Nephrol Dial Transplant, 2023, **38**, 2607–2616
https://doi.org/10.1093/ndt/gfad151
Advance access publication date: 11 July 2023

Results of the first nationwide cohort study of outcomes in dialysis and kidney transplant patients before and after vaccination for COVID-19

Julia Wijkström[1,2], Aurora Caldinelli[1,3], Annette Bruchfeld[1,4], Alexandra Nowak[1,2], Angelica Artborg[1,2], Maria Stendahl[5,6], Mårten Segelmark[6,7,8], Bengt Lindholm[1], Rino Bellocco[3,9], Helena Rydell[1,2,6] and Marie Evans[1,2,6]

[1]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden
[2]Department of Renal Medicine, Karolinska University Hospital, Stockholm, Sweden
[3]University of Milano-Bicocca, Department of Statistics and Quantitative Methods, Milano, Italy
[4]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden
[5]Department of Internal Medicine, Ryhov Hospital, Jönköping, Sweden
[6]Swedish Renal Register, Jönköping, Sweden
[7]Department of Clinical Sciences, Lund University, Lund, Sweden
[8]Department of Endocrinology, Nephrology and Rheumatology, Skane University Hospital, Lund, Sweden
[9]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
Correspondence to: Julia Wijkström; E-mail: Julia.Wijkstrom@ki.se, Marie Evans; E-mail: Marie.Evans@ki.se

ABSTRACT

Background. Patients on kidney replacement therapy (KRT) have been identified as a vulnerable group during the coronavirus disease 2019 (COVID-19) pandemic. This study reports the outcomes of COVID-19 in KRT patients in Sweden, a country where patients on KRT were prioritized early in the vaccination campaign.

Methods. Patients on KRT between January 2019 and December 2021 in the Swedish Renal Registry were included. Data were linked to national healthcare registries. The primary outcome was monthly all-cause mortality over 3 years of follow-up. The secondary outcomes were monthly COVID-19-related deaths and hospitalizations. The results were compared with the general population using standardized mortality ratios. The difference in risk for COVID-19-related outcomes between dialysis and kidney transplant recipients (KTRs) was assessed in multivariable logistic regression models before and after vaccinations started.

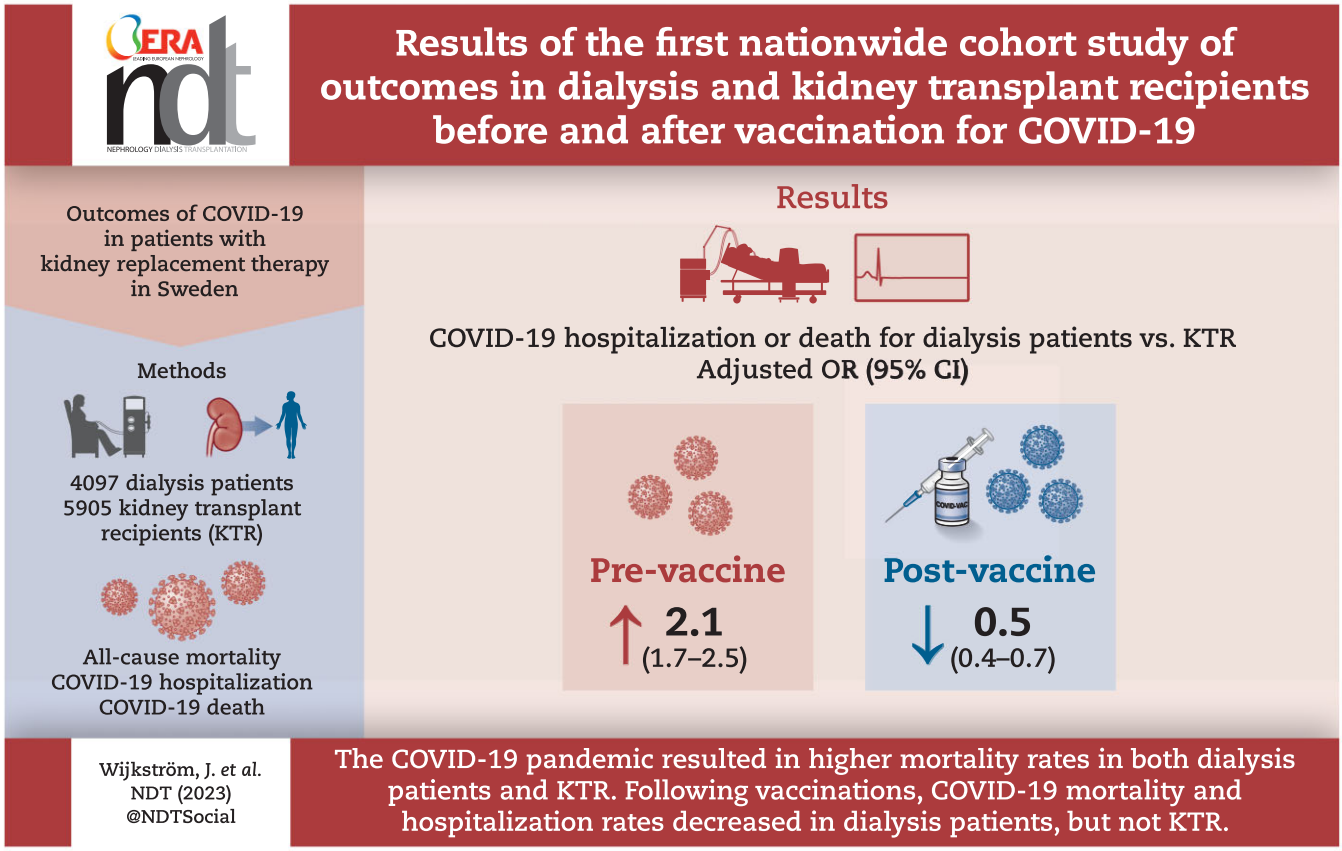
Results. On 1 January 2020, there were 4097 patients on dialysis (median age 70 years) and 5905 KTRs (median age 58 years). Between March 2020 and February 2021, mean all-cause mortality rates increased by 10% (from 720 to 804 deaths) and 22% (from 158 to 206 deaths) in dialysis and KTRs, respectively, compared with the same period in 2019. After vaccinations started, all-cause mortality rates during the third wave (April 2021) returned to pre-COVID-19 mortality rates among dialysis patients, while mortality rates remained increased among transplant recipients. Dialysis patients had a higher risk for COVID-19 hospitalizations and death before vaccinations started {adjusted odds ratio [aOR] 2.1 [95% confidence interval (CI) 1.7–2.5]} but a lower risk after vaccination [aOR 0.5 (95% CI 0.4–0.7)] compared with KTRs.

