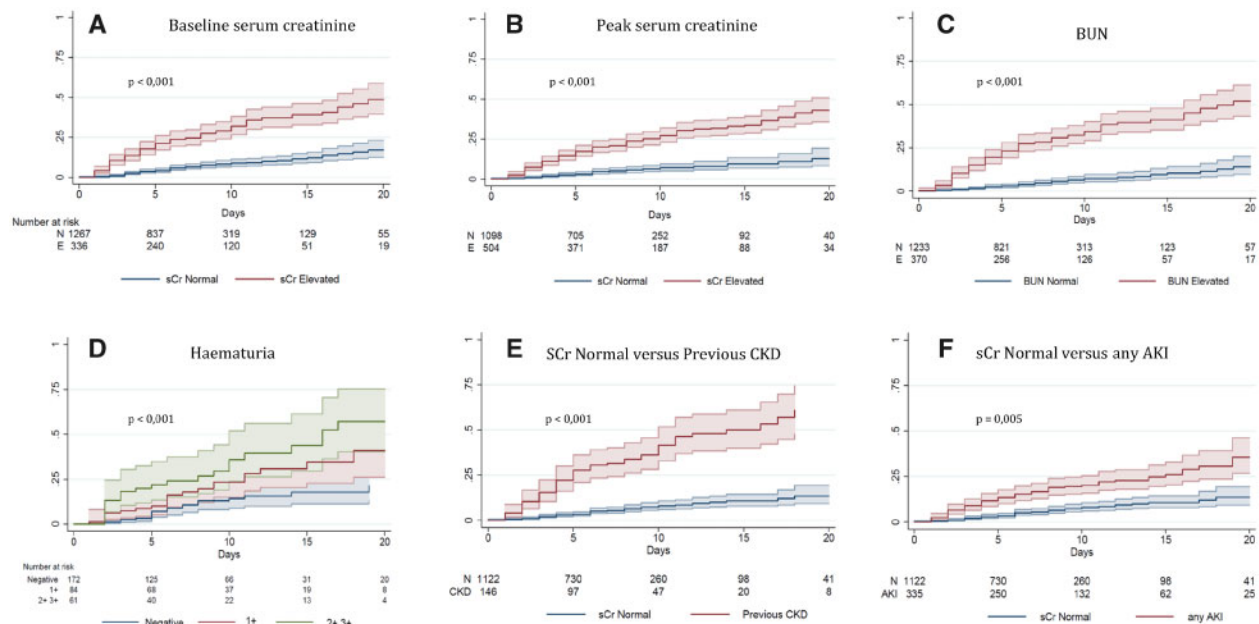


FIGURE 2: Kaplan–Meier analysis of cumulative incidence for in-hospital death of patients with COVID-19 disease. Criteria by: (A) baseline sCr, (B) peak sCr, (C) baseline BUN, (D) haematuria (0, 1+, 2+ to 3+), (E) previous CKD versus normal sCr, (F) AKI anytime versus sCr normal.

clinical condition were discharged and follow-up was performed by a general practitioner (72.3%), and those with severe disease were discharged and programmed to a close follow-up by hospital staff (15.4%).

Kidney disease markers

Some patients showed altered kidney function parameters on admission and others developed them during hospital stay. On admission, 21.0% presented increased sCr, and 43.5% of them have been previously diagnosed of CKD Stage 3 or higher. Some patients who presented normal sCr developed AKI during hospitalization (11.4%) and the rest maintained normal values throughout the stay. For those with AKI, peak sCr was 1.1 (0.7–1.4) mg/dL. Only 17 (5.1%) patients needed acute dialysis [11 started with continuous venovenous haemofiltration and 6 with conventional haemodialysis (HD)] and only one remained on HD by the time of discharge. Many patients developed urine abnormalities such as proteinuria (37.8%), haematuria (45.6%) or leucocyturia (31.8%).

Patients with an elevated sCr value were older, more comorbid, showed more frequently proteinuria and/or urine abnormalities and had higher values on inflammatory, coagulation and cardiac or hepatic function markers as summarized in Table 2. However, we did not find significant differences in AST, ALT, lymphocytes and other values previously described as potential risk markers.

