Impact of different COVID-19 waves on kidney replacement therapy epidemiology and mortality: REMER 2020

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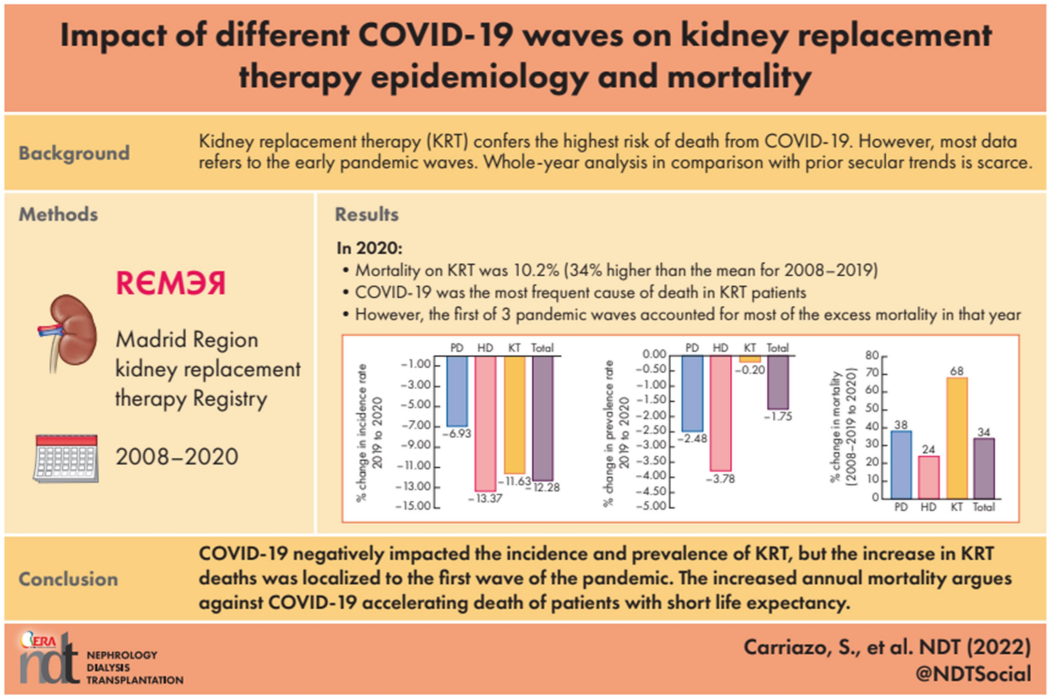
GRAPHICAL ABSTRACT



ABSTRACT

Background. Kidney replacement therapy (KRT) confers the highest risk of death from COVID-19. However, most data refer to the early pandemic waves. Whole year analysis in comparison with prior secular trends are scarce.

Methods. We present the 2020 REMER Madrid KRT registry, corresponding to the Spanish Region hardest hit by COVID-19.

Results. In 2020, KRT incidence decreased 12% versus 2019 while KRT prevalence decreased (-1.75%) for the first time since records began and the number of kidney transplants (KT) decreased by 16%. Mortality on KRT was 10.2% (34% higher than the mean for 2008-2019). The 2019 to 2020 increase in mortality was larger for KT (+68%) than for HD (+24%) or PD (+38%). The most common cause of death was infection (n=419, 48% of deaths), followed by cardiovascular (200, 23%). Deaths from infection increased by 167% year over year and accounted for 95% of excess deaths in 2020 over 2019. COVID-19 was the most common cause of death (68% of infection deaths, 33% of total deaths). The bulk of COVID-19 deaths (209/285, 73%) occurred during the first COVID-19 wave, which roughly accounted for the increased mortality in 2020. Being a KT recipient was an independent risk factor for COVID-19 death.

Conclusions. COVID-19 negatively impacted the incidence and prevalence of KRT, but the increase in KRT deaths was localized to the first wave of the pandemic. The increased annual mortality argues against COVID-19 accelerating death of patients with short life expectancy and the temporal pattern of COVID-19 mortality suggests that appropriate healthcare may improve outcomes.

Keywords: chronic kidney disease, COVID-19, hemodialysis, kidney replacement therapy, kidney transplantation, mortality, peritoneal dialysis

KEY LEARNING POINTS

What is already known about this subject?

- Kidney replacement therapy (KRT) confers the highest risk of death from COVID-19.
- However, most data refer to the early pandemic waves.
- There is scarce information on whole year analysis of the impact of COVID-19 on the epidemiology and mortality of patients on KRT in comparison with prior secular trends.

What this study adds?

- In a large regional registry, COVID-19 was the most frequent cause of death among KRT patients in 2020 and changed the epidemiology of KRT, resulting in a decreased incidence and prevalence of KRT and in an increased all-cause mortality
- However, most COVID-19 deaths in KRT patients occurred during the first pandemic wave, in which the healthcare system collapsed. The first COVID-19 wave roughly accounted for the excess mortality of KRT patients observed in the whole of 2020
- Even in the absence of vaccine, the number of COVID-19 deaths decreased in subsequent pandemic waves. However, the lack of a subsequent decrease in mortality during the ensuing 7 months suggests that COVID-19 did not replace other causes of death in fragile patients with short life expectancy.

What impact this may have on practice or policy?