Conclusions. The COVID-19 pandemic in Sweden resulted in increased mortality and hospitalization rates among KRT patients. After vaccinations started, a distinct reduction in hospitalization and mortality rates was observed among dialysis patients, but not in KTRs. Early and prioritized vaccinations of KRT patients in Sweden probably saved many lives.

Keywords: COVID-19, hospitalization, mortality, observational study, renal replacement therapy

Received: January 27, 2023; Editorial decision: May 15, 2023

GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Dialysis patients and kidney transplant recipients have been identified as vulnerable groups for severe COVID-19.
- Nationwide reports of outcomes in dialysis patients and KTRs before and after vaccination for COVID-19 have been lacking.

This study adds:

- Mortality increased by 10% in dialysis patients and 22% in KTRs during the COVID-19 pandemic's first year.
- After vaccinations for severe acute respiratory syndrome coronavirus 2 started, all-cause mortality rates among dialysis patients rapidly decreased to pre-pandemic levels, while no immediate decline was seen in KTRs.
- During the 9 months following vaccination initiation, KTRs had a higher risk of COVID-19-related hospitalization and death compared with dialysis patients.
- Compared with the general population, the age and sex standardized mortality ratio for 2019–2021 remained stable for dialysis patients but increased for KTRs.

Potential impact:

- The study results indicate that early and prioritized vaccination of dialysis patients probably saved many lives in Sweden.
- The delayed response following vaccination in KTRs indicates that this group should be prioritized and followed up closely after new vaccinations.
- Our results could help guide future healthcare planning if new virulent COVID-19 strains emerge.

INTRODUCTION

Patients on kidney replacement therapy (KRT) have been identified as a risk group for severe infection and mortality due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19) [1–3]. Sweden' s first confirmed COVID-19 case was reported on 31 January 2020 [4], with the first wave of COVID-19 hospitalizations peaking in April 2020, followed by the second wave peaking in December 2020–January 2021 and the third wave in April 2021 (Fig. 1) [5].

At the beginning of the pandemic, Sweden's government and health authorities had a different mitigation approach regarding transmission of COVID-19 as compared with other countries in Europe and did not comply with the recommendations from the World Health Organization and the European Centre for Disease Prevention and Control. Whereas the neighbouring countries closed schools and workplaces, the Swedish policy was to rely mostly on recommendations and voluntary restrictions to reduce transmission of the virus. There was no strict 'lockdown' and

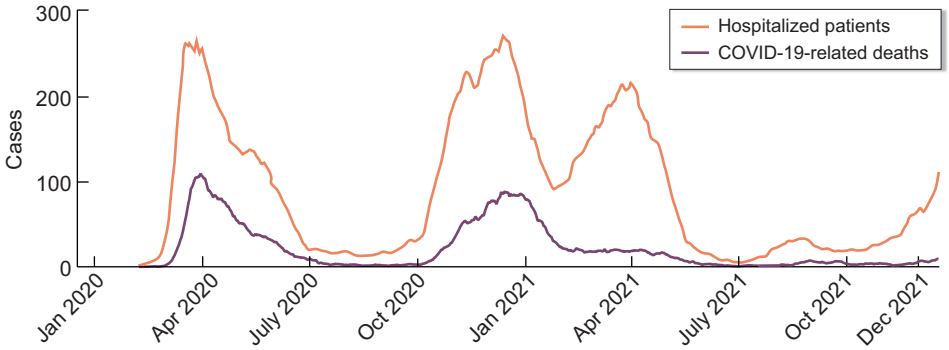


Figure 1: Incidence of new COVID-19 hospitalizations (grey dotted line) and COVID-19-related deaths (black line) in Sweden from January 2020 to December 2022. Lines show the 7-day moving average. First COVID-19 wave peak is seen in April 2020, second wave peak in December 2020–January 2021 and third wave peak in April 2020. From data available at the Swedish National Board of Health and Welfare [5].

public transportation, restaurants, day care centres and primary schools remained open [6]. However, distance learning for university and high school students was introduced and many Swedes followed the recommendations of working from home and avoiding contact with people from outside the household. Recommendations regarding the use of facemasks were introduced at the end of 2020.

