





ORIGINAL ARTICLE

Evolving spectrum but persistent high mortality of COVID-19 among patients on kidney replacement therapy in the vaccine era: the Spanish COVID-19 KRT Registry

Borja Quiroga ^{1,*}, Alberto Ortiz ^{2,*}, Carlos Jesús Cabezas-Reina³,
María Carmen Ruiz Fuentes⁴, Verónica López Jiménez⁵,
Sofía Zárraga Larrondo⁶, Néstor Toapanta ⁷, María Molina Gómez⁸,
Patricia de Sequera ⁹ and Emilio Sánchez-Álvarez¹⁰; the Spanish COVID-19
KRT Registry collaborative group

¹IIS-La Princesa, Nephrology Department, Hospital de la Princesa, Madrid, Spain, ²IIS-Fundación Jimenez Diaz, School of Medicine, Universidad Autónoma de Madrid, Fundación Renal Iñigo Alvarez de Toledo-IRSIN, REDinREN, Instituto de Investigación Carlos III, Madrid, Spain, ³Nephrology Department, Hospital Universitario de Toledo, Toledo, Spain, ⁴Nephrology Department, Hospital Virgen de las Nieves, Granada, Spain, ⁵Nephrology Department, Hospital Regional Universitario de Málaga, Universidad de Málaga, Instituto de Investigación Biomédica de Málaga, RICORS2040 (RD21/0005/0012), Malaga, Spain, ⁶Nephrology Department, Hospital Universitario de Cruces, Bizkaia, Spain, ⁷Nephrology Department, Vall d'Hebrón University Hospital, 08035 Barcelona, Spain, ⁸Nephrology Department, University Hospital Germans Trias i Pujol (HUGTiP) & REMAR-IGTP Group, Germans Trias i Pujol Research Institute (IGTP), Can Ruti Campus, Badalona Barcelona, Spain, ⁹Nephrology Department, Hospital Universitario Infanta Leonor – Universidad Complutense de Madrid, Madrid, Spain and ¹⁰Nephrology Department, Hospital Universitario de Cabueñes, Gijón, Spain

*These authors contributed equally to this work.

Correspondence to: Patricia de Sequera; E-mail: psequerao@gmail.com; Emilio Sánchez-Álvarez; E-mail: jesastur@hotmail.com

ABSTRACT

Background. Kidney replacement therapy (KRT) conferred a high risk for coronavirus disease 2019 (COVID-19) related mortality early in the pandemic. We evaluate the presentation, treatment and outcomes of COVID-19 in patients on KRT over time during the pandemic.

Methods. This registry-based study involved 6080 dialysis and kidney transplant (KT) patients with COVID-19, representing roughly 10% of total Spanish KRT patients. Epidemiology, comorbidity, infection, vaccine status and treatment data were recorded, and predictors of hospital admission, intensive care unit (ICU) admission and mortality were evaluated.

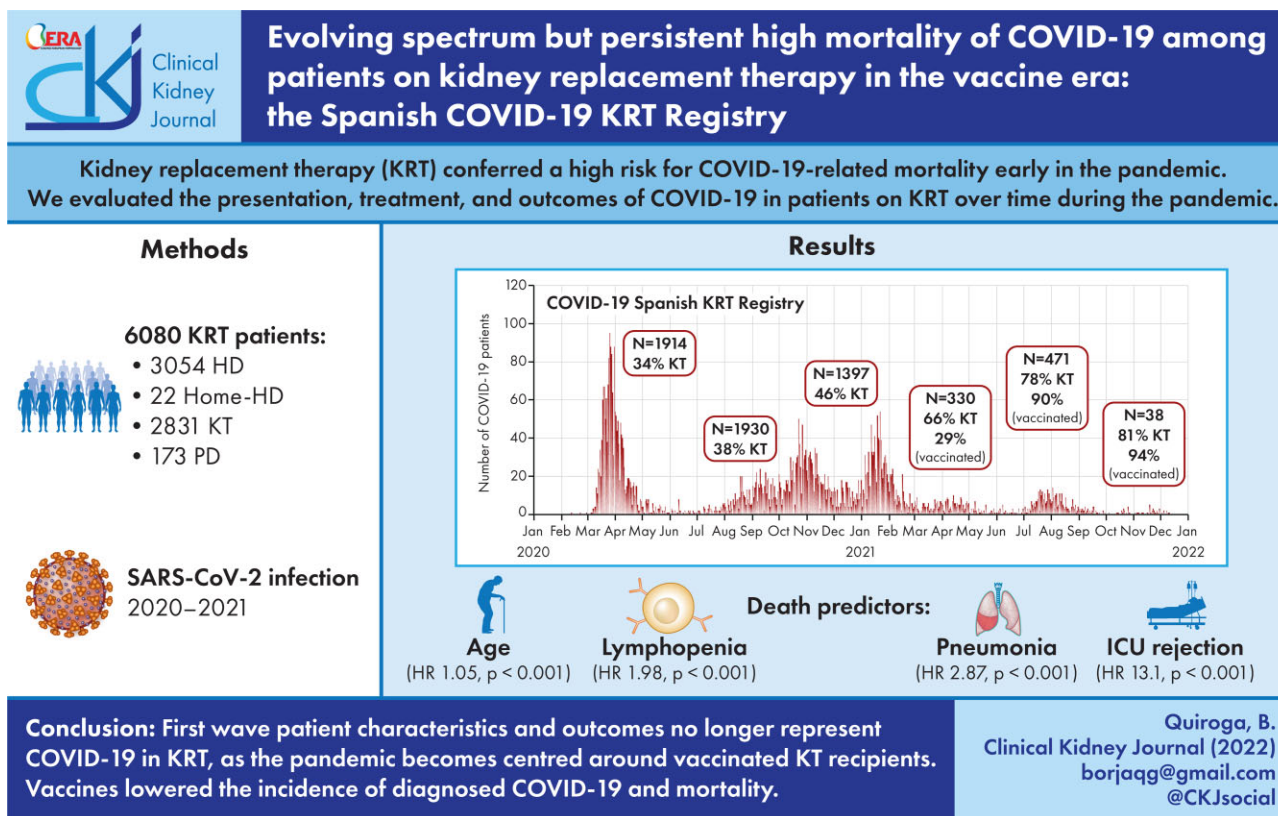
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Results. Vaccine introduction decreased the number of COVID-19 cases from 1747 to 280 per wave. Of 3856 (64%) COVID-19 KRT patients admitted to the hospital, 1481/3856 (38%) were admitted during the first of six waves. Independent predictors for admission included KT and the first wave. During follow-up, 1207 patients (21%) died, 500/1207 (41%) during the first wave. Among vaccinated patients, mortality was 19%, mostly affecting KT recipients. Overall, independent predictors for mortality were older age, disease severity (lymphopaenia, pneumonia) and ICU rejection. Among patient factors, older age, male sex, diabetes, KT and no angiotensin receptor blockers (ARB) were independent predictors of death. In KT recipients, individual immunosuppressants were independent predictors of death. Over time, patient characteristics evolved and in later pandemic waves, COVID-19 was mainly diagnosed in vaccinated KT recipients; in the few unvaccinated dialysis patients, ICU admissions increased and mortality decreased (28% for the first wave and 16–22% thereafter).

Conclusions. The clinical presentation and outcomes of COVID-19 during the first wave no longer represent COVID-19 in KRT patients, as the pandemic has become centred around vaccinated KT recipients. Vaccines lowered the incidence of diagnosed COVID-19 and mortality. However, mortality remains high despite increased access to ICU care.

GRAPHICAL ABSTRACT



Keywords: COVID-19, dialysis, kidney transplant, mortality, SARS-CoV-2

INTRODUCTION

Patients with chronic kidney disease (CKD) and, specifically, those needing kidney replacement therapy (KRT) were among those having the highest mortality during the first wave of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, a time when healthcare systems were frequently overwhelmed, limiting access to intensive care units (ICU), empirical therapy was later found to be ineffective and vaccination was not available [1–3]. However, dynamic factors such as new virus variants, decreased saturation of healthcare systems, approval of effective treatments and more importantly, SARS-

CoV-2 vaccines may have modified the nature and outcomes of coronavirus disease 2019 (COVID-19) in patients on KRT [4].