Association of kidney involvement with in-hospital death

The raw in-hospital mortality rate was higher in patients with increased sCr (32.4%), those with previous CKD (41.1%) and for those developing AKI during hospital admission (15.9%) compared with those with normal sCr (5.8%). Kaplan–

Meier analysis revealed a higher in-hospital death for patients with elevated sCr on admission, for those with haematuria and for those developing AKI, but not for patients with proteinuria or leucocyturia (Figure 2). Univariate Cox regression identified that older age and diabetes, but not other comorbidities, were associated with in-hospital death.

Several kidney disease markers such as high sCr on admission, haematuria, previous CKD or AKI on arrival or during hospital stay were associated with higher in-hospital death in the univariate Cox regression analysis (Table 3). In the multivariate analysis, we selected four models including all patients for basal sCr, haematuria, peak sCr or pre-existing CKD adjusted by age, sex and any comorbidity. We also have prepared four multivariate submodels by groups: previous CKD versus AKI on arrival, AKI on arrival versus normal sCr, in-hospital AKI versus normal sCr without AKI, and AKI anytime versus normal sCr without AKI (Table 4).

Drug treatment

Supplementary data, Table 1 summarizes the medication used in all patients and divided by a group of kidney function status (normal kidney function, previous CKD or AKI) or according to sCr on admission. Treatment included antiviral agents (58.8%)—mainly lopinavir/ritonavir; HCQ or its analogues (90%); immunomodulators such as prednisone (57.3%) or tocilizumab (14.9%); low-molecular-weight heparin (LMWH 90.6%) prophylaxis and finally antibiotics (79.0%) or antifungal agent (1.7%) for superimposed infections. Patients with elevated sCr on arrival received less antivirals (45.8% versus 62.2%, $P = 0.001$) but the same HCQ (90% versus 90.6%) as those with normal sCr. CKD patients were treated less frequently with lopinavir/ritonavir ($P < 0.001$) and α/β interferon ($P < 0.05$), receiving steroidal treatment more frequently

Table 3. Univariate Cox regression analysis of association between kidney disease and in-hospital death in patients with COVID-19

	HR	95% CI
Age (years)	1.09	1.07–1.10
Age >60 (years)	4.28	2.07–8.89
Gender (female)	1.08	0.81–1.44
Any comorbidity	1.20	0.90–1.60
Diabetes	1.83	1.34–2.50
Hypertension/CV	1.19	0.89–1.58
Obesity	1.22	0.63–2.33
Immunosuppression	1.48	0.78–2.80
Basal elevated sCr versus normal	4.07	3.07–5.39
Previous CKD versus no CKD	4.17	3.08–5.66
Previous CKD versus AKI on arrival	1.79	1.23–2.61
AKI on arrival versus normal sCr	2.24	2.19–2.30
In-hospital AKI versus normal sCr	1.98	1.22–3.21
AKI anytime versus normal sCr	2.92	2.08–4.11
Urinary red cells (0 ref)	Ref	
1+	1.80	1.00–3.26
2+ 3+	3.01	1.69–5.38
Urinary leucocytes (0 ref)	Ref	
1+	1.26	0.65–2.47
2+	0.65	0.20–2.11
3+	1.85	0.97–3.53
D Dimer >1.7 g/mL	3.61	2.70–4.81
Activated partial thromboplastin time >35 s	1.47	1.08–2.00
Lymphopenia	2.82	2.12–3.74
High-sensitivity CRP	1.01	1.00–1.01
Ferritin >1072 (p75)	1.08	0.75–1.56
Serum potassium	1.72	1.40–2.10
LDH	1.00	1.00–1.00

($P < 0.001$). The use of immunomodulators, LMWH and antibiotics was higher in AKI patients, probably reflecting a more severe disease.

DISCUSSION

Our study is the first large prospective cohort study in Europe conducted in a tertiary hospital to evaluate the burden of kidney disease during the outbreak of SARS-CoV-2 infection. We have found that 21% of patients have had any kidney involvement on arrival and that 11.4% developed AKI during their hospital admission. We have also demonstrated that CKD and elevated sCr on arrival was strongly associated with higher risk for in-hospital death even after correction for other previously reported risk factors.