The vaccination campaign started in Sweden in January 2021 and initially octogenarians and people in nursing homes were prioritized. Due to the high mortality rates among individuals with advanced chronic kidney disease observed early in the pandemic, dialysis patients were among the first risk groups to be vaccinated in Sweden (March 2021), followed shortly thereafter by organ transplant patients. For both groups, messenger RNA (mRNA) vaccines (BioNTech/Pfizer BNT162b2 or Moderna mRNA-1273) were used, given in two doses 4 weeks apart. Generally, dialysis patients were vaccinated at their dialysis unit and transplanted patients in an outpatient setting. In September 2021, a third dose of vaccine was recommended for both groups.

This study describes the evolution of all-cause mortality rates, COVID-19-related mortality and hospitalization rates in patients on KRT, with dialysis patients and kidney transplant recipients (KTRs) analysed separately over the first 2 years of the pandemic in Sweden (2020–2021) in the relation to the year before (2019). We also investigated how mortality and hospitalization rates for COVID-19 changed before and after the vaccination campaign and compare the mortality among KRT patients with the general Swedish population.

MATERIALS AND METHODS

Study population and setting

In our analyses, we included patients from the Swedish Renal Register (SRR) who were on KRT [dialysis (haemodialysis or peritoneal dialysis) or with kidney transplant] on 1 January 2019 or initiated KRT during follow-up (until 30 November 2021). Patients were followed until 31 December 2021 or death, whichever came first. To describe the overall cohort characteristics, we used a cross-sectional sample of the cohort who were alive on KRT on 1 January 2020, ≈1–2 months before the COVID-19 pandemic started.

In order to continuously reflect the population at risk, we used a time-updated analysis for our description of KRT and general population mortality. At the start of each month, KRT was updated with data from the SRR and the patients were classified as being on dialysis or with a working kidney transplant. For simplicity, patients remained in their assigned modality until the end of each month. For the comparison of outcomes before and after vaccination in dialysis and KTRs we instead used two cohorts: all patients alive on KRT on 1 March 2020 with follow-up until 28 February 2021 and all patients alive on KRT on 1 March 2021 with follow-up until 31 December 2021.

The SRR is a nationwide register with almost complete coverage (>97%) of patients with KRT [7]. Information was linked using the personal Swedish national identification number to healthcare data sources at the National Board of Health and Welfare and was then anonymized. Data were retrieved from the National Patient Register (diagnostic codes for specialized outpatient and in-hospital care), the National Prescribed Drug Register (prescribed and dispensed drugs from pharmacies) and the Cause of Death Register (main and contributing causes of deaths). Data on the total population of Sweden, including monthly mortality rates, were obtained from Statistics Sweden.

According to Swedish law, patients are informed about their participation in the SRR and have the ability to opt out, but they do not need to provide written consent for the specific research project. The study was approved by the Ethical Review Committee in Stockholm (Dnr2018/1591-31/2, 2020-04778, 2021-00675).

COVID-19 hospitalization and mortality waves in Sweden were illustrated using aggregated data from the National Board of Health and Welfare [5] (Fig. 1).

Outcomes

The primary outcome was all-cause monthly mortality rates between January 2019 and December 2021 in patients on dialysis or with a kidney transplant. Information on all-cause mortality was obtained from the SRR records and enriched with information from the Cause of Death Register. The secondary outcomes were monthly COVID-19-related deaths and hospitalizations over the same period. Hospitalization and death from COVID-19 was defined as an International Classification for Diseases, Tenth Revision (ICD-10) code for verified COVID-19 infection (U071) as the main (hospitalization and death) or contributing (death) diagnosis.

Variables

The SRR collects information on date and type of KRT, changes between modalities and primary kidney disease. For the cross-sectional analysis on 1 January 2020 we obtained information on comorbidities from the National Patient Register. Medication use was collected from the National Prescribed Drug Register. A

patient was considered exposed to a drug if there was at least one drug dispensation within 6 months prior. The ICD-10 codes and Anatomical Therapeutic Chemical codes used for comorbidities and medication are presented in Supplementary Table S1.

Statistical analysis

Descriptive statistics for continuous variables were calculated using median and interquartile range (IQR), while proportions were used for categorical variables.

The crude overall mortality rate was computed every time-updated month for dialysis and KTRs ≥18 years of age separately. For each of the 36 months during follow-up we calculated the number of deaths divided by the person-time represented by the population at risk of death for that period (the number of people in the group at the beginning of the month multiplied by the number of days in the month). The crude overall mortality rate in the Swedish population was estimated similarly, using data from Statistics Sweden.

Using a similar methodology, we calculated the crude COVID-19 mortality and hospitalization rates between January 2020 and December 2021. In the analyses of hospitalization, we considered a second hospitalization when the episodes were >90 days apart.

We performed indirect standardization (by age group, sex and month) to estimate the expected mortality in the general population if it had the rates of the dialysis and kidney transplant groups. For this analysis we also included people <18 years of age in the SRR in order to have comparable groups with the available aggregated data from Statistics Sweden. Subsequently we computed the standardized mortality ratios (SMRs) by KRT group compared with the general Swedish population. The SMR describes whether a specific population (in this case the KRT group) is more, less or equally likely to die than a reference population.