- Although multiple reports have stressed the high mortality of COVID-19 in KRT patients, most data reflect the first pandemic wave, and this dismal outcome may not apply when the healthcare system is working properly, the population has had contact with SARS-CoV-2 or the SARS-CoV-2 strain evolves
- Thus, these very high mortality rates early in the pandemic should not be used to deny life-saving care to KRT patients in future waves and continuous monitoring of the risk of death of KRT patients and appropriate update of textbooks in this regard is necessary

Patients with chronic kidney disease (CKD) represent the highest number of persons at increased risk of death from coronavirus disease 2019 (COVID-19) worldwide, as well as the population at highest risk of COVID-19 death (1-3). Specifically, patients on kidney replacement therapy (KRT) by dialysis or kidney transplantation (KT) are the subgroups of patients at highest risk of death from COVID-19 (1, 2). However, these data represent the situation in the early waves of the pandemic, in which face masks were in short supply and national health authorities recommended against their use, access to personal protective equipment (PPE) was limited, healthcare systems were frequently overwhelmed by severe COVID-19 cases and access to intensive care unit (ICU) care was restricted, potentially toxic and ineffective therapies were administered, and vaccines were not available (4-6). The region of Madrid was at the epicenter of the COVID-19 pandemic in Spain from early March 2020 and the collapse of Madrid healthcare drove the decision for a national strict lockdown on March 14, 2020 (7-9). High mortality rates were reported from Madrid hospitals among KRT patients and there was a gradient in COVID-19 cases among KRT patients that radiated from Madrid to the periphery of the country (9-12). During 2020, the initial catastrophic first wave was followed by a second wave and eventually by a third wave, that built up from the reopening of the economy. In these waves, the number of diagnosed COVID-19 cases was higher than in the first wave, but healthcare facilities were not overwhelmed, the therapeutic approach to severe COVID-19 had improved, PPE were widely available and face masks were recommended by health authorities and were mandatory in some circumstances. We now report on the impact of the COVID-19 pandemic on the incidence, prevalence, and mortality of KRT patients using data from the Madrid **RE**gistro **M**adrileño de **E**nfermos **R**enales (REMER) KRT Regional Registry in 2020 as compared to 2019 and prior years since its creation and assess the impact of the successive pandemic waves on mortality. As Spain is one of the countries with highest life expectancy in the general population and with the highest prevalence of KT recipients among patients on KRT (13,14), information from the Spanish regions hardest hit by COVID-19 may offer insight into the interaction of COVID-19 with KRT over time during the pandemic.

MATERIALS AND METHODS

REgistro Madrileño de Enfermos Renales (REMER)

REMER is the Regional Registry of patients on KRT of the Autonomous Community of Madrid, in Spain. REMER was created on 23 September 2008 by Order 685/2008 of the Consejería de Sanidad (Regional Ministry of Health) of the Regional Government (15). All centers caring for KRT patients must enter data into REMER. These data are used to generate a publicly available annual report and are submitted to the Registro Español de Enfermos Renales (REER, Spanish Registry of Kidney Patients) and to the European Renal Association (ERA) Registry (14-18).

New or incident cases are patients that start KRT for the first time due to stage 5 CKD, including hemodialysis, peritoneal dialysis (PD), or preemptive kidney transplantation (KT), i.e. KT recipients not on hemodialysis or PD, independently of the duration of KRT. This time criterion differs from criteria used by the European Renal Association (ERA: at least 90 days on KRT) and the Spanish Registry of Kidney patients (REER: at least 45 days on KRT) (14), which should be considered when comparing incidence and mortality parameters, since most exits within the first 45 or 90 days of KRT are due to death, while recovery of kidney function is unusual. Only patients residing in the Madrid Region are included. Prevalent cases are patients that receive KRT (hemodialysis, PD or are KT recipients) as of December 31 of the year. For the prevalence analysis, KT recipients included all patients who had a functioning kidney graft on December 31.

Registry data are provided by healthcare professionals and, for KT data, by the Regional Transplant Organization (ORCT), and are then verified. Mortality data are crossed with mortality databases annually, in collaboration with the General Directorate of Public Health, allowing the capture and confirmation of mortality events occurring outside the Healthcare System. COVID-19 as a cause of death was assigned according to the General Directorate of Public Health database, i.e. to official government figures. These were derived from death certificates in which the cause of death was assigned to COVID-19 if there was a positive PCR test for SARS-CoV-2 at admission and the clinical manifestations were compatible with COVID-19 or (especially in the early weeks of the pandemic, in which the availability of PCR testing was limited) if the clinical manifestations were highly suggestive of

COVID-19, such a bilateral pneumonia without other infectious agent identified and associated with new onset lymphopenia.

Data analysis and statistics

For data analysis, the REMER database was downloaded, underwent recodification and depuration, and was analyzed using SPSS V26©. Population data used to calculate rates were obtained from the Statistics Institute of the Community of Madrid. Rates were expressed per million population (pmp). Tables of Primary Kidney Disease (PKD) and mortality used the codes and groups of the ERA Registry (16,19).

Epidemiological weeks are according to Instituto de Salud Carlos III (8,20). The first epidemiological week of 2020 ended on January 5, 2020. During 2020, the Spanish Public Health Institute defined three pandemic waves: first wave from January 31, 2020 (epidemiological week 5); second wave from July 1, 2020 (epidemiological week 27); third wave from December 1, 2020 (epidemiological week 49) (20). The third wave peaked in the third week of 2021 (21), however, only data until December 31, 2020 were included in the 2020 Registry analysis. Data are expressed as mean±SD or n (%). For multivariate analysis of risk factors for COVID-19 death, we used a multinomial logistic model, using reference categories and 100 iterations maximum, with estimates at 95% CI, with hierarchical in and out of terms, using the following variables: gender, age, KRT at death, KRT vintage and cause of CKD.

Secular trends are presented for incidence and prevalence rates of KRT, annual mortality and main causes of death, and mortality is compared with the mean of all years available from the creation of the Registry (i.e. for the 2008-2019 period). Additionally. a detailed comparison is provided for 2020 and the most recent previous year (2019).

Ethics statement

The ethics committee of IIS-FJD indicated that ethical committee approval was not required for mandatory registries.