Specific characteristics of KRT patients may have modified SARS-CoV-2 exposure and outcomes differentially from the general population over time through the pandemic [5]. On one hand, KRT patients present multiple comorbidities and poly-medication that may increase fragility and haemodialysis (HD) patients have limited ability to shield due to their need to access healthcare facilities thrice weekly [6, 7]. On the other hand, KRT patients have been excluded from the prescription of certain drugs and even from mechanical ventilation or ICU admission because of their worse prognosis, especially when

healthcare systems were overwhelmed [8]. Finally, the response of kidney transplant recipients (KT recipients) to vaccines may be suboptimal, at least from the point of view of antibody development [9]. Only an analysis of presentation and outcomes of COVID-19 in KRT patients over the successive pandemic waves may identify persistent risk factors for adverse outcomes as well as characterizing the current prognosis of patients with CKD on KRT.

The aim of the present study was to evaluate the dynamic presentation features and outcomes across the six waves of the SARS-CoV-2 pandemic in Spain in a registry-based population of patients on KRT. As Spain was one of the earliest and hardest-hit countries and currently is one of the countries with the highest uptake of vaccines (80% of the total population on 29 December 2021), changes over time in Spain may be of special interest to understand the interaction between SARS-CoV-2 and healthcare measures.

MATERIALS AND METHODS

The Spanish COVID-19 KRT Registry is an initiative of the Spanish Society of Nephrology open to all nephrology and dialysis centres in Spain. It was set up on 18 March 2020 with a prospective design. It includes all patients treated with in-centre HD, home HD (HHD), peritoneal dialysis (PD) or kidney transplant recipients (KT recipients) that have developed a confirmed SARS-Cov-2 infection. Diagnosis of COVID-19 was based on the positivity of one of the following tests: reverse transcription-polymerase chain reaction (RT-PCR), rapid antigen tests or SARS-CoV-2 anti-spike antibodies before vaccination.

This analysis included the full cohort until 12 December 2021. During follow-up, local coordinators were asked to immediately report cases from their centres through a centralized web page (www.senefro.org) only accessible to registered users. Until now, the Spanish Public Health Institute has defined six pandemic waves [10], according to the following dates: first wave from 31 January 2020, second wave from 1 July 2020, third wave from 1 December 2020, fourth wave from 1 March 2021, fifth wave from 1 June 2021 and sixth wave from 1 November 2021. These dates were used for the present analysis.

Variables

At baseline, epidemiological factors (sex and age), KRT (KT, HD, PD and HHD), KRT vintage and cause of CKD, concomitant treatments [angiotensin-converting-enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and non-steroidal anti-inflammatory drugs (NSAID)] and immunosuppressive drugs were recorded.

At diagnosis, symptoms, lymphopaenia (total lymphocyte count $<500/\text{mm}^3$) and pneumonia were registered. Prescribed medications for SARS-CoV-2 infection and, in KT, the need for adjustment of immunosuppressants were also collected. Invasive or non-invasive mechanical ventilation was registered.

Vaccination

In Spain, the SARS-CoV-2 vaccination started on 27 December 2020. The following four vaccines have been used: BNT162b2 (Pfizer-BioNTech®), mRNA-1273 (Moderna®), ChAdOx1-S (AstraZeneca®) or Ad26.COV.2 (Janssen®) [9]. Prescription of individual vaccines was guided by local public health authorities and mainly driven initially by vaccine availability and later by successive modifications of the age range for ChAdOx1-S.

Vaccination status was collected during the present study and considered when the full vaccination schedule was completed before SARS-CoV-2 infection. The course of the first full (i.e. two doses except for Ad26.COV.2) vaccine schedule was uneven, as decisions were taken at the regional level and not all regions assigned the same priority to patients on KRT or to the different KRT modalities. However, for KRT patients, it was generally completed in the first semester of 2021 [9]. The booster dose was generally administered to KRT patients from October to early November 2021, i.e., before the sixth wave.

Outcomes

During follow-up, the following outcomes were registered in patients infected by SARS-CoV-2: admission to hospital, intensive care unit (ICU) admission and mortality. Investigators could report that patients had been rejected for ICU admission.

Ethics

The registry was approved by the Regional Ethical Committee of Asturias.

Statistics

Data are expressed as mean (standard deviation) or median [interquartile range (IQR)] depending on the distribution of the variables, tested with the Shapiro–Wilk test. Categorical variables were compared using the Fisher test and continuous variables with t-test or Mann–Whitney, according to the variable distribution. For comparison of continuous variables from more than two groups, ANOVA or Kruskal–Wallis tests were used.

Univariate logistic regressions were performed for assessing associations between the outcomes (admission, ICU admission and mortality) and the registered variables. To identify factors associated with admission, ICU admission and mortality differentially over time, two different analyses were performed. The first analysis compared the first with subsequent waves. The rationale is that the first wave differed from other waves in several aspects: the healthcare system was overwhelmed, health authorities were advising against the widespread use of face masks, and there was use of potentially toxic ineffective drugs and a lack of awareness about the need to prevent thrombosis. The second analysis compared the first three waves with the subsequent waves. The rationale is to compare the waves before and after vaccine availability.

Multivariate regression models were adjusted for variables with $P < .1$ in univariate analyses and those considered confounders.

The statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 6080 KRT patients with SARS-CoV-2 infection were included (36% female, age 63 ± 15 years). Among them, 2832 (46%) were KT recipients, 3063 (50%) were on in-centre HD, 173 (3%) on PD and 22 (<1%) on HHD. Prior to infection, 501 (8%) patients had received a SARS-CoV-2 vaccine (Table 1). Baseline characteristics for the successive pandemic waves are shown in Table 1. SARS-CoV-2 vaccination was common among those infected in the fifth and sixth waves. Differences between KRT

Table 1. Baseline characteristics, infection related variables and outcomes in different waves