We computed the mean unadjusted COVID-19 hospitalization and death rates in dialysis patients and KTRs during the period before (March 2020–February 2021) and after (March 2021–December 2021) vaccinations were started and compared these to the rates during the year 2019. We then used multivariable logistic regression models to compare the odds of a (first) COVID-19 hospitalization or COVID-19 death during the two periods separately in dialysis and kidney transplant patients, adjusting for age, sex, hypertension, heart failure, chronic obstructive pulmonary disease and diabetes.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Figure 1 was made using Prism 9.0.0 (GraphPad Software, San Diego, CA, USA).

RESULTS

There were 10 002 patients alive on KRT in Sweden on 1 January 2020, of which 4097 were dialysis patients and 5905 were KTRs. Clinical characteristics are presented in Table 1. The majority were men, 65.5% in the dialysis group and 63.9% in the transplant group, and the median age was 70 years and 58 years, respectively. The most common primary kidney disease for dialysis patients was diabetic nephropathy (24.6%) and for KTRs it was glomerulonephritis (32.2%). Patients on dialysis had a higher comorbidity burden (e.g. 36.8% had diabetes and 19.3% had previous myocardial infarction) as compared with KTRs (30.0% and 8.8%, respectively).

There were major differences in immunosuppression medication between the groups; 79.8% of the KTRs had at least one dispensation of corticosteroids in the previous 6 months, compared with 20.0% of the dialysis patients. A total of 61.2% of the KTRs and 2.9% of the dialysis patients were on three or more immunosuppressants.

All-cause mortality

During the first two waves of the pandemic an immediate increase in the monthly mortality rates was observed in both dialysis patients and KTRs (Fig. 2). Between March 2020 and February 2021, a total of 804 dialysis patients died, compared with 720 the preceding year (March 2019–February 2020). This corresponded to a 10% higher absolute mortality rate of 0.53/1000 patient-months, compared with the mean pre-pandemic mortality rate of 0.48/1000 patient-months, with a peak in mortality rate of 0.62/1000 patient-months in April 2020. Among KTRs, 206 died between March 2020 and February 2021, compared with 158 deaths the year before. The mean mortality rate for KTRs thus increased by 22%, from 0.07/1000 patient-months during 2019 to 0.09/1000 patient-months during March 2020–February 2021, with a peak at 0.13/1000 patient-months in April 2020.

After vaccinations started for dialysis patients (around March 2021), mortality rates decreased and were substantially lower (0.42/1000 patient-years) during the third wave of the pandemic (April 2021) as compared with the first two waves. In fact, the absolute mortality rates for dialysis patients remained lower than the pre-pandemic mean mortality rate from vaccination start in March 2021 until December 2021. On the other hand, for KTRs the mortality rate during the third wave (0.11/1000 patient-months) was higher than the mean mortality rate during the year preceding the pandemic (0.07/1000 patient-months) (Fig. 2).

Hospitalization and COVID-19-related mortality

During the first two waves and before vaccinations started, dialysis patients consistently had higher hospitalization rates compared with KTRs (Fig. 3A). After vaccinations started, hospitalization rates immediately decreased for dialysis patients, while they remained high for KTRs and exceeded the hospitalization rates for dialysis patients in April–May 2021 and during the autumn of 2021. Mortality rates for COVID-19 showed a similar pattern as the hospitalization rates, with a marked increase in mortality for dialysis patients during the first and second waves (Fig. 3B). In total, 160 dialysis patients and 64 KTRs died from COVID-19 in Sweden between March 2020 and December 2021. After vaccinations were launched, a significant decrease in COVID-19-related mortality was observed for dialysis patients, but not for KTRs. The absolute COVID-19 mortality rates for KTRs even exceeded the rates for dialysis patients in April 2021 and remained similar or slightly higher during the rest of the follow-up.

Outcomes before and after vaccination

During the period before vaccinations started (March 2020–February 2021) there were 134 COVID-19-related deaths in the dialysis group (19% of all deaths in the dialysis group) and 34 in the transplant group (17% of all deaths). After vaccinations started (March 2021–December 2021) there were 20 COVID-19 deaths in the dialysis group (4% of all deaths) and 32 deaths in the transplant group (18% of all deaths). Multivariable adjusted logistic regression comparing dialysis patients with KTRs over these two periods shows a higher risk of COVID-19 mortality or hospitalization for dialysis patients before vaccinations started {odds ratio [OR] 2.1 [95% confidence interval (CI) 1.7–2.5]}. After vaccinations, the dialysis patients had a lower risk for the combined endpoint [OR 0.5 (95% CI 0.4–0.7)] (Table 2).

Table 1: Characteristics of dialysis patients and KTRs in Sweden before the COVID-19 pandemic (1 January 2020).