RESULTS

Incidence and prevalence of KRT

In 2020, 742 patients started KRT in the Madrid region: 592 of them hemodialysis, 125 PD and 25 underwent preemptive KT (**Table 1**). The largest difference in incidence between 2019 and 2020 was observed during the first wave of the pandemic (March-May 2020) (**Table S1**). The mean age was 64.1±15.8 years and 68.6% were males (**Table S2**). Overall, 15.9% less women and 12.8% less men started KRT in 2020 compared to 2019. The age range most represented among patients starting KRT was 45-64 years and saw a 14.5% decrease in incidence of KRT compared to 2019 (**Table S2**). Nearly 30% of patients starting KRT were over 74-year-old in both years and a decrease in incidence of 13.4% was observed in this age range in 2020 vs 2019.

The 2020 incidence rate was 111.4 pmp, a 12% drop versus 2019 and a return to lower incidence rates not seen since 2008-2012 (**Figure 1.A**). The decrease in incidence rate from 2019 was more noticeable in HD (13.37% decrease) and pre-emptive KT (11.63%) than in PD (6.93%) (**Figure 1.B**).

On 31 December 2020, there were 7.731 prevalent KRT patients in Madrid, 2990 on hemodialysis, 424 on PD and the majority, 4317, were KT (**Table 1**). The mean age was 61.7±15.7 years and 63.8% were males (**Table S3**). 2802 women were on KRT on this date, 2.0% less than in 2019, while the number of men decreased by 2.4% In 2020, 39% of prevalent patients were in the 45-to-64-year-old group and in this group, prevalence decreased by 1.1% (**Table S3**) while prevalence in older groups (aged 65 years or higher) showed the largest decrease (3.6%) when compared to 2019.

The continuous increase in the prevalence rate of KRT observed since 2008 was replaced by a year-on-year decrease of 1.75% in 2020, the first decrease since REMER was created (**Figure 1.C**). The largest decrease in the prevalence rate from 2019 was observed in hemodialysis (3.78%), followed by PD (2.48%) and KT (0.20%) (**Figure 1.D**).

The number of KT performed in 2020 was 359, a 15.7% decrease from the 426 KT performed in 2019 and a 14.1% decrease over the mean of 418±14.8 KT/year performed from 2008 to 2019. Despite the large decrease in the number of KT, the transplant waiting list only increased from 730 in 2019 to 778 in 2020 (6.6%).

Mortality

During 2020, mortality among patients on KRT in Madrid was 10.2%, which was 34% higher than the mean for 2008-2019 of 7.58±0.35% (**Figure 2.A**). The year-on-year percentual increase was larger among KT (68% increase from a mean of 2.92±0.28% to 4.9%, corresponding to an absolute increase of 1.98%) than among HD (24% increase from a mean of 13.51±0.66% to 16.8%, corresponding to an absolute increase of 3.29%) or PD patients (38% increase from a mean of 7.25±1.23% to 10%, corresponding to an absolute increase of 2.75%)(**Figure 2.B, C**).

Overall, during 2020, 875 KRT patients died: 605 hemodialysis patients, 223 KT and 47 PD patients. Of these deaths, 603 (69%) occurred in men. The mean age at death was 73.9±11.1 years vs 74.9±11.1 years in 2019 (p ns). **Figure 3.A** and **3.B** show the age and sex pyramid for prevalent KRT patients in 2020 and for KRT patients that died in 2020. The number of deaths increased with age, being more conspicuous above the age of 55 years in men and of 60 years in women. Indeed, 2020 mortality surpassed 20% in men and women over the age of 80 years and 30% above the age of 90 years (**Figure 3.C**).

Causes of death are presented in **table 2**. The most common cause of death in 2020 was infection, accounting for 419 (48% of deaths), followed by cardiovascular which accounted for 200 (23%) deaths. In 2019, there were 557 deaths, and the most common cause of death was cardiovascular, accounting for 193 (35%) deaths, followed by infection which accounted for 157 (28%) deaths. Thus, deaths from infection increased by 167% year over year and accounted for 95% of excess deaths in 2020 over those of 2019, while deaths from cardiovascular disease remained stable. **Figure 4** shows the main causes of death over the years.

In 2020, infection was the most common cause of death among hemodialysis patients (46%), KT recipients (55%) and PD patients (47%). By contrast, in 2019, infection was the cause of death in 28% of hemodialysis patients, 29% of KT recipients and 26% of PD patients.

COVID-19 mortality

Overall, COVID-19 was the cause of death in 285 patients (**Table 2**), representing the most common cause of death in KRT patients in 2020, 68% of infection deaths and 33% of total deaths. Of COVID-19 deaths, 194 (68%) occurred in men. The mean age at death was 74.3±10.5 years, compared to

73.6±11.3 years for non-COVID-19-related deaths. (p=0.387). The number of COVID-19 deaths peaked among 80- to 85-year-old males and 70- to 75-year-old females (**Figure 3.D**). COVID-19 mortality expressed as percentage of prevalent KRT patients increased progressively with age, and above the age of 80 years, 10 % or more of prevalent KRT patients died from COVID-19 (**Figure 3.E**). However, in relative terms with respect to all deaths, COVID-19 represented 20-40% of all deaths in most age groups above the age of 40 years, without large differences between groups (**Figure 3.F**).

The bulk of COVID-19 deaths (209/285, 73%) occurred during the first COVID-19 wave, in epidemiological weeks 11 to 21, corresponding to March 9 through May 24, 2020 (**Figure 5.A-C**). This number roughly accounted for the increased mortality in 2020 over the mean mortality for the preceding decade. In fact, 156/285 (55%) COVID-19 deaths occurred within a 4-week period in the first wave, from March 16 through April 11, 2020. The first wave differed from subsequent waves in that women represented 37% of COVID-19 deaths, as opposed to 20% over the second and third waves (p=0.0078 chi square)(**Figure 5.D**). Additionally, patients who died from COVID-19 in the first wave were older than those who died from COVID-19 during the second and third waves (75.2±9.7 vs 71.8±12.1 years old respectively; p=0.015) and there was a steeper gradient in the contribution of increasing age categories to the overall number of COVID-19 deaths: in the first wave, 14% of COVID-19 deaths occurred in 45- to 64-year-olds and 54 % of COVID-19 deaths occurred in those older than 74 years while in subsequent waves, the corresponding numbers were 24% and 43%, respectively (**Figure 5.E**).