	Total (n = 6080)	First (n = 1914)	Second (n = 1930)	Third (n = 1397)	Fourth (n = 330)	Fifth (n = 471)	Sixth (n = 38)	P
Sex (male), n (%)	3901 (64)	1236 (64)	1226 (63)	901 (65)	204 (62)	312 (66)	22 (58)	.719
Age (years)	63 ± 15	67 ± 14	62 ± 15	64 ± 15	60 ± 14	58 ± 15	60 ± 15	<.001
Diabetic kidney disease, n (%)	1199 (21)	408 (25)	378 (21)	282 (21)	56 (17)	72 (16)	3 (8)	<.001
KRT, n (%):								<.001
KT	2831 (47)	648 (34)	922 (48)	644 (46)	217 (66)	369 (78)	31 (81)	
HD	3054 (50)	1198 (63)	946 (49)	703 (5)	108 (33)	93 (20)	6 (16)	
PD	173 (3)	62 (3)	52 (3)	46 (3)	5 (1)	7 (1)	1 (3)	
HHD	22 (<1)	6 (<1)	10 (<1)	4 (<1)	0 (0)	2 (0)	0 (0)	
Haemodialysis unit location (external), n (%)	1460 (53)	488 (48)	462 (52)	392 (58)	55 (52)	61 (68)	2 (40)	<.001
KRT vintage (months)	44 (17–95)	38 (15–83)	45 (17–97)	45 (18–97)	48 (18–110)	53 (19–111)	60 (61–101)	<.001
Symptoms at onset, n (%)								
Asymptomatic	1225 (22)	259 (15)	498 (28)	339 (26)	58 (19)	68 (16)	3 (9)	<.001
Fever	3525 (60)	1300 (71)	1037 (56)	677 (50)	188 (59)	298 (66)	25 (68)	<.001
Cough/rhinorrhoea	3512 (60)	1161 (63)	1004 (54)	792 (59)	212 (67)	319 (71)	24 (69)	<.001
Dyspnoea	2196 (39)	742 (43)	629 (35)	492 (38)	130 (42)	193 (44)	10 (29)	<.001
Gastrointestinal	1279 (23)	424 (24)	419 (23)	236 (18)	71 (23)	120 (27)	9 (26)	<.001
Lymphopenia, n (%)	3584 (63)	1358 (75)	1037 (57)	725 (56)	196 (63)	257 (58)	11 (38)	<.001
Pneumonia, n (%)	3148 (53)	1260 (68)	843 (45)	616 (45)	179 (56)	238 (52)	12 (39)	<.001
Hospital admission, n (%)	3856 (64)	1481 (78)	1104 (58)	757 (55)	207 (64)	292 (63)	15 (47)	<.001
ICU admission, n (%) ^a	561 (15)	127 (9)	179 (17)	123 (17)	39 (19)	90 (32)	3 (21)	<.001
ICU rejection, n (%) ^a	431 (12)	208 (16)	77 (7)	109 (16)	15 (8)	19 (7)	1 (8)	<.001
Mechanical ventilation, n (%) ^a	656 (19)	210 (17)	170 (17)	143 (22)	46 (25)	84 (31)	3 (23)	<.001
Treatment at onset, n (%)								
lopinavir/ritonavir	611 (12)	596 (35)	9 (1)	1 (<1)	0 (0)	5 (1)	0 (0)	<.001
Hydroxychloroquine	1425 (27)	1419 (80)	5 (<1)	1 (<1)	0 (0)	0 (0)	0 (0)	<.001
Interferon	60 (4)	5 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	<.001
Tocilizumab	468 (9)	172 (11)	132 (8)	79 (7)	33 (11)	52 (14)	0 (0)	<.001
Steroids	2565 (48)	587 (35)	862 (50)	661 (53)	183 (61)	261 (63)	11 (41)	<.001
No treatment	1740 (35)	253 (16)	705 (44)	539 (45)	92 (32)	135 (34)	16 (57)	<.001
Baseline ACEi, n (%)	768 (13)	231 (12)	246 (13)	158 (12)	49 (15)	80 (18)	4 (11)	.014
Baseline ARB, n (%)	1343 (23)	384 (21)	455 (24)	317 (24)	72 (23)	106 (24)	9 (25)	.181
Previous NSAID, n (%)	181 (3)	63 (3)	61 (3)	43 (3)	6 (2)	7 (2)	1 (3)	.326
Immunosuppression, n (%)								
Prednisone	2268 (81)	461 (74)	745 (82)	531 (83)	181 (83)	323 (89)	27 (90)	<.001
Ciclosporin	3 (<1)	0 (0)	0 (0)	2 (<1)	1 (<1)	0 (0)	0 (0)	.219
Tacrolimus	2449 (95)	511 (92)	814 (96)	564 (96)	198 (97)	333 (96)	29 (100)	.006
Mycophenolate	1945 (76)	382 (69)	654 (77)	446 (76)	156 (76)	281 (81)	23 (79)	.001
mTORi	412 (16)	124 (22)	114 (13)	93 (16)	35 (17)	44 (13)	2 (7)	<.001
Azathioprine	29 (1)	8 (1)	11 (1)	3 (<1)	3 (1)	3 (1)	1 (3)	.470
SARS-CoV-2 vaccination, n (%)	500 (8%)	0 (0)	0 (0)	8 (1)	66 (20)	396 (84)	30 (79)	<.001
Immunosuppressants adjusted, n (%)	458 (65)	13 (72)	16 (42)	78 (60)	88 (69)	246 (67)	17 (81)	.015
Mortality, n (%)	1207 (21)	500 (28)	292 (16)	265 (20)	52 (17)	94 (22)	4 (19)	<.001
Mortality in vaccinated, n (%)	86 (19)	NA	NA	1 (12)	8 (12)	75 (21)	2 (15)	.382
Mortality in symptomatic patients, n (%)	1010 (25)	412 (30)	244 (20)	225 (25)	46 (20)	80 (25)	3 (19)	<.001

^a% of admitted.

Data are displayed as mean ± standard deviation or median (interquartile range) unless otherwise indicated. KRT, kidney replacement therapy, KT, kidney transplant; HD, in-centre haemodialysis; PD, peritoneal dialysis; HHD, home haemodialysis; ICU, intensive care unit; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; NSAID, non-steroidal anti-inflammatory drugs; mTORi, mammalian target of rapamycin inhibitors; NA, not applicable.

modalities are shown in Supplementary data, Table S1. SARS-CoV-2-infected KT recipients were younger but had longer KRT vintage than HD patients and also had a higher rate of SARS-CoV-2 vaccination.

Regarding immunosuppressive drugs, KT recipients were mostly receiving prednisone (81%), tacrolimus (95%) and mycophenolate (76%) for chronic immunosuppression before developing COVID-19 (Table 1). The chronic immunosup-

pressive medication of KT recipients that were diagnosed with COVID-19 evolved during the pandemic: over time the percentage of patients on prednisone ($P < .001$), tacrolimus ($P = .006$) and mycophenolate ($P = .001$) increased and the percentage of patients on mTORi inhibitors ($P < .001$) decreased. Most of these differences were evident between the first and subsequent waves (Supplementary data, Table S2). However, only prednisone was significantly more frequent for chronic

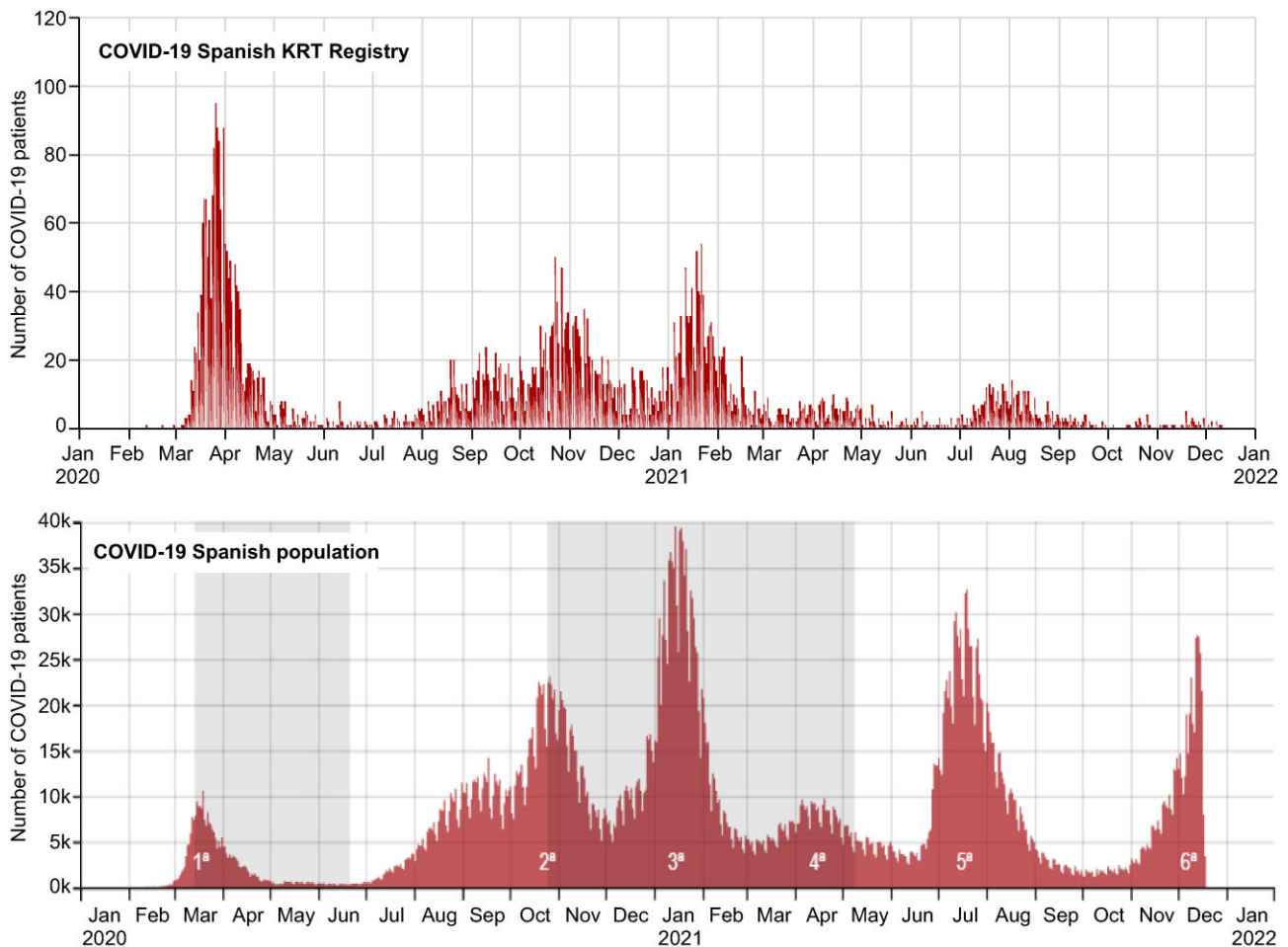


FIGURE 1: SARS-CoV-2 infections over time in the COVID-19 Spanish KRT Registry and in the general Spanish population during the pandemic.

immune suppression during the vaccine era (Supplementary data, Table S2). In fact, chronic immune suppression with prednisone was observed in 80% of KT recipients before vaccines became available (waves 1–3) and in 88% in waves 4–5, when over 85% of KT recipients with SARS-CoV-2 infection were vaccinated.