Characteristics	Category	Dialysis patients (*n*= 4097)	KTRs (*n* = 5905)	*P*-value[a]
Age (years), median (IQR)		70 (58–77)	58 (47–67)	<.0001
Age group (years), *n* (%)	18–38	205 (5.0)	757 (12.8)	<.001
	39–48	284 (6.9)	851 (14.4)	
	49–58	582 (14.2)	1418 (24.0)	
	59–68	819 (20.0)	1558 (26.4)	
	>68	2207 (53.9)	1321 (22.4)	
Female, *n* (%)		1412 (34.5)	2134 (36.1)	.08
Haemodialysis, *n* (%)		3215 (78.5)		
Peritoneal dialysis, *n* (%)		882 (21.5)		
Diseased donor (versus live donor), *n* (%)			3539 (59.9)	
Pre-emptive, *n* (%)			1060 (17.9)	
Years after transplantation, median (IQR)			8 (4–15)	
Previous transplant, *n* (%)		550 (13.4)		
Primary kidney disease, *n* (%)				
	Glomerulonephritis	651 (15.9)	1899 (32.2)	<.001
	Diabetic nephropathy	1007 (24.6)	767 (13.0)	
	Hypertensive/renovascular	787 (19.2)	349 (5.9)	
	Polycystic kidney disease/hereditary	296 (7.2)	805 (13.6)	
	Pyelonephritis	164 (4.0)	218 (3.7)	
	Other specified kidney disease	802 (19.6)	1329 (22.5)	
	Unknown kidney disease	390 (9.5)	538 (9.1)	
Years on dialysis,[b] median (IQR)		2 (0–4)	1 (0–2)	.9
Comorbidity, *n* (%)	Hypertension	3947 (96.3)	5552 (94.0)	<.0001
	Stroke	543 (13.3)	430 (7.3)	<.0001
	Myocardial infarction	791 (19.3)	517 (8.8)	<.0001
	Heart failure	1293 (31.6)	524 (8.9)	<.0001
	Vascular disease	1571 (38.3)	1124 (19.0)	<.0001
	Chronic pulmonary/asthma	350 (8.5)	126 (2.1)	<.0001
	Rheumatoid arthritis	205 (5.0)	229 (3.9)	.007
	Diabetes mellitus	1508 (36.8)	1769 (30.0)	<.0001
	Cancer (except skin)	918 (22.5)	825 (14.1)	<.0001
	Skin tumours	547 (13.4)	1414 (24.2)	<.0001
	Venous thromboembolism	502 (12.3)	763 (12.9)	.3
	Fracture	1327 (32.4)	1760 (29.8)	.006
	Hospitalization for severe infection in the previous 12 months	620 (15.1)	567 (9.6)	<.0001
	Urinary tract infection	305 (7.4)	647 (11.0)	<.0001
Medication, *n* (%)				
Immunosuppression	Systemic corticosteroids	821 (20.0)	4713 (79.8)	<.0001
	Number of immunosuppressants			.0001
	≤1	3724 (90.9)	311 (5.3)	
	2	257 (6.3)	1977 (33.5)	
	≥3	116 (2.9)	3618 (61.2)	
Antihypertensive	RAAS inhibitors	1729 (42.2)	3195 (54.1)	<.0001
	Beta blocker	2863 (69.9)	3463 (58.6)	<.0001
	Calcium channel blocker	2164 (52.8)	2987 (50.6)	.03
	Alfa receptor antagonist	807 (19.7)	585 (9.9)	<.0001
	Diuretic	2522 (61.1)	1783 (30.2)	<.0001
	Number of antihypertensive drugs			<.0001
	0	446 (10.9)	812 (13.8)	
	1–2	1595 (38.9)	2942 (49.8)	
	3	976 (23.8)	1347 (22.8)	
	≥4	1080 (26.3)	804 (13.6)	
Oral anticoagulation		522 (12.7)	6781 (11.5)	.07
Antiplatelet		1643 (40.1)	1639 (27.8)	<.0001
Antidiabetic drugs	Oral antidiabetic drugs	304 (67.4)	670 (11.3)	<.0001
	Insulin	1035 (25.3)	1021 (17.3)	<.0001
Antidepressants		806 (19.7)	779 (13.2)	<.0001
Lipid-lowering drugs		2101 (51.3)	3309 (56.0)	<.0001
Proton pump inhibitor		2282 (55.7)	2947 (49.9)	<.0001

[a]P-values from test for quantitative variable and chi-squared for qualitative variables.
[b]Years on dialysis for dialysis patients. For kidney transplanted patients, years on dialysis before they were transplanted.