Overall, 185 (65%) of COVID-19 deaths occurred in hemodialysis patients, 88 (31%) in KT and 12 (4%) in PD patients and there were no significant differences in the distribution of COVID-19 deaths among KRT modalities between the first and subsequent waves (p=0.853, not shown). However, in weeks in which COVID-19 deaths were persistently occurring (i.e. weeks 11 to 22 in the first wave and weeks 35-53 of the second and third wave), a shift was observed in the contribution of COVID-19 deaths to overall mortality within each KRT modality. Thus, in the first wave, COVID-19 deaths contributed 63% to 65% of all deaths for those weeks among hemodialysis and KT recipients, while during the second and third waves, COVID-19 caused 25% of all hemodialysis deaths for the period, while it caused over 40% of all KT deaths for the period (**Figure 6**). Six percent of patients on HD, 3% of patients on PD and 3% of KT patients died in 2020 due to COVID-19.

The impact of COVID-19 was heterogeneous across healthcare catchment areas, as COVID-19 represented from 11% to 44% of KRT deaths in different health areas (**Suppl figure 1**).

In multivariate analysis, only being on PD or hemodialysis were independent factors for a lower risk of COVID-19 death, as compared to being a KT recipient (**Table 3**). The lack of association between older age and risk of death is striking and may be explained in part by the younger age of KT recipients.

DISCUSSION

The main findings of the present study are that COVID-19 led to an unprecedented increase in mortality in KRT patients, that occurred mostly during the first wave, a period characterized by a collapsed healthcare system that accounted for most of the full year excess mortality. COVID-19 thus had a significant negative impact on the epidemiology of KRT leading to a decreased incidence and prevalence of KRT. Thus, although most publications on COVID-19 and KRT refer to this early period of the pandemic, it may not be representative of the later impact of COVID-19 on KRT patients, even in the absence of vaccines, as vaccination did not start in Spain until the last days of December 2020. In this regard, dialysis and, mainly hemodialysis patients appear to have been very hard hit during the first wave. Inability to shield and rejection for advanced life-saving care may have contributed to this high impact on mortality. This is relevant to prevent future rejection of dialysis patients from advanced life support based on the outcomes observed early in the COVID-19 pandemic. Finally, the fact that the excess mortality during the first pandemic wave was not associated to a subsequent decrease in mortality during the rest of the year suggests that, contrary to some speculation, the impact of COVID-19 in a setting of a collapsed healthcare system was severe and not limited to replacing other causes of death or accelerating the death of fragile patients with short (i.e. a few months) life expectancy.

During 2020, both the incidence and prevalence of KRT decreased in Madrid. Indeed, the prevalence decreased for the first time since records began. Several factors could have contributed to this decrease. Madrid was one the hardest and earliest hit regions in Europe, after Northern Italy, and the national health authorities had not predicted, nor prepared for the pandemic. It was the only Spanish region that exceeded a COVID-19 hospitalization rate over 7 days of 150 persons per 100.000, doubling that of Catalonia (22). On March 8, 2020, during epidemiological week 10, the national Government had promoted a large demonstration in Madrid that was mainly attended by women, but by the end of the week, on March 14, 2020, a hard confinement was decreed in which citizens were forbidden to leave home except to buy food and few other exceptions, as the number of COVID-19 cases sky-rocketed and the healthcare system collapsed (7,23). Triaging became necessary for hospital or ICU admission. At one

point, 90% of inpatients in large hospitals were COVID-19 patients. Nephrologists became COVID-19 specialists. Thus, a combination of a high mortality among prospective KRT patients and strained healthcare resources may have contributed to the decreased incidence of KRT, the decreased number of KT performed and the lower-than-expected growth of the KT waiting list, while both the decreased KRT incidence and the record-breaking mortality on KRT contributed to the decreased prevalence of KRT. However, our data suggest that the healthcare system was able to adequately care for KRT patients in the subsequent COVID-19 waves, which resulted in a larger number of population-wide COVID-19 cases, as the first wave accounted for most of the excess mortality in the year. Thus, we suggest that to correctly assess the impact of COVID-19 on KRT patients, the widely published and cited outcomes observed during the first COVID-19 wave (2) should be updated, and research should focus on outcomes during subsequent COVID-19 waves, both in the absence of available vaccine, as the present report, or in the vaccine era, as the collapse of the healthcare system was a confusion factor regarding the true impact of COVID-19 in a well-functioning healthcare system. Thus, although most publications on COVID-19 and KRT refer to the early phase of the pandemic, this phase may not be representative of the current impact of the disease on KRT patients, especially dialysis patients, when the healthcare system is performing as usual and not under unprecedented stress. Research should focus on current impact of COVID-19 on patients on different KRT modalities. Overall, the risk of death from COVID-19 was higher for KT recipients. However, an analysis of the timeline of the pandemic suggests that the increased risk of death for KT recipients persisted over time while the risk for dialysis patients decreased. This decreased risk in dialysis patients during subsequent waves was potentially related to better control of risk factors for infection (from masking to avoidance of risk exposures), as well as to the wider availability of ICU care or evolving SARS-CoV-2 strains (5,6). Thus, KT recipients became the KRT population of highest concern already in the pre-vaccine era, and, unfortunately, reports on vaccine effectiveness on KT recipients are not promising, at least for current vaccines and dosing schedules (24,25).