Changing patterns of SARS-CoV-2 infection and treatment

Figure 1 shows the incidence of SARS-CoV-2 infection in the Spanish COVID-19 KRT Registry and in the general Spanish population [3]. In the KRT cohort, more SARS-CoV-2 infections occurred during the first wave than in subsequent waves ($P < .001$), unlike in the general population. The pandemic affected more frequently in-centre HD patients in the initial wave and KT recipients from the fourth wave, i.e. after the vaccine had become available (Fig. 2) (Supplementary data, Tables S2 and S3). Following the availability of vaccines, the number of COVID-19 cases among KRT patients decreased dramatically. However, an interesting pattern is observed in which most COVID-19 cases in KT recipients in the fifth and sixth waves occurred among vaccinated persons, while in the sixth wave, i.e. after the booster had been offered, most infections in HD occurred in unvaccinated patients.

Symptoms varied across waves. A total of 1025 (22%) patients were asymptomatic and the frequency increased from

the first wave (15%) to the second and third wave (28% and 26%, respectively), likely representing changes in HD units screening patterns, and then decreased to 9% ($P < .001$). In this regard, KT recipients and patients on PD were less likely to be asymptomatic ($P < .001$) and had higher rates of pneumonia ($P < .001$) (Supplementary data, Table S1). A total of 3148 (53%) patients developed pneumonia (Table 1). The most common symptoms were fever (60%) and cough/rhinorrhoea (60%).

The prescription of drugs to treat COVID-19 changed during the pandemic. Lopinavir/ritonavir (35%) and hydroxychloroquine (80%) were used only in the first wave and then became obsolete ($P < .001$ for both). Steroids (48%) were the most frequent treatment initiated for the cytokine storm phase of COVID-19, while 35% of patients were untreated (Table 1). KT recipients were treated more frequently with drugs targeting the cytokine storm (i.e. steroids or tocilizumab) than the other cohorts ($P < .001$ for both) (Supplementary data, Table S1).

Among KT recipients, 458 (65%) required an adjustment of immunosuppressive treatment during the infection, the most common being a reduction or withdrawal of mycophenolate in 384 (98%), followed by a reduction in calcineurin inhibitors [tacrolimus in 232 (68%) patients, cyclosporine in 5 (20%)] and an increase in steroid dose in 289 (82%) patients. A decrease/withdrawal of mTOR inhibitors was uncommon (3 patients, 5%).

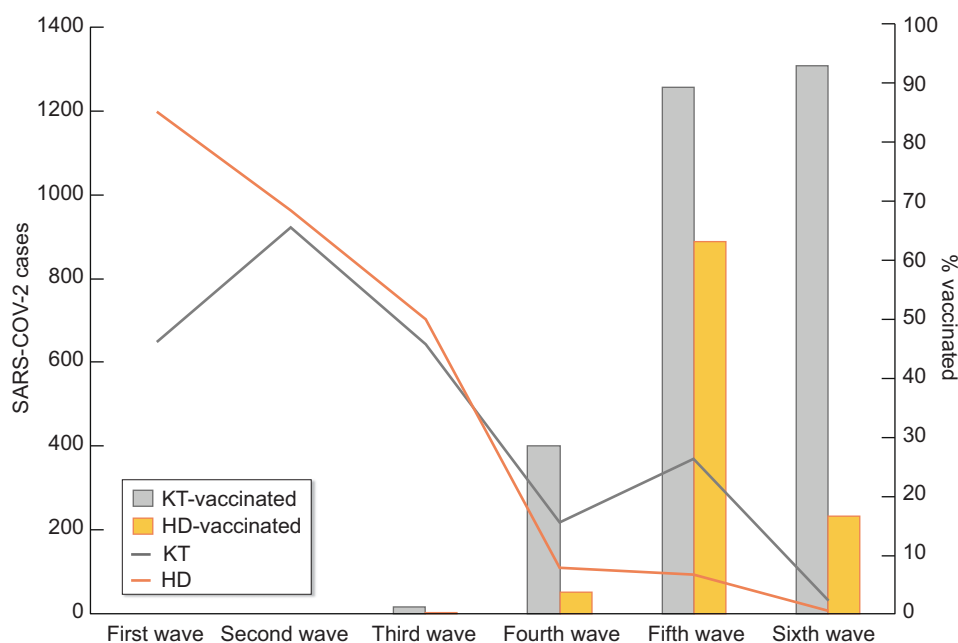


FIGURE 2: SARS-CoV-2 cases and vaccination status among kidney transplant recipients and haemodialysis. Continuous lines refer to total cases in the different cohorts. Bars indicate the percentage of vaccination among infected patients. KT, kidney transplant; HD, haemodialysis.

Factors associated with admission

Among infected patients, 3856 (64%) were admitted to hospital. Factors associated to admission are summarized in Table 2.

A total of 658 (11%) patients required mechanical ventilation. Mechanical ventilation use increased over time ($P < .001$) (Table 1), potentially reflecting improved capacities of healthcare facilities to absorb the case load.

In multivariate analysis, patient (older age, male sex, KT recipient), COVID-19 severity (baseline lymphopaenia, pneumonia) and pandemic (first wave) factors were independent predictors for admission (Table 3). Sensitivity analyses exploring different pandemic wave categories yielded similar results (Supplementary data, Tables S4 and S5).

Factors associated with ICU admission

Among infected patients, 562 (9%) were admitted to ICU, corresponding to 15% of patients admitted to hospital. In 439 patients (7%) were rejected from ICU admission despite severity criteria for ICU admission. The pattern of ICU admissions also evolved during the pandemic, being lower during the first wave (in which rejection from ICU was higher), likely reflecting overwhelmed healthcare systems (Supplementary data, Table S2).

Factors associated with ICU admission are summarized in Table 2. Multivariate analysis identified patient (younger age, KT recipient, shorter KRT vintage), COVID-19 severity (baseline lymphopaenia, pneumonia) and pandemic (infection outside the first wave) factors as independent predictors for ICU admission (Table 3). Sensitivity analyses exploring different pandemic wave categories yielded similar results (Supplementary data, Tables S6 and S7).

Factors associated with mortality

During follow-up, 1207 patients (21%) died, 4539 (74%) recovered and 344 (6%) were lost to follow-up. Figure 3 shows the mortality

in the Spanish COVID-19 KRT Registry and COVID-19 mortality in the general Spanish population [3]. COVID-19 mortality among KRT patients was more frequent during the first wave (28%) than in other waves (18%) ($P < .001$) (Supplementary data, Table 2) and grossly paralleled those of the general population. From the fourth wave, i.e. after vaccines became available, the number of deaths decreased dramatically and occurred mainly in KT recipients (Fig. 4). However, among breakthrough diagnosed with COVID-19 in the vaccinated, mortality was 19% (Table 1). Of the 86 vaccinated KRT patients that died, a majority (77, 89%) were KT recipients (Supplementary data, Table 1).

COVID-19 mortality was higher in HD and PD (24 and 22%, respectively) than in KT (18%) or HDD (14%) patients ($P < .001$). Patient (male sex, older age, diabetic kidney disease, in-centre HD), COVID-19 severity (baseline lymphopaenia, pneumonia), COVID-19 treatment (ACEi and ARB withdrawal, ICU rejection) and pandemic (first wave) factors were also associated to mortality.

In multivariate analysis, patient factors (older age), COVID-19 severity (baseline lymphopaenia, pneumonia) and COVID-19 treatment (ICU rejection) factors were independent predictors of mortality (Table 3). Sensitivity analyses exploring different pandemic wave categories yielded similar results (Supplementary data, Tables S8 and S9).

While COVID-19 severity is an expected driver of mortality, the identification of additional patient factors associated with mortality, potentially by increasing disease severity, may be of interest. Focussing only on patient factors, multivariate analysis identified older age, male sex, diabetes and KT as independent risk factors for death, while ARB use was protective (Supplementary data, Table S10). An analysis focussed on KT recipient factors confirmed the higher risk conferred by older age, male sex and diabetes and, additionally, identified an association with immunosuppressants: mTORi-free and calcineurin inhibitor-free regimens were associated with mortality, while prednisone-free regimens were associated with lower mortality (Supplementary data, Table S11).