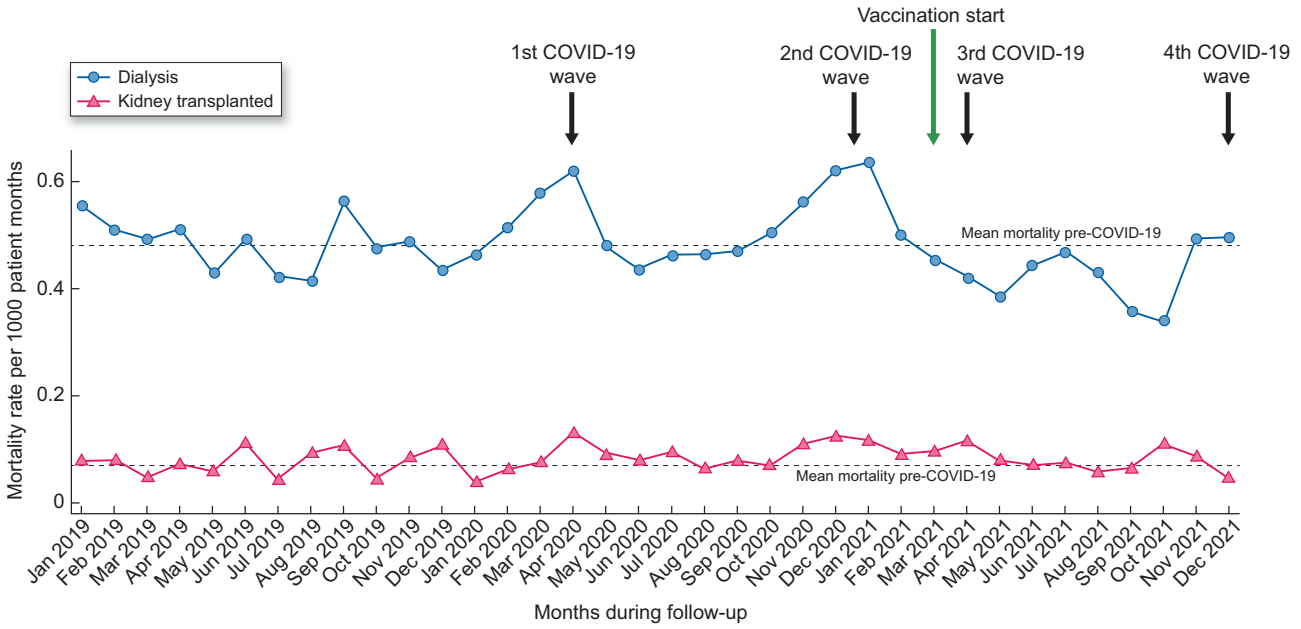


Figure 2: Monthly all-cause mortality rates for dialysis (line with circles) and KTRs (line with triangles) January 2019–December 2021. Dotted line represents mean mortality for each group pre-COVID-19 (March 2019–February 2020).

All-cause mortality compared with the general population

During the follow-up, all-cause mortality rates were consistently higher among both KRT groups as compared with the general population (Fig. 4). The yearly standardized mortality ratio (SMR) for dialysis patients was 7.19 (95% CI 6.67–7.72) in 2019, 7.15 (95% CI 6.65–7.65) in 2020 and 7.07 (95% CI 6.54–7.59) in 2021, i.e. mortality rates for dialysis patients compared with the general population were not much affected during the pandemic. For KTRs, the yearly SMR was 2.11 (95% CI 1.79–2.43) in 2019, 2.20 (95% CI 1.89–2.52) in 2020 and 2.47 (95% CI 2.11–2.82) in 2021, indicating that the mortality rate for transplanted patients as compared with the mortality rate of the general population increased during the period 2019–2021 (Fig. 4).

DISCUSSION

This study describes the health outcomes for all KRT patients in Sweden during the first 2 years of the COVID-19 pandemic. Our results show that dialysis patients displayed high hospitalization and mortality rates during the first two waves of the pandemic, with a rapid decline after the start of vaccination against SARS-CoV-2. In KTRs, the hospitalization rates for COVID-19 were lower than for dialysis patients and increased to a lesser extent during the first two waves. However, during the third and the beginning of the fourth waves the absolute hospitalization rates were similar in both groups. The mortality rates due to COVID-19 remained elevated directly after the start of vaccinations among KTRs, while it dropped rapidly in dialysis patients. A direct comparison between the dialysis and transplant groups indeed showed a higher risk for COVID-19 death and hospitalizations for dialysis patients before vaccination started, but after vaccinations the KTRs displayed a substantially higher risk (Table 2). Over the study period, the SARS-CoV-2 strains dominating in Sweden were all of high virulence (early strains, March 2020–February 2021; Alpha strain, March 2020–February 2021; Delta strain, March 2021–December 2021) [8]. Both the Alpha strain and the Delta strain were associated with higher intensive care admission rates and 28-day mortality rates compared with earlier strains, with the Delta strain having more impact on unvaccinated patients compared with previous variants [9–11]. The Omicron strain, reported to be less virulent [10], became the dominant strain in Sweden in January 2022, which is later than the studied period. These observations make us believe that the observed decline in mortality in dialysis patients in spring 2021, after vaccinations were introduced, was likely due to vaccination and not to less-virulent SARS-CoV-2 strains. In view of the fact that the Alpha and Delta variants were even more contagious than the earlier strains [12, 13], the effect of vaccination in dialysis patients cannot be overstated.

There are many ways in which a pandemic can influence health outcomes, including testing capacity, community spread and restrictions. But other factors, such as healthcare organizations, access to care and thresholds to seek care for other symptoms such as chest pain, may also play a role. In this study we found that COVID-19 affected dialysis patients and KTRs differently during the first three waves of the pandemic in Sweden. There are several possible reasons for the differences. The KTRs in our study were both younger and healthier as compared with the dialysis patients. Age and comorbidities have been identified as risk factors for severe COVID-19, also in KRT patients [14]. This may explain why KTRs were not as often hospitalized for COVID-19 compared with dialysis patients at the beginning of the pandemic. In an early report of the pandemic in Swedish haemodialysis patients, age >70 years, longer dialysis vintage, higher C-reactive protein and male sex were associated with an increased risk of dying from COVID-19 [15]. The high mortality during the first two waves may also have influenced the results of our study. If the most vulnerable and older patients died at the beginning of the pandemic, it may have resulted in lower mortality rates in dialysis patients following the first two waves. Statistics from the SRR show that the number of transitions between dialysis modalities were similar in magnitude over the follow-up period and compared with before the pandemic [16], and although kidney transplantation frequency declined, we do not believe that these changes had anything but a marginal effect on our results.