It is also noteworthy that the excess mortality during the first pandemic wave translated into an overall excess mortality for KRT patients over the year. The lack of a subsequent decrease in mortality during the ensuing 7 months suggests that COVID-19 did not replace other causes of death in fragile patients with short (i.e. months) life expectancy. Rather, a higher-than-expected mortality was observed during the first wave in patients that may otherwise have survived at least into the next year, as was the case in prior years. A potential impact of triaging for access to ICU care should be acknowledged. The

challenge now is to prevent that this high mortality in a context of a collapsed healthcare system will in the future translate into recommendations to limit access to ICU care or KRT patients based on their high risk of death when ICU care may have not been provided as needed or when more modern tools to treat COVID-19 were not available. While we cannot exclude the contribution of other factors to explain the very high mortality of the first wave compared to later waves (e.g. changes in the viral genome, decrease in inoculum size due to widespread use of masks, reinfection of hosts who had had prior contact with SARS-CoV-2 or others), the war-like conditions of healthcare in this first wave would be expected to have contributed to the high mortality.

A striking observation is the higher impact of the first wave on COVID-19 deaths in women as compared to subsequent COVID-19 waves. Potential reasons may include the epidemiological situation, as on epidemiological week 10, large women demonstrations were held and there was an overrepresentation of women among COVID-19 cases nationally, or a negative bias towards women accessing ICU care, among other potential reasons that should be further analyzed. Thus, during the first wave in Spain, women represented 58% of COVID-19 cases, while from June 22, 2020 onwards they represented 51% of cases, which is in line with women representing 51% of the Spanish population (22) Both the epidemiological situation regarding gender at the time and any impact of gender on triaging would be external to the actual impact of COVID-19 on the outcomes of infected KRT women. Thus, the negative impact of the first wave on KRT women outcomes should not be considered into subsequent decision algorithms, especially in those related to triaging.

During the first COVID-19 wave in Spain, median age at death was 83 (75-89) years which was 9 years older than in Madrid KRT patients, further supporting the increased risk of death among KRT patients (26).

Large differences on the impact of COVID-19 on mortality were observed between different healthcare catchments area. This merits further study to understand the underlying causes that may range from the differential impact of the pandemic on different locations of the Madrid region to socioeconomic factors to the age pyramid to epidemic bouts in dialysis facilities or other factors.

Some limitations should be acknowledged, inherent to the observational and Registry-based nature of the report. However, this is compensated by the compulsory nature of the Registry, that has been curated and linked to other administrative databases and spans all KRT patients in Madrid. Furthermore, it provides an expanded view of the impact of COVID-19 in Madrid, a region that provided

key contributions to the literature on COVID-19 and KRT mainly originating on the first wave, given that it was among the first major cities or regions overwhelmed by COVID-19 (10,12,27-32). In this regard, the current report represents a full-year update that puts these early reports into perspective. As additional limitations, this study did not include the full impact from the third wave because it started on December of 2020 and extended into 2021 and it did not formally assess the impact of COVID-19 on life expectancy or the impact of specific measures of healthcare (e.g. access to hospital or ICU beds) on outcomes. Finally, the case definition evolved during the pandemic due to limitations in the access to diagnostic tests in the first weeks of the pandemic.

In conclusion, COVID-19 negatively impacted incidence and prevalence of KRT, but the increase in KRT deaths was localized to the first wave of the pandemic, in which healthcare collapsed. The increased annual mortality and the wide distribution of COVID-19 deaths across age groups argues against COVID-19 accelerating death of patients with short (a few months) life expectancy and the temporal pattern suggests that appropriate healthcare may improve outcomes.

CONFLICT OF INTEREST STATEMENT

AO 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. AO was the Editor-in-Chief for CKJ up to May 2022.

AUTHORS' CONTRIBUTIONS

All authors provided data and critically read and approved the last version of the manuscript. MIAM curated the data, performed the statistical analysis and provided initial tables and figures, AO and SC wrote the first draft and the manuscript and figures.

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APPENDIX

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Table 1. Incidence and prevalence of KRT in 2019 and 2020. Prevalence refers to 31 December of the year.

	Incidence		Prevalence	
	2019	2020	2019	2020
Total KRT (n)	861	742	7907	7731
HD	695	592	3123	2990
DP	137	125	437	424
KT	29	25	2674	4317
Age (years),	64.0±16.3	64.1±15.8	61.9±15.7	61.7±15.7
Male (n, (%))	584 (67.8)	509 (68.6)	5048 (63.8)	4929 (63.7)
Deaths (n)	-	-	651	875

Age presented as mean ±SD

Table 2. Causes of death in KRT patients in the Region of Madrid in 2020, by type of KRT modality and ERA cause of death groups. Results shown as number of patients. All other causes and also broken down into cardiovascular, suicide, refusal of treatment, withdrawal, cachexia, malignancy, miscellaneous, unknown.