Table 2. Factors associated with outcomes after SARS-CoV-2 infection in univariate analysis

	Hospital admission		ICU admission		Mortality	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Sex (male)	1.30 (1.17–1.45)	<.001	1.13 (0.93–1.36)	.226	1.25 (1.10–1.43)	.001
Age (per year)	1.02 (1.02–1.03)	<.001	0.97 (0.96–0.97)	<.001	1.06 (1.05–1.06)	.001
Diabetic kidney disease (yes)	1.39 (1.21–1.59)	<.001	0.82 (0.65–1.03)	.093	1.43 (1.23–1.66)	<.001
KRT (KT)	1.15 (1.03–1.28)	.010	3.75 (3.07–4.59)	<.001	0.73 (0.64–0.83)	<.001
Haemodialysis unit location (in-centre)	0.76 (0.65–0.89)	.001	0.98 (0.68–1.42)	.932	1.02 (1.00–1.44)	.045
KRT vintage (per month)	1.00 (1.00–1.00)	.331	1.00 (1.00–1.00)	.055	1.00 (0.99–1.00)	.871
Lymphopaenia (yes)	15.1 (13.3–17.3)	<.001	3.75 (2.59–5.42)	<.001	6.52 (5.35–7.95)	<.001
Pneumonia (yes)	104 (82–132)	<.001	11.6 (6.80–19.9)	<.001	10.7 (8.8–13.07)	<.001
Treatment during admission (yes):	–	–	28.0 (16.1–48.7)	<.001	2.34 (1.95–2.83)	<.001
Lopinavir/ritonavir	–	–	7.05 (5.84–8.51)	<.001	1.83 (1.58–2.12)	<.001
Hydroxychloroquine	–	–	33.7 (4.67–243)	<.001	3.52 (2.15–5.76)	<.001
Interferon	–	–	93.3 (29.9–290)	<.001	2.98 (2.43–3.65)	<.001
Tocilizumab	–	–	26.1 (21.5–31.7)	<.001	3.49 (3.02–4.04)	<.001
Steroids	–	–	–	–	–	–
Baseline ACEi (yes)	1.09 (0.93–1.28)	.265	1.11 (0.85–1.44)	.431	0.92 (0.76–1.12)	.39
ACEi withdrawal at admission (yes)	–	–	2.94 (1.68–5.15)	<.001	5.09 (3.17–8.19)	<.001
Baseline ARB (yes)	0.88 (0.77–0.99)	.047	1.47 (1.19–1.81)	<.001	0.75 (0.63–0.88)	<.001
ARB withdrawal at admission (yes)	–	–	3.43 (2.28–5.17)	<.001	4.38 (3.08–6.21)	<.001
Previous NSAID (yes)	1.06 (0.77–1.45)	.701	0.19 (0.07–0.53)	.001	0.95 (0.65–0.14)	.805
Immunosuppressive medication (yes)	0.82 (0.69–0.99)	.046	0.71 (0.52–0.97)	.030	0.78 (0.59–1.02)	.075
Prednisone-free regimen	1.39 (0.93–2.10)	.110	0.78 (0.45–1.36)	.380	1.18 (0.74–1.89)	.480
CNI-free regimen	0.86 (0.68–1.08)	.199	1.56 (1.11–2.19)	.011	1.51 (1.10–2.07)	.011
mTORi-free regimen	1.15 (0.95–1.39)	.148	0.56 (0.42–0.75)	<.001	0.87 (0.67–1.11)	.260
Mycophenolate-free regimen	–	–	–	–	–	–
SARS-CoV-2 wave (first)	2.61 (2.30–2.96)	<.001	0.41 (0.33–0.51)	.001	1.74 (1.53–1.99)	<.001
ICU admission (yes)	–	–	–	–	3.78 (3.13–4.58)	<.001
ICU rejection (yes)	–	–	–	–	17.0 (12.9–22.3)	<.001
Vaccination status (yes)	0.89 (0.74–1.09)	.261	2.74 (2.09–3.58)	<.001	0.88 (0.69–1.13)	.315

The increased OR of UCI admission in univariate analysis among the vaccinated appears to be related to the availability of vaccines in most recent pandemic waves, in which ICU access was easier than in previous waves when the healthcare system was overwhelmed.

KRT; kidney replacement therapy; KT, kidney transplant; ACEi, angiotensin-converting enzyme inhibitors; ARB; angiotensin receptor blockers; NSAID, non-steroidal anti-inflammatory drugs; CNI, calcineurin inhibitors; mTORi, mammalian target of rapamycin inhibitors; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR (95%CI), odds ratio (95% confidence interval).

DISCUSSION

The key finding of our study is that, although lower than in the first wave, the mortality of KRT patients diagnosed with COVID-19 remains high (around 19% for vaccinated KRT patients) despite advances in treatment and higher availability of ICU care in the era of vaccines. This is 13-fold higher than the 1.55% mortality of confirmed COVID-19 in the general population in Spain [11]. However, the vaccine era witnessed a dramatic decrease in the number of diagnosed COVID-19 cases in the KRT population as compared with the general population, as well as in the absolute number of deaths, and mortality of vaccinated KRT patients was for the most part limited to KT recipients. Thus, a shift was observed from HD patients to KT recipients, for both cases and deaths, likely reflecting the lower efficacy of vaccines in KT recipients [9]. In this regard, the increased prevalence of chronic immunosuppressive regimens containing steroids among COVID-19-infected KT recipients over time should be considered in the context of reports that associate chronic im-

munosuppressive regimens containing steroids with poorer humoral responses to vaccines [9]. In contrast, almost half of the HD patients infected in the fifth wave and most of the few HD patients infected in the sixth wave were unvaccinated, supporting the efficacy of booster vaccine doses in this population.

Several changes in the presentation, treatment and outcomes of COVID-19 were evident over time and through the successive pandemic waves. One of the most striking features was the shift in the KRT patient population with COVID-19. The first wave mainly affected HD patients while the fifth and sixth waves, following vaccination, were the KT recipient waves. In the first wave, the healthcare system was unprepared to prevent the spread of the virus, but HD patients needed to access healthcare facilities thrice weekly and could not shield themselves [7, 12, 13, 14]. The more recent shift to KT recipients appears related to their suboptimal response to vaccines [9]. In this regard, although the case fatality ratio was similar among vaccinated KT recipients and vaccinated HD patients, there were 8.5-fold more deaths among vaccinated KT recipients

Table 3. Multivariate logistic regression for outcomes after SARS-CoV-2 infection

	Hospital admission		ICU admission		Mortality	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age (per year)	1.01 (1.01–1.02)	<.001	0.97 (0.96–0.98)	<.001	1.05 (1.04–1.06)	<.001
Sex (male)	1.21 (1.01–1.46)	.034	–	–	–	–
KRT (KT)	1.81 (1.46–2.23)	<.001	2.90 (2.28–3.68)	<.001	–	–
Lymphopenia (yes)	5.58 (4.64–6.65)	<.001	3.23 (2.16–4.82)	<.001	1.98 (1.48–2.64)	<.001
Pneumonia (yes)	50.7 (39.4–65.4)	<.001	16.9 (8.64–33.4)	<.001	2.87 (2.15–3.83)	<.001
KRT vintage (month)	–	–	0.99 (0.99–0.99)	.008	–	–
SARS-CoV-2 wave (first)	1.57 (1.28–1.93)	<.001	0.43 (0.34–0.54)	<.001	–	–
ICU rejection (yes)	–	–	–	–	13.1 (9.81–17.5)	<.001

Models adjusted for diabetic kidney disease. KRT, kidney replacement therapy; KT, kidney transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OR (95% CI): odds ratio (95% confidence interval).