SARS-CoV-2 infection initiates by entering via the oral, nasal or conjunctiva mucosae from droplets or contaminated fomites. This virus tends to expand into the body by direct respiratory mucosae extension, although a mild viraemia is also considered [15]. Studies have shown similarities with the SARS-CoV, and both viruses share the same cell entry receptor, ACE2 [16]. ACE2 is expressed in humans mainly in type II alveolar cells of the lung, but also in small intestine, heart, liver and kidney. In autopsy samples obtained from patients infected by previous SARS-CoV, histochemical examination revealed virions, RNA and antigens in lung and other organs, including the kidney [17, 18]. This may explain the extra-pulmonary manifestations of COVID-19 and hence the kidney involvement [19, 20].

Table 4. Cox regression multivariate models for in-hospital death: main variables adjusted by age, sex and any comorbidity

Models	Variables	HR	95% CI
Model 1 ($n = 1603$)	sCr elevated (ref sCr normal)	2.40	1.79–3.22
	Age (per year)	1.08	1.07–1.10
	Gender (female)	0.85	0.63–1.15
	Any comorbidity	0.74	0.54–1.01
Submodel 1a ($n = 336$)	Previous CKD (ref AKI on arrival)	1.59	1.06–2.37
	Age (per year)	1.05	1.03–1.07
	Gender (female)	0.89	0.58–1.35
	Any comorbidity	0.62	0.39–0.96
Submodel 1b ($n = 1457$)	AKI on arrival (ref sCr normal)	1.96	1.37–2.79
	Age (per year)	1.09	1.07–1.11
	Gender (female)	0.73	0.51–1.05
	Any comorbidity	0.82	0.57–1.17
Submodel 1c ($n = 1267$)	In-hospital AKI (ref sCr normal non-AKI)	1.50	0.92–2.44
	Age (per year)	1.09	1.07–1.12
	Gender (female)	0.91	0.59–1.40
	Any comorbidity	0.72	0.46–1.12
Submodel 1d ($n = 1457$)	Any AKI (ref sCr normal non-AKI)	1.93	1.37–2.72
	Age (per year)	1.09	1.07–1.11
	Gender (female)	0.71	0.5–1.03
	Any co-morbidity	0.79	0.55–1.13
Model 2 ($n = 1603$)	Previous CKD (ref non-CKD)	1.94	1.44–2.64
	Age (per year)	1.08	1.07–1.10
	Gender (female)	0.83	0.62–1.12
	Any comorbidity	0.74	0.54–1.01
Model 3 ($n = 1603$)	Peak creatinine (ref sCr normal)	2.51	1.81–3.49
	Age (per year)	1.08	1.07–1.09
	Gender (female)	0.85	0.63–1.14
	Any comorbidity	0.72	0.53–0.99
Model 4 ($n = 1603$)	Haematuria (ref Neg)		
	1+	1.68	0.92–3.06
	2+ 3+	2.69	1.49–4.87
	Age (per year)	1.04	1.02–1.06
	Gender (female)	0.86	0.52–1.42
	Any comorbidity	1.54	0.81–2.94

HR for confusion factors are shown even non-significant.

Model 1a: only in patients with elevated sCr on admission.

Model 1b: AKI on arrival or AKI during admission.

Model 1c: only in patients with normal sCr on admission.

Model 1d: normal sCr on admission without AKI versus AKI on or during admission.

CV, Cardiovascular; sCr, serum Creatinine, aPTT, activated partial thromboplastin time; CRP, c-reactive protein; LD, Lactate dehydrogenase; n , number of patients.

Other factors such as sepsis by bacterial or fungal co-infections, drug toxicity, rhabdomyolysis, pre-renal factors associated to diarrhoea or reduced hydration in institutionalized or unattended patients may also play a crucial role [8]. Although we have found that AKI at any time increases risk, all these factors may associate different clinical profiles for in-hospital AKI and on-arrival AKI that explain a higher risk for the latter. A clinical attention focused only on the pulmonary aspects of the disease may lead to inadvertent kidney damage in the emergency and overcrowded scenario of the pandemic.

The prevalence of kidney involvement varies widely among different reports and may depend on health system facilities, level of complexity of the centre, epidemiologic strategy with viral testing (how many and for whom), local protocols, available

therapies, restrictive hospital admission policy or AKI definitions [10, 21]. An early study of 138 COVID-19 patients reported that ~4% of them developed AKI [22], while Huang *et al.* [10] found a 10% increase in sCr on admission and 7% incidence of AKI in their series of 41 COVID-19 patients. A study conducted in a tertiary hospital in Wuhan on >700 COVID-19 patients reported that 13% of them had associated evidence of kidney damage on arrival and 5.1% developed AKI during hospital stay [7]. On the other hand, a report from a different region found only 0.4% with AKI and concluded that AKI is not relevant in COVID-19 [23]. Both are good examples of how a different strategy for admission may lead to different mortality rates and kidney disease burden. Our study includes patients who were 10 years older, with more comorbidities and probably with a more severe disease than those in the reports that found minor kidney involvement [23].