Cause of death		PD		HD		KT		Total
		Male	Female	Male	Female	Male	Female	
COVID-19	**2019**	0	0	0	0	0	0	0
	2020	9	3	129	56	56	32	285
Other infections	**2019**	3	4	92	47	35	15	196
	2020	5	4	59	32	23	11	134
All other causes	**2019**	14	5	234	101	64	37	455
	2020	19	7	240	89	63	38	456
Cardiovascular*	2019	8	3	108	39	18	14	190
	2020	8	4	97	45	28	18	200
Suicide, refusal of treatment	2019	1	0	5	5	1	5	12
	2020	0	0	4	2	1	0	7
Withdrawal	2019	1	0	30	19	0	2	52
	2020	1	1	38	13	0	0	53
Cachexia	2019	1	0	4	1	1	2	9
	2020	0	1	5	3	0	1	10
Malignancy	2019	2	2	30	8	26	6	
	2020	7	1	42	15	22	12	99
Miscellaneous	2019	1	0	57	27	14	12	111
	2020	3	0	49	10	8	6	76
Unknown	2019	0	0	0	2	4	1	7
	2020	0	0	5	1	4	1	11

* Ischemic heart disease, heart failure, cardiac arrest, stroke

Table 3. Risk factors for COVID-19 death

	Total deaths (n)	COVID-19 deaths (n)	Univariant (X^2_{M-H}) OR	95% CI	p	Multivariant (rlog) OR	95% CI	p
Gender								
Woman (Ref.)	272	91	1			1		
Man	603	194	1.06	0.78-1.44	0.708	1.08	0.79-1.48	0.632
Age								
0-44 y (Ref.)	10	1	1			1		
45-64 y	153	48	4.11	0.51-33.39	0.155	4.30	0.52-35.29	0.175
64-74 y	263	90	4.68	0.58-37.53	0.112	5.12	0.63-41.61	0.126
>74 y	449	146	4.34	0.54-34.55	0.132	4.83	0.60-39.07	0.140
KRT at Death								
KT (Ref.)	223	88	1			1		
PD	47	12	0.53	0.26-1.07	0.073	0.45	0.21-0.95	**0.036**
HD	605	185	0.68	0.49-0.93	**0.016**	0.59	0.41--0.86	**0.006**
KRT vintage								
0-1 y (Ref.)	199	54	1			1		
2-4 y	237	87	1.56	1.03-2.35	0.033	1.45	0.96-2.20	0.076
5-9 y	212	71	1.35	0.89-2.06	0.162	1.14	0.73-1.77	0.572
10-14 y	84	30	1.49	0.87-2.57	0.150	1.14	0.64-2.03	0.666
>14 y	143	43	1.16	0.72-1.86	0.553	0.75	0.43-1.29	0.291
Cause of CKD								
Other (Ref.)	330	104	1			1		
Diabetes mellitus	273	87	4.65	3.29-6.56	**0.000**	1.05	0.73-1.50	0.803
Vascular	142	43	0.94	0.62-1.45	0.791	0.95	0.61-1.49	0.837
GN	130	51	1.40	0.92-2.14	0.115	1.51	0.97-2.35	0.066

GN: glomerulonephritis

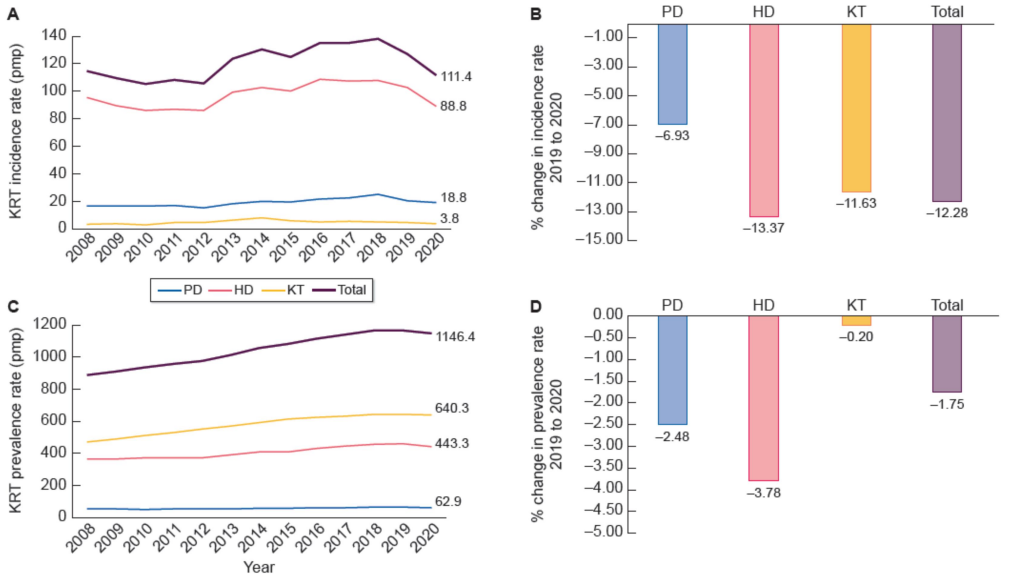

Figure 1. Incidence and prevalence rates of KRT in the Madrid region. A) Incidence rate of KRT in pmp over the years since the creation of REMER. Numbers shown in labels correspond to 2020 data. **B)** Percentual change in incidence rate of KRT and different modalities of KRT from 2019 to 2020. **C)** Prevalence rate of KRT in pmp over the years since the creation of REMER. Numbers shown in labels correspond to 2020 data. **D)** Percentual change in prevalence rate of KRT and different modalities of KRT from 2019 to 2020. PD: peritoneal dialysis, HD: hemodialysis, KT: kidney transplantation.