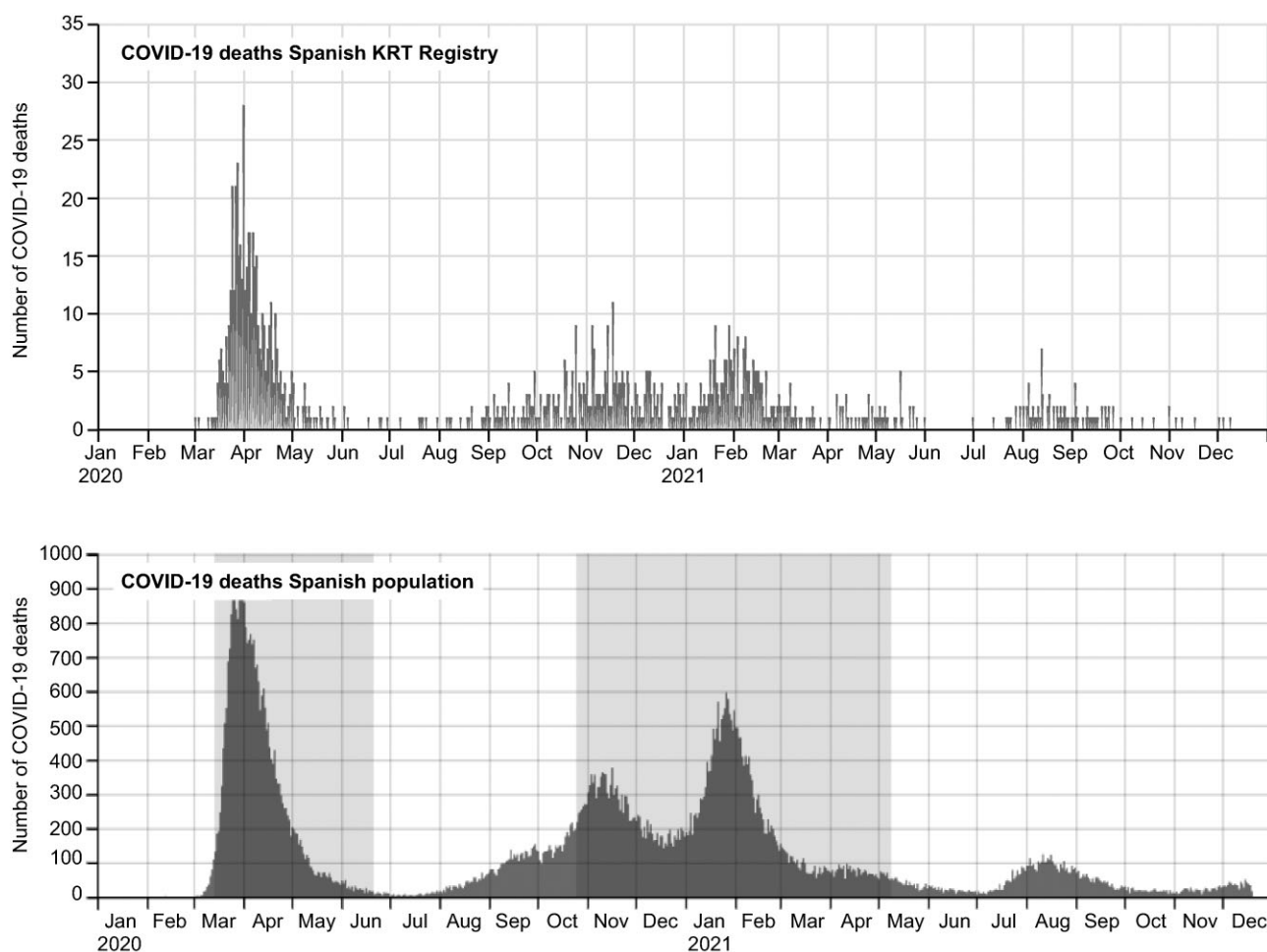


FIGURE 3: COVID-19 mortality over time in the COVID-19 Spanish KRT Registry and in the general Spanish population during the pandemic.

than among vaccinated HD patients, likely reflecting the higher number of breakthrough SARS-CoV-2 infections despite vaccination in KT recipients. To put these data into perspective, the number of KT recipients with functioning grafts in Spain is 1.35-fold higher than the number of patients on HD [15].

A key finding is a potential role of therapeutic nihilism in the high mortality of KRT patients during the first COVID-19 wave, especially among HD and PD patients. In this regard, KT

recipients were admitted more frequently, with more symptoms and more frequent pneumonia and received more ICU care, but mortality was lower than in PD or HD patients. Multivariate analysis identified refusal of ICU care as an independent risk factor for death, among other patient and disease severity factors. Difficult decisions had to be made early in the COVID-19 pandemic when ICUs were overwhelmed. This observation is confirmed in our data, where young patients were more

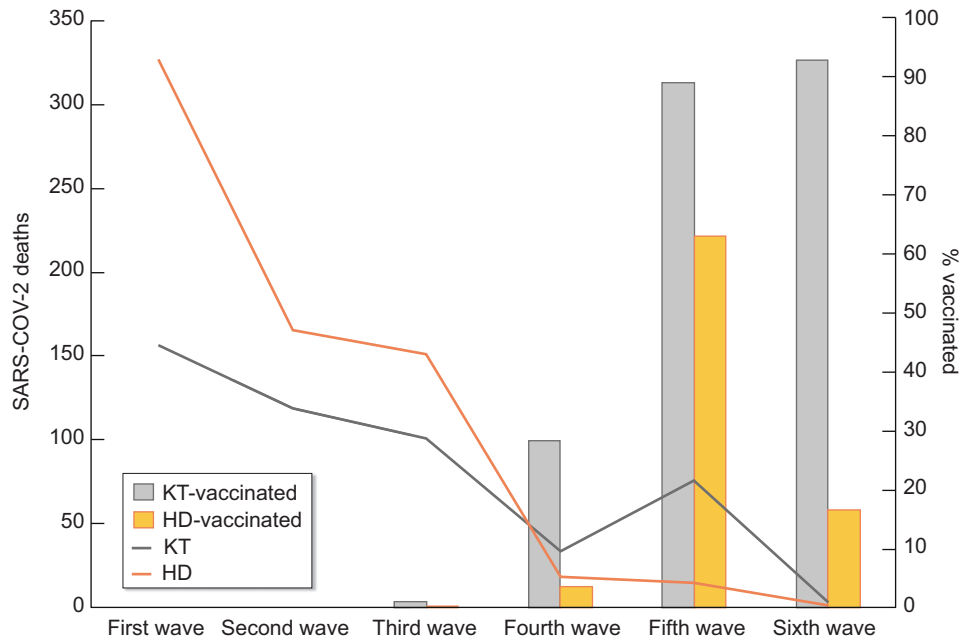


FIGURE 4: SARS-CoV-2 deaths and vaccination status among kidney transplant recipients and haemodialysis patients. Continuous lines refer to total deaths in the different cohorts. Bars indicate the percentage of vaccination among patients dying from COVID-19. KT, kidney transplant; HD, haemodialysis.

frequently accepted for ICU admission. However, we should strive to prevent the rejection of KRT patients during the first pandemic wave becoming a self-fulfilling prophecy and KRT patients being refused advanced life support in the future because of that earlier high mortality. Indeed, our data show that KRT patients with COVID-19 during the first wave were 2.3-fold less likely to be admitted to ICUs than in subsequent waves. In this regard, in the most recent pandemic waves, when vaccines are available and therapies such as dexamethasone are widely used [16], most KRT patients with breakthrough COVID-19 survived. Moreover, in KRT patients, unlike in the general population, additional comorbidities, such as diabetes, hypertension, coronary artery disease and chronic lung disease, do not further add to the risk of death and the impact of older age on the risk of death is up to 6-fold lower than in the general population [1, 3].

Beyond access to advanced life support, other treatment factors may influence the risk of death. In addition to the prescription of antivirals or steroids, adjustment of chronic immunosuppression could be a successful strategy in KT recipients. In this regard, mTORi-free and calcineurin inhibitor-free regimens were associated with higher mortality, while steroid-free regimens were consistently associated with lower hospital admissions, lower ICU admissions and lower mortality. Data on the prevalence of chronic immunosuppressive regimens containing steroids among infected KT recipients over time also points to the negative impact of steroids-containing immune suppressive regimens on sensitivity to COVID-19 and also, to severe and potentially lethal COVID-19. This may be, at least in part, related to reports that associate steroids-containing immunosuppressive regimens with poorer humoral responses to SARS-CoV-2 vaccines [9]. Interestingly, steroids are beneficial when used acutely in COVID-19 [17]. This controversy can be understood in light of the anti-inflammatory effect of high doses of corticosteroids on the cytokine storm phase of COVID-19, in contrast to the chronic immunosuppression with steroids prescription that may dampen antiviral and vaccine responses.