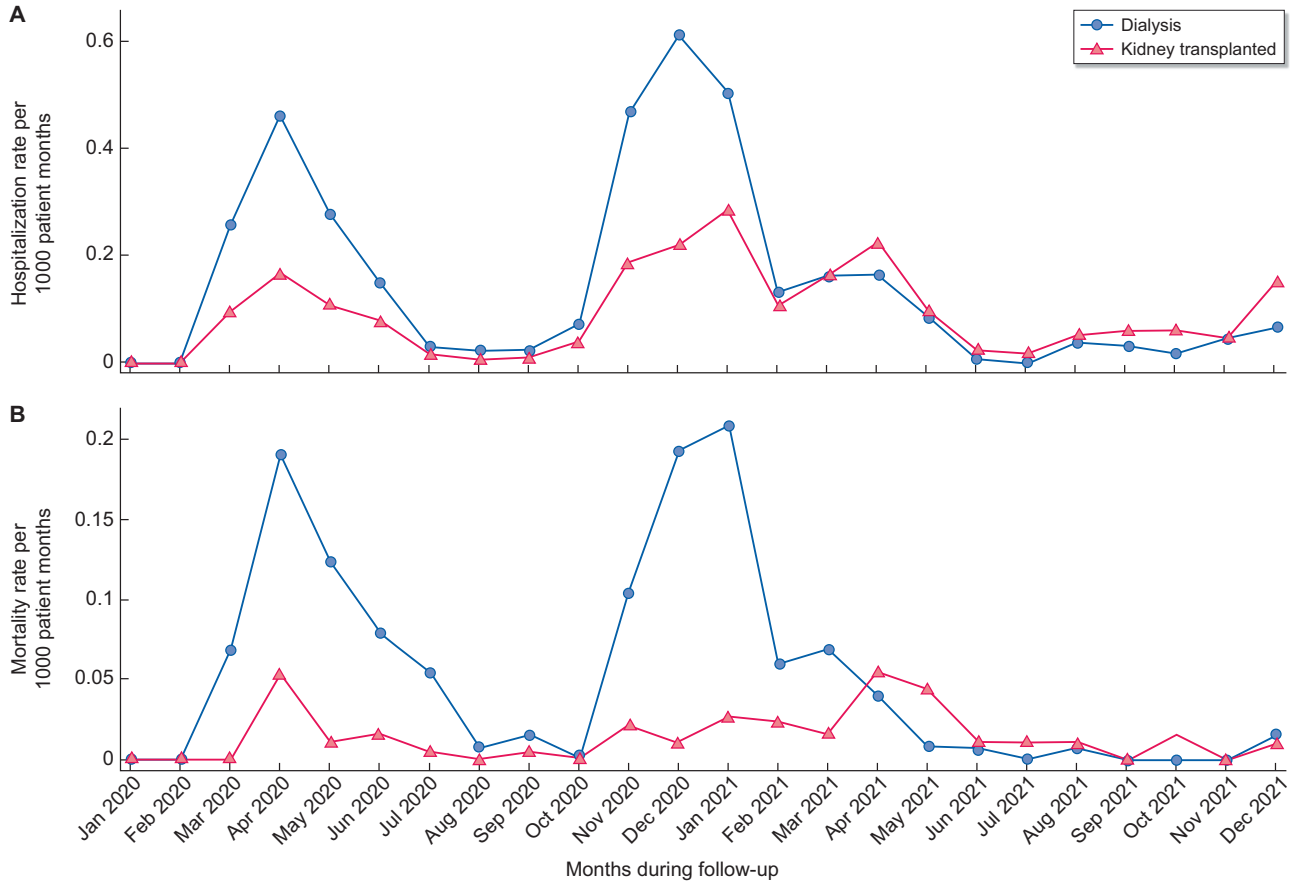


Figure 3: Monthly **(A)** hospitalization rates and **(B)** mortality rates for COVID-19 for patients on dialysis (line with circles) and KTRs (line with triangles), January 2020–December 2021.

Table 2: Risk for COVID-19-related outcomes in dialysis patients as compared with KTRs in the period before (March 2020–February 2021) and after (March 2021–December 2021) SARS-CoV-2 vaccinations started.

	Period before vaccination		Period after vaccination	
Outcome	Univariate model, (95% CI)	Multivariate model, (95% CI)	Univariate model, (95% CI)	Multivariate model, (95% CI)
COVID-19 death	5.9 (4.0–8.6)	3.1 (2.0–4.7)	0.9 (0.5–1.6)	0.5 (0.3–0.9)
COVID-19 death or hospitalization	2.5 (2.1–2.9)	2.1 (1.7–2.5)	0.6 (0.5–0.8)	0.5 (0.4–0.7)

Multivariate model adjusted for age, sex, hypertension, heart failure, chronic obstructive pulmonary disease and diabetes.