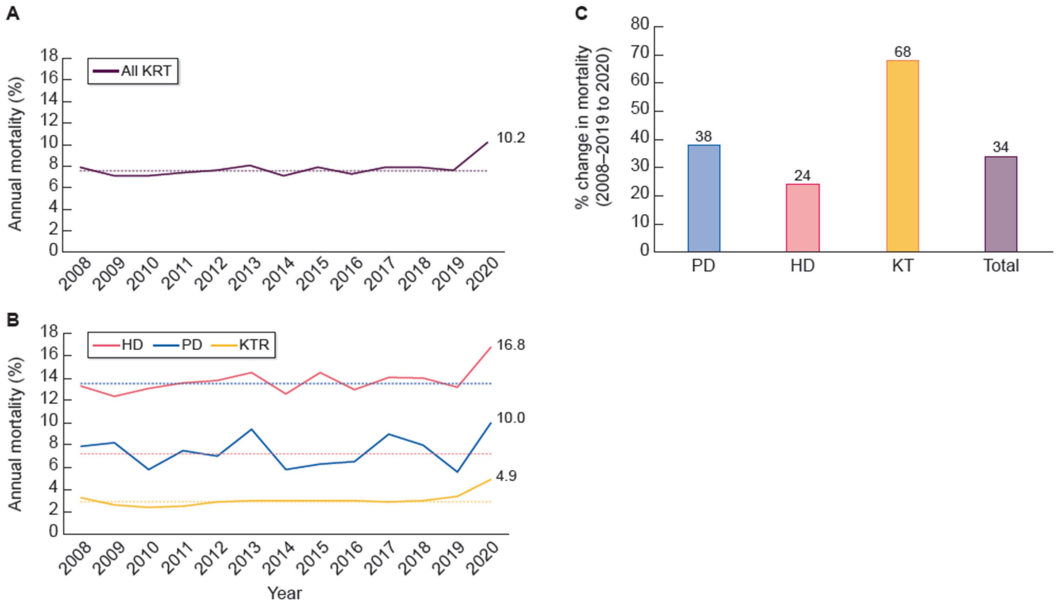

Figure 2. Annual mortality of KRT patients in the Madrid region over time. A) Annual mortality over the years since the creation of REMER for all modalities of KRT combined expressed as % of the KRT population. Numbers shown in labels correspond to 2020 data. **B)** Annual mortality over the years since the creation of REMER for specific modalities of KRT expressed in % of each KRT population. Numbers shown in labels correspond to 2020 data. **C)** Percentual change in mortality from 2019 to 2020 for each KRT modality and for all KRT. PD: peritoneal dialysis, HD: hemodialysis, KT: kidney transplantation.

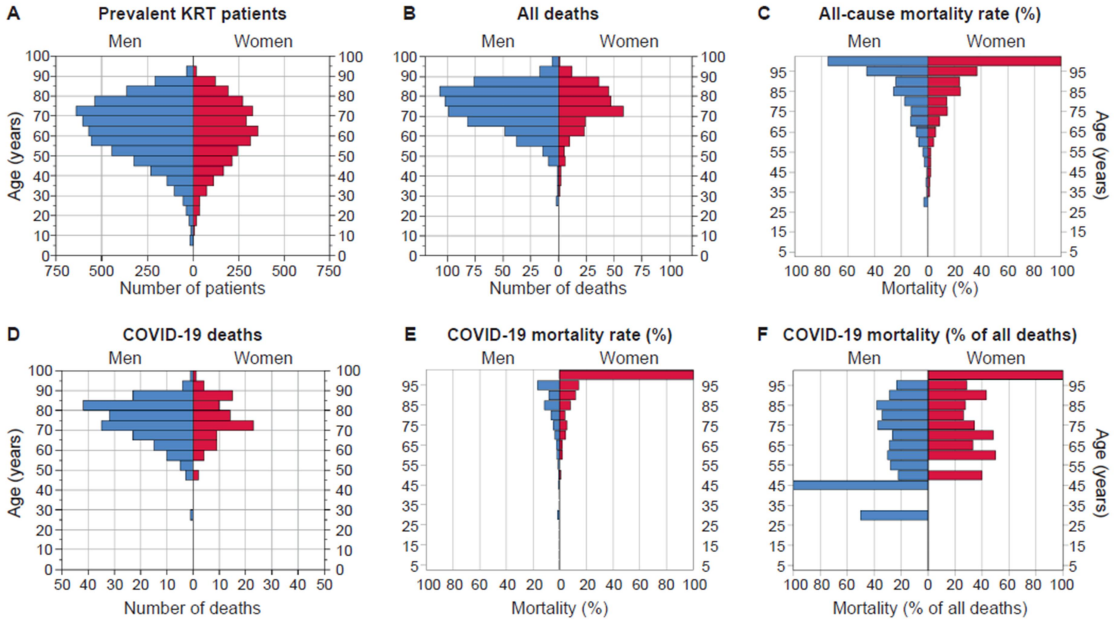

Figure 3. Age and sex distribution of prevalent patients on KRT, total deaths and COVID-19 deaths in 2020 in the Madrid region. A) Age pyramid for the prevalent KRT population in 2020. **B)** Age pyramid for KRT patients who died in 2020. **C)** Age pyramid for all-cause mortality expressed as % of KRT patients in each age group who died in 2020 from any cause. **D)** Age pyramid for KRT patients who died from COVID-19 in 2020. **E)** Age pyramid for mortality from COVID-19 expressed as % of patients in each age that died from COVID-19. **F)** Age pyramid for COVID-19 mortality expressed as % of all deaths within each age group. Note that the scale and units for the horizontal axis differs for the different panels.

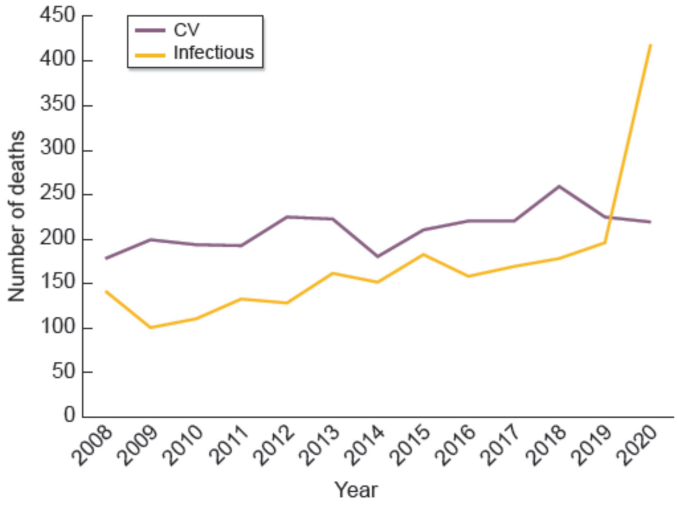

Figure 4. Main causes of death of KRT patients in the Madrid region over the years. The number of cardiovascular (CV) disease and infection deaths are shown. Cardiovascular (CV) deaths include cardiac, vascular and sudden death.