A meta-analysis of >76 993 COVID-19 patients estimated the pooled prevalence of CKD comorbidity as 0.83% [95% confidence interval (CI) 0.37–1.43], and hypertension, cardiovascular disease and diabetes in people infected with SARS-CoV-2 were estimated as 16.37% (95% CI 10.15–23.65), 12.11% (4.40–22.75) and 7.87% (6.57–9.28%), respectively [24]. Patients with a previous diagnosis of CKD frequently share comorbidities that have been identified as a risk factors for poor outcome, such as older age, cardiovascular (CV) disease or diabetes mellitus, and may explain our results on multivariate analysis. Although dialysis patients have been excluded from our study, patients with a functioning kidney graft were included. In this group of patients, previous immunosuppressive treatment plus many drug interactions may play a paramount role in both kidney and patient outcomes.

We have also found remarkable urine sediment changes like proteinuria, haematuria or leucocyturia alone or in association with increase of sCr. Experimental data identify podocytes and proximal tubule cells as kidney host cells for SARS-CoV-2 and suggest that podocytes are extremely sensitive to viruses [19]. Some authors suggest that these early signs should be taken into account to detect kidney damage and to protect kidney function [25]. However, mild-to-severe haematuria, but not leucocyturia or proteinuria, was unusually associated with poor outcome. Urinary catheterization had to be used in many patients; therefore, haematuria could reflect both the need for urinary manipulation and the existence of coagulation disorders commonly seen in severe disease more often than glomerular kidney involvement. However, this fact would need to be further addressed.

To our knowledge, this is the first European study with a clinical description of the kidney involvement in the COVID-19 pandemic outbreak as compared with Chinese studies. The health policy has been completely different among countries. Wuhan's strategy was the general use of facial masks, complete home lockdown, massive test sampling and admission of all positive COVID-19 patients in first-level conventional or new-built hospitals like those reported by Wang *et al.* [23] and in specifically developed high-complexity hospitals like those referred in the report by Cheng *et al.* [7]. In our region, mild symptomatic patients were considered as a possible COVID-19 case and managed by in-house lockdown with a remote daily

medical follow-up [26]. Those patients that required medical assistance were evaluated in the emergency room and classified for hospital admission or home treatment based on clinical situation and medical support needed [27].

The specifics of our centre can also explain some of the differences found in this study. Our institution is a tertiary teaching hospital with a complete health care portfolio and high complexity that includes active programmes for haemopoietic and solid organ transplantation. It attends half a million population in Madrid, the region with the highest incidence of COVID-19 in our country. In Madrid, during this period, 58 487 persons were diagnosed with COVID-19, 31 911 were admitted to hospitals and 7351 (5468) have died [28]. During the COVID-19 outbreak, new wards had to be built and hospital structure and function were re-designed in order to cope with the coronavirus pandemic. The number of hospital beds increased from 600 to 900, 65 of them belonging to the ICU. In the first weeks of the COVID-19 pandemic outbreak, our centre had to attend a huge number of high-complexity patients. This fact may partially explain the different AKI incidence rates and outcomes when compared with the above-mentioned reports.

The mortality rate of COVID-19 patients that develop AKI is higher than the global COVID-19 mortality in our centre and as reported previously by others; this points to considering AKI as a relevant risk factor for poor outcome. Even in those reports with low AKI incidence, the risk was higher for these patients.

We have carried out a complex multivariate analysis to dissect the effects of different renal function status. Our estimations of hazard ratio (HR) using previous CKD as a comorbidity or increased sCr on arrival might be included in future risk scores from COVID-19 onset, and could be distinguished from AKI during the evolution of the disease.