Regarding acute steroid prescription, an indication bias should be noted, as they were prescribed to treat severe COVID-19, and we believe that this underlies the association with mortality. Among other pre-existent therapies, baseline use of ARBs was a patient factor associated with lower mortality in the full KRT population, albeit not in KT recipients. While this should be confirmed in a wider KRT population, there is biological plausibility for the relationship, since angiotensin receptor-1 (AT-1), the target of ARBs, was recently shown to facilitate SARS-CoV-2 entry into cells mediated by soluble angiotensin-converting enzyme 2 (sACE2) [18]. Thus, ARBs could potentially interfere with this port of entry of SARS-CoV-2 into cells and we can only speculate that, based on the clinical observation, this viral entry pathway may be more relevant in dialysis patients. This hypothesis merits being pursued in further research as it may be clinically relevant.

The main impact of vaccines appeared to be the reduction in the number of cases, as mortality among vaccinated KRT patients diagnosed with COVID-19 was similar to among non-vaccinated KRT patients diagnosed with COVID-19. However, mortality among vaccinated COVID-19 patients was almost exclusively found in KT recipients, pointing to a suboptimal response to vaccination in those patients who died despite vaccination. Thus, as the pandemic shifts from the wider KRT population to vaccinated KT recipients, the urge to optimize the vaccination regimens increases. This may imply transient adaptation of immune suppression regimens, more common use of the mRNA-1273 vaccine, additional booster doses or novel vaccines [9].

The presentation of SARS-CoV-2 infection and the case fatality ratio may have been influenced by the criteria used to perform diagnostic tests. Thus, early in the pandemic, testing seemed to be reserved for more symptomatic patients, given supply chain issues. Later, testing of even asymptomatic patients was performed in HD units for outbreak monitoring, but not in at-home dialysis or KT recipients [19, 20]. This may explain the lower likelihood of being asymptomatic and

higher rates of pneumonia in KT recipients and PD patients. Indeed, asymptomatic infections in the second and third waves were 26–28% and decreased to <20% when the epidemiological context changed and preventive screening protocols became outdated. However, the combination of strictly observed isolation measures (e.g. masks during transport to and from dialysis centres and during HD sessions) and vaccines appears to be more effective in the KRT population than vaccines in combination with more relaxed measures in the general population, as judged by the lower number of infections recorded upon vaccine implementation in KRT patients than in the general population. Thus, vaccination and booster doses should continue to be promoted in KRT patients and isolation measures should be maintained. In this regard, early in the pandemic lack of face masks during transport to and from dialysis and suboptimal personal protective equipment were identified as risk factors for infection in KRT patients and healthcare personnel [7, 11, 12].

Some limitations should be acknowledged. In this registry-based study, inherent bias includes some incomplete data, limited variables (such as body mass index or treatment duration) or loss of follow-up. However, first, this is a multicentric prospective study involving a large cohort of patients on KRT infected by SARS-CoV-2 in Spain, corresponding to roughly 10% of Spanish patients on KRT [12], so data and conclusions are thought to be representative. Second, information on vaccination dates or antibody response is not available. In Spain, the first vaccine dose was administered at the end of December 2020, but widespread vaccination started in January 2021 and reached KRT patients at some point between February and April 2021. Third, subclinical or asymptomatic infections probably went unnoticed, especially beyond the third wave, when systematic periodic screening of HD units was no longer performed, so the studied outcomes could be overestimated. However, this makes the data more comparable to the general population, for which widespread screening of asymptomatic individuals is not performed [15]. Fourth, the sixth wave data predate the introduction and expansion of the Omicron variant in Spain and thus, the impact of this strain is not reflected in the data. Finally, some variables, such as rejection from ICU admission, did not have a universal definition and should be analysed from a subjective point of view.

In conclusion, the features of the COVID-19 pandemic in KRT patients (patient characteristics, treatment and outcomes) keep evolving, shifting towards vaccinated KT recipients and unvaccinated dialysis patients. Vaccines are associated with a lower incidence of diagnosed COVID-19, but mortality remains high despite ICU care, although most patients survive. Further improvement in KRT patient outcomes may be obtained by optimizing vaccination and immune suppression protocols in KT recipients, promoting vaccination and boosting dialysis patients and providing access to life support care if needed.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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DATA AVAILABILITY STATEMENT

Data are available upon a reasonable request.

CONFLICT OF INTEREST STATEMENT

B.Q. has received honoraria for conferences, consulting fees and advisory boards from Vifor-Pharma, Astellas, Amgen, Bial, Ferrer, Novartis, AstraZeneca, Sandoz, Laboratorios Bial, Esteve, Sanofi-Genzyme and Otsuka. He is the present secretary of the Spanish Society of Nephrology. 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. He is the former Editor-in-Chief of CKJ. M.M.G. has received honoraria for conferences, consulting fees and advisory boards from Astellas and Chiesi. P.deS. reports honorarium for conferences, consulting fees and advisory boards from Amgen, Astellas, AstraZeneca, Baxter, Braun, Fresenius, Nipro, Vifor-Pharma. She is the present president of the Spanish Society of Nephrology (S.E.N.). E.S.-Á. has received honoraria for conferences, consulting fees and advisory boards from AstraZeneca, Vifor, Astellas, Novo Nordisk and Baxter.

C.J.C.-R., M.C.R.F., V.L.J., N.T. and S.Z.L. do not present any disclosure.

APPENDIX

The Spanish COVID-19 KRT Registry collaborative group:

Victoria Oviedo
 Antoni Bordils Gil
 María Luisa Navarro López
 María Isabel Martínez Marín
 Amparo Bernat García
 Isabel Berdud Godoy
 M^a Victoria Guijarro Abad
 María del Mar Rodríguez de Oña
 Elena Vaquero Párrizas
 María Antonia Fernández Solís
 Jose Antonio Gomez Puerta
 Alvaro Ossorio Anaya
 Elena Calvo
 Carmen Cabré Menéndez
 Nuria García Fernández
 Paloma Leticia Martín Moreno
 M^a José Fernández-Reyes Luis
 Cristina Lucas Álvarez
 Guadalupe Taberero fernández
 Manuel Heras Benito
 Pilar Fraile Gómez
 Joaquin Manrique Escola
 Enrique Pelaez Perez
 Luz María Cuiña Barja