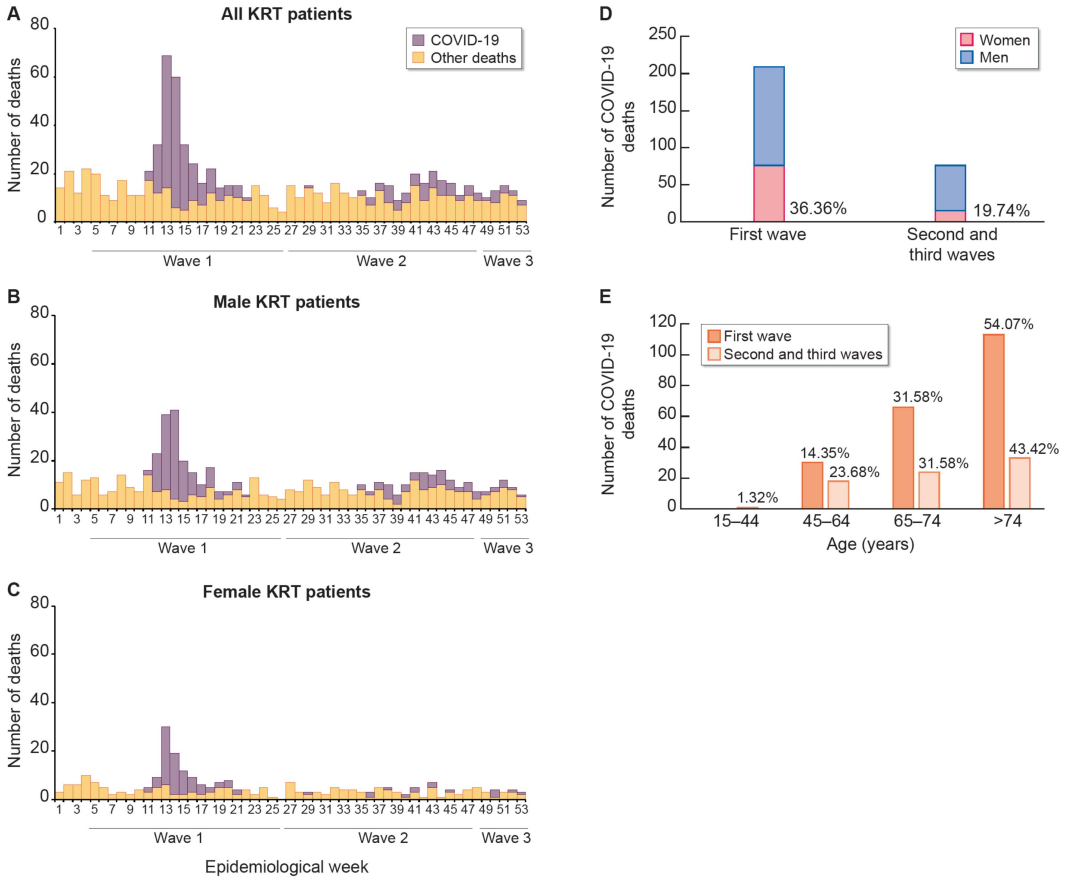

Figure 5. Timeline of COVID-19 and non-COVID-19 deaths among KRT patients in the Madrid region over 2020. A) All COVID-19 (red) and non-COVID-19 (blue) deaths. **B)** Male deaths. **C)** Female deaths. **D)** Number of COVID-19 deaths for male and female KRT patients in the first wave as compared with the second and third waves. Numbers in labels represents % of females in each time window. **E)** Number of COVID-19 deaths among KRT patients in different age categories in the first wave as compared with the second and third waves. Numbers in labels represents the % contribution of each age category to the 100% of COVID-19 deaths in each time window (first wave vs second and third waves). Epidemiological week 11 was 9 to 15 March 2020

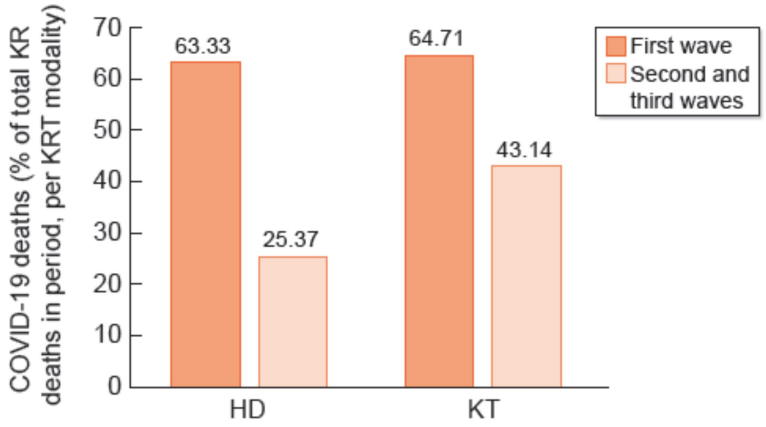

Figure 6. Contribution of COVID-19 deaths to total deaths in the first (weeks 11 to 22) and second and third waves (weeks 35-53) of the pandemic. Results expressed as % of total deaths that were COVID-19 deaths. A single COVID-19 death occurred outside the period shown. The 12 PD deaths are not represented, but the pattern was similar than for hemodialysis (HD), and the contribution of COVID-19 to total PD deaths decreased from 55.56% in the first wave to 18.18% in subsequent waves.