We found some differences among therapeutic strategies of early reports from Wuhan and European therapy recommendations [29, 30]. In the absence of specific guidelines or solid evidence based on clinical trials, the treatment approach for COVID-19 is changing as new results are released. The standard of care for COVID-19 is for the time being based on the experimental use of different antiviral agents (mainly lopinavir and ritonavir) in the earlier phases. Recent publications have drawn attention to the possible benefit of HCQ or its analogues with or without azithromycin in the treatment of patients with SARS-CoV-2 infection, and it has been a common practice in Europe [31, 32]. Based on these results, a Phase 2b trial has been promoted using higher HCQ doses for severe cases. However, a preliminary report on the study of 88 patients suggests that this strategy should not be recommended because of its potential safety hazard, although the findings cannot be extrapolated to patients with less severity [22].

For the second phase of the disease, the cytokine storm seems to be crucial, and immunosuppression (prednisone) and use of direct immunomodulators (tocilizumab) has been advocated. In addition, the high incidence of thrombotic complications has prompted prophylaxis use of LMWH for most patients with early diagnosis of the disease [33]. Finally, antibiotic, antifungal or other antiviral agents could be indicated as treatment for superimposed infections. The analysis of the different drug strategies is outside the scope of our study, but we

have found different uses of drugs according to kidney involvement, and the tendency to avoid lopinavir/ritonavir or interferon in favour of steroidal treatment could have affected the outcome of CKD patients.

Our study presents some limitations previously highlighted, and our results may not be the same as in other hospitals or regions with different patient profiles or organizational features. Although we have tried to collect data on many confounders and laboratories, other unidentified risk factors may play a significant role in our results. However, our strength is the reliability of the data and the inclusion of a huge cohort without exclusions.

We conclude that the relevance of kidney injury in COVID-19 is higher in our Spanish study than in the early reports from Wuhan: AKI is more prevalent in our series, and both acute and chronic kidney disease were significantly associated with poor outcome, and this effect persisted after adjusting by covariates. The characteristics of hospitalized patients in this series, among other factors, may contribute to this difference; however, genetic or environmental factors cannot be ruled out. Long-term outcomes of kidney damage in this setting, the effect of different therapeutic approaches on kidney outcomes and specific mechanisms of COVID-19-induced kidney injury should be analysed in the future.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt](http://ndt.oxfordjournals.org/) online.

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AUTHORS' CONTRIBUTIONS

J.P. and P.L.-S. have designed study and performed statistical analysis; J.P., M.M., P.L.-S. and M.d.V. have drafted the document. All authors have participated in data collection and interpretation. Besides, all authors have reviewed and approved final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in the scope of this study. The results presented in this paper has not been presented previously in whole or part.

(See related article by Meijers and Hilbrands. The clinical characteristics of coronavirus-associated nephropathy. *Nephrol Dial Transplant* 2020; 35: 1279–1281)

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Recurrent acute kidney injury: predictors and impact in a large population-based cohort

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ABSTRACT

Background. This study examined the impact of recurrent episodes of acute kidney injury (AKI) on patient outcomes.

Methods. The Welsh National electronic AKI reporting system was used to identify all cases of AKI in patients ≥ 18 years of age between April 2015 and September 2018. Patients were grouped according to the number of AKI episodes they experienced with each patient's first episode described as their index episode. We compared the demography and patient outcomes of those patients with a single AKI episode with those patients with multiple AKI episodes. Analysis included 153 776 AKI episodes in 111 528 patients.

Results. Of those who experienced AKI and survived their index episode, 29.3% experienced a second episode, 9.9% a third episode and 4.0% experienced fourth or more episodes. Thirty-day mortality for those patients with multiple episodes of AKI was significantly higher than for those patients with a single episode (31.3% versus 24.9%, $P < 0.001$). Following a single

episode, recovery to baseline renal function at 30 days was achieved in 83.6% of patients and was significantly higher than for patients who had repeated episodes (77.8%, $P < 0.001$). For surviving patients, non-recovery of renal function following any AKI episode was significantly associated with a higher probability of a further AKI episode (33.4% versus 41.0%, $P < 0.001$). Furthermore, with each episode of AKI the likelihood of a subsequent episode also increased (31.0% versus 43.2% versus 51.2% versus 51.7% following a first, second, third and fourth episode, $P < 0.001$ for all comparisons).

Conclusions. The results of this study provide an important contribution to the debate regarding the need for risk stratification for recurrent AKI. The data suggest that such a tool would be useful given the poor patient and renal outcomes associated with recurrent AKI episodes as highlighted by this study.

Keywords: acute kidney injury, CKD, CKD-EPI equation, epidemiology, survival analysis