Teresa Cordal Martinez
 Maria Jesus Castro Vilanova
 Silvia Moreno Loshuertos
 Francisco Javier Ahijado Hormigos
 Ana Roca Muñoz
 Carlos Jesús Cabezas Reina
 Jesús Grande Villoria
 Ana Isabel Díaz Mareque
 Anabertha Narváez Benítez
 Argimiro Gándara Martínez
 M^ª Gloria Rodríguez Goyanes
 Maria Crucio Lopez
 Alfonso Iglesias
 Laureano Perez Oller
 Carlos Antonio Soto Montañez
 Juan Villaro Gumpert
 Ana Beatriz Muñoz Díaz
 Gustavo Useche Bonilla
 Maria Noel Martina Lingua
 Diana Pazmiño Zambrano
 Sandra Castellano Gasch
 Guadalupe Caparrós Tortosa
 Silvia Soto Alarcón
 Mercedes Albaladejo Pérez
 Ignacio Cidraque Vella
 Cristina Canal Girol
 Silvia Benito García
 Montserrat Picazo Sánchez
 Anna Patrícia Balius Matas
 Núria Garra Moncau
 Rodrigo Avellaneda Campos
 Ana María Ramos Verde
 Laura Muñoz Pacios
 Alfonso Pobes Martínez de Salinas
 Maria Jimenez Herrero
 Liliana Morán Caicedo
 M^ª Dolores Prados Garrido
 Mariana Garbiras
 Laura Sanchez Rodríguez
 María Dolores Albero Molina
 Elena Gutiérrez Solis
 Ana Hernández Vicente
 Angel.M Sevillano Prieto
 Teresa Bada Bosch
 Hernando Trujillo Cuéllar
 Helena Díaz Cambre
 Cassandra Emma Puig Hooper
 Adriana Maria Cavada Bustamante
 Boris Gonzales Gandía
 Miguel Rodeles del Pozo
 Miquel Blasco Pelicano
 José Jesús Broseta Monzó
 Jaime Sanz García
 Jose Antonio Herrero Calvo
 Isabel Maria Pérez Flores
 Virginia López de la Manzanara Pérez
 Javier Vian Pérez
 Sara Huertas Salazar
 Armando Coca Rojo
 R. Alvarez
 Miguel Angel González Rico
 Ana Isabel Martinez Diaz
 Elena Giménez Civera
 Ignacio Lopez Alejaldre
 Claudio José Hornos Hornos
 Zakariae Koraichi Rabie Senhaji
 Enriqueta González Rodríguez
 Andrea Patricia Zapata Balcázar
 Cecilia Montoyo Castillo
 David Tura Rosales
 Raúl Edilberto Alvarado Gutiérrez
 Rafael Garcia Maset
 Rosa Garcia Osuna
 Maria Eugenia Palacios Gómez
 Sergio García Marcos
 Francisco Roca Oporto
 Manuel Ramirez de Arellano Serna
 Elena Olivar Pérez
 Oihana Larrañaga Zabaleta
 M^ª Dolores Arenas Jiménez
 Marta Crespo Barrio
 Silvia Collado Nieto
 María Dolores Redondo Pachón
 Anna Buxeda i Porras
 Laura Llinàs Mallo
 Alberto Mendoza-Valderrey
 Carola Arcal Cunillera
 Basilio Martin Urcuyo
 Adelaida Morales Umpiérrez
 Aránzazu Márquez Corbella
 Eva Gavela Martínez
 Julia Kanter
 Sandra Beltrán Catalán
 Mercedes Gonzalez Moya
 July Vanessa Osma Capera
 Alejandro Valero Anton
 Elena Castellón Lavilla
 Juan Casas Todolí
 Amir Shabaka Fernández
 Ainhoa Hernando Rubio
 Inmaculada Lorenzo Gonzalez
 Francisco Llamas fuentes
 Francisco Javier Centellas Pérez
 Ana Pérez Rodríguez
 Alejandra Rodriguez
 Jorge Reichert
 Rosa Sanchez Hernández
 Luis Fernando Domínguez Reina
 Antonio Franco Esteve
 Eduardo Muñoz de Bustillo Llorente
 Dioné González Ferri
 Alejandro Pérez Alba
 Luis Guillermo Piccone Saponara
 María Esperanza Moral Berrio
 Silvia Ros Ruiz
 Leonidas Cruzado Vega
 Eduardo Bosque Muñoz
 Joaquín de Juan Ribera
 Josefa Martin Rivas
 Inés Aragoncillo Sauco
 Luis Alberto Sánchez Cámara
 Antonio Pérez Pérez
 M^ª José Navarro Parreño
 Gracia M^ª Alvarez Fernández
 Marisol Ros Romero
 Diana Manzano Sánchez
 Maria Molina Gomez
 Javier Juega
 Andrés Villegas Fuentes
 Laura Espinosa Román
 Cristóbal Donapetry García
 Pablo Castro de la Nuez

Antonio Crespo Navarro	Ernesto Francisco Valga Amado
Neus Rodriguez Farre	Gabriel De Arriba De La Fuente
Jesus Martin Garcia	Marta Sánchez Heras
Antonio Gascón Mariño	Concepción Alamo Caballero
Secundino Cigarran Guldris	Maria Pilar Perez del Barrio
Margarita Montserrat Pousa Ortega	Clara María Moriana Domínguez
Roberto Holgado Salado	Sara Blázquez Roselló
Margarita Delgado Cordova	Gema Velasco Barrero
Natalia Blanco Castro	Jary Perello Martinez
Elvira Esquivias de Motta	Manuel Ramos Díaz
Veronica Lopez Jimenez	Marina Almenara Tejederas
Belen Gómez Giralda	Martín Giorgi González
María Verónica Torres Jaramillo	Beatriz Diez Ojea
Juan Cristobal Santacruz Mancheno	Vicente Paraíso Cuevas
Beatriz María Durá Gúrpide	Fernando Tornero Molina
Paula Munguía Navarro	David Rodríguez Santarelli
Belen Moragrega	Jessica Isabel Urdaneta Colmenares
Marta Luzon Alonso	Luis Alberto Blázquez Collado
Fernando Gil Catalinas	Maria Teresa Rodrigo De Tomas
Emma Huarte Loza	Fernando Simal Blanco
Cecilia Dall'Anese Siegenthaler	Marta Albalate Ramón
Pedro Jesús Labrador Gómez	Patricia de Sequera Ortiz
Silvia González Sanchidrián	Rafael Lucena Valverde
Yanina García Marcote	Raquel Diaz Mancebo
Bruna Natacha Leite Costa	Rocio Echarri Carrillo
Joan Manuel Gascó Company	Gabriel Ledesma Sanchez
Juan Rey Valeriano	Ernesto Jose Fernandez Tagarro
Sheila Cabello Pelegrin	Iván Chamorro Bucheli
Paloma Livianos Arias-Camisón.	Joan Albert Fernández Roig
María Teresa García Falcón	Isabel Garcia Mendez
Ana Rodriguez-Carmona	Carlos Jimenez Martin
Antía López Iglesias	María Ovidia López Oliva
Felipe Sarró Sobrín	M ^a Elena González García
María Luisa Martin Conde	María Auxiliadora Bajo Rubio
Javier Arrieta Lezama	Laura Alvarez García
Iñigo Moina Eguren	Jesus Calviño Varela
Olga Gonzalez Peña	Juan Carlos Ruiz San Millán
Maria del Carmen Díaz Corte	Celestino Piñera Haces
María Luisa Suarez Fernandez	Rosa Palomar Fontanet
Pedro Vidau Arguelles	Rosalía Valero San Cecilio
Elena Astudillo Cortés	M. Jose Aladrén Regidor
Lucía Sobrino Díaz	Alejandro Soria Villén
Alba Rivas Oural	Cristina Medrano Villarroya
Luis Fernando Morán Fernández	Orlando Siverio Morales
Oscar Rolando Durón Vargas	Diego Rodríguez Puyol
Clara Sanz García	María Pérez Fernández
Adriana Maria Cavada Bustamante	Jose Portoles Perez
Carmen Robledo Zulet	Charo Llopez Carratala
Oscar Garcia Uriarte	Auxiliadora Mazuecos
María Begoña Aurrekoetxea Fernandez	Juan Manuel Cazorla Lopez
María Isabel Jimeno Martín	Maríaa Gabriela Sánchez Márquez
Guillermo Alcalde Bezhold	Carolina Lancho Novillo
Rosa María Ruiz-Calero Cendrero	Lien Winderickx
Roman Hernandez Gallego	Carlos Íñiguez Villalón
María Victoria Martin Hidalgo-Barquero	Cristina Galeano Álvarez
Pedro Abáigar Luquin	Sara Jiménez Álvaro
Emilio Sanchez	Esmeralda Castillo Rodríguez
Sagrario García Rebollo	Daniel Eduardo Villa Hurtado
María Lourdes Pérez Tamajón	Milagros Fernandez Lucas
Alejandra Maxorata Alvarez Gonzalez	Alberto Rodríguez Benot
Greissi Jeniree Garcia Bonilla	Sagrario Soriano Cabrera
Eva Alvarez	Raquel Ojeda López
Sofía Zarraga Larrondo	Jose Luis Pérez Canga
Alfonso Cubas Alcaraz	Ana Cristina Andrade López
M ^a Teresa Naya Nieto	Anna Gallardo Pérez
Fernando Henriquez Palop	Aniana Oliet Palá
Raquel Santana Estupiñán	María Sanchez Sanchez

Juan Manuel Buades Fuster
 María Eugenia Palacios Gómez
 Felisa Martínez Sanchez
 Cristina Jimeno Griñó
 Adoración Martínez Losa
 Isabel María Saura Luján
 Luis Gil Sacaluga
 Gabriel Bernal Blanco
 María Jose Marco Guerrero
 Ana Isabel Martínez Puerto
 M^o Jesús Moyano Franco
 Elena Araceli Jiménez Víbora
 Nuria Aresté Fosalba
 María de los Ángeles Rodríguez Pérez
 Ramos Escorihuela
 Ramón Jesús Devesa Such
 Isabel Beneyto Castelló
 Edoardo Melilli
 María José Soler Romeo
 Francesc Moreso Mateos
 Nestor Gabriel Toapanta Gaibor
 Alfonso Pobes Martínez de Salinas
 Begoña Rincón Ruiz
 M^ocarmen Ruiz Fuentes
 Ramón López-Menchero Martínez
 Miguel Angel Suarez Santisteban
 Carlos Jarava Mantecón
 Fernando Fernandez Giron
 Omar Miranda Espinal
 Juan Carlos Martínez Ocaña
 Raúl García Castro
 Florentino Villanego Fernández
 Montserrat Belart Rodríguez
 Camino García Monteavaro

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