On the other hand, KTRs are treated with immunosuppressants, which makes them more susceptible to infections [17]. About one in five dialysis patients in our cohort had at least one dispensation of corticosteroids, which is a rather high prevalence. It is likely that many of these patients only used these drugs temporarily since the majority did not have systemic inflammatory diseases or were previously kidney transplanted. An early European study during the pandemic reported a 28-day mortality rate of 21% in KTRs, being only slightly lower than the mortality rate of 25% in dialysis patients despite the former being younger (mean age 60 ± 13 and 67 ± 14 years, respectively) [18]. The first Swedish study of the first wave reported that KTRs had a 9.3% 30-day all-cause mortality rate after SARS-CoV-2 infection [19]. Furthermore, immunosuppression reduces the vaccine antibody response and non-response after two doses of SARS-CoV-2 vaccine has been reported in 21–98% of KTRs [20–23]. In addition, in 2021 the more contagious strains of the SARS-CoV-2 virus, the Alpha and Delta strains, became dominant in Sweden. The combination of a lower vaccination response rate, more contagious strains and possibly a slower vaccination campaign in KTRs could be the reason why KTRs surpassed dialysis patients in our study in both COVID-19 hospitalization and mortality rates in April/May 2021, just after the vaccinations started [24–26].

Another factor that likely contributed was differences regarding the exposure to SARS-CoV2. Most of the haemodialysis patients in Sweden undergo intermittent dialysis at a dialysis unit and are thus not able to isolate [27]. On the other hand, transplant recipients were informed to strictly isolate from people outside the household and work from home. From August 2020, KTRs could collect a reimbursement provided by the state to compensate for loss of income if working from home was not possible. This voluntary isolation, resulting in lower infection rates, could

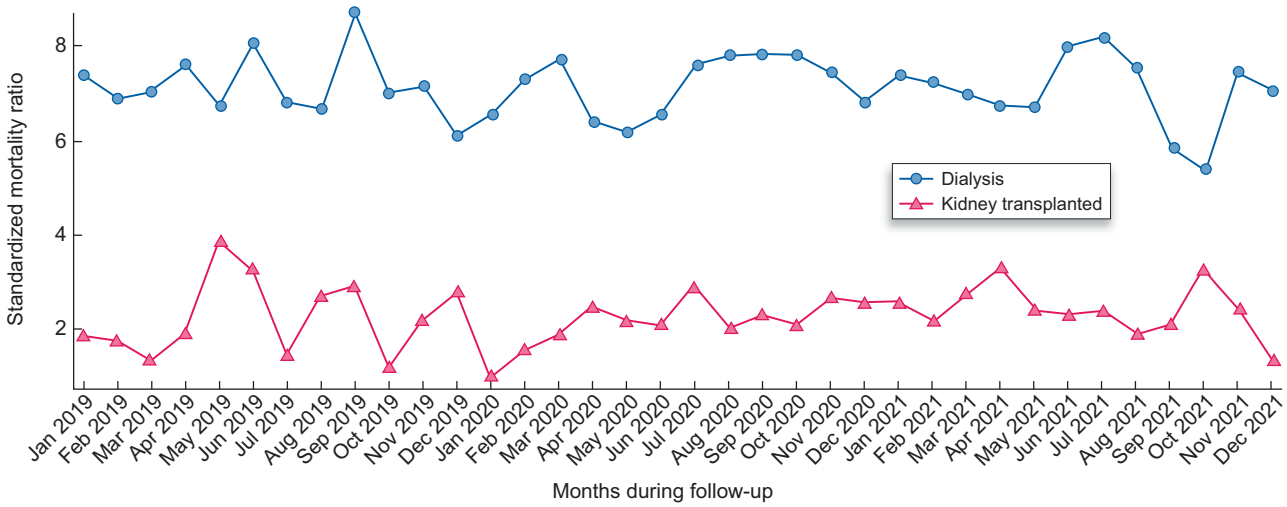


Figure 4: Direct standardized mortality ratio in dialysis patients (line with circles) and KTRs (line with triangles) compared with the general Swedish population, January 2019–December 2021.

have contributed to the relatively low number of KTRs hospitalized for COVID-19 in Sweden.

Even though KTRs had a relatively low absolute COVID-19 mortality, it is noteworthy that the relative increase in all-cause mortality during the pandemic was higher in transplant recipients than in dialysis patients; the mortality rates increased by 10% among dialysis patients and by 22% among KTRs during the pandemic's first year.

Another Swedish study found an overall excess mortality of 30% among KTRs and 9% among dialysis patients (compared with 8% in the general population) between March 2020 and March 2021 [28]. A registry study from the US reported an even greater impact on mortality rates, with an 41% increase above the expected number of deaths among KTRs during the same period [29]. Among KRT patients in Madrid, Spain, a 35% higher mortality was found in 2020 as compared with before the pandemic [30]. The European Renal Registry reported a 28-day COVID-19-attributable mortality rate of ≈20% for both dialysis and transplant recipients [14]. During the second wave the 28-day mortality was slightly lower (19% and 13%, respectively) [31]. The protective effect of vaccination in the dialysis group observed in our study has also been reported from other dialysis cohorts and further strengthens the rationale for recommending vaccination in this vulnerable group [32–34].

Interestingly, compared with the general population, the SMR for patients on KRT did not display distinct peaks during the first and second waves. Overall, mortality rates were always substantially higher than in the general population, especially for those on dialysis. But, in the monthly standardized comparison, the relationship between the general population and dialysis patients remained stable or even declined slightly (SMR 7.19 for 2019, 7.15 for 2020 and 7.07 for 2021). The relative decline in the SMR indicates a higher mortality than usual in the general population in the same age groups. Possible explanations could be a high community dissemination giving rise to high mortality rates in care homes of vulnerable older adults in the first wave, earlier vaccinations/higher vaccination rates among dialysis patients than the general population, regular healthcare contacts at the dialysis unit regarding other diseases (while the general population may have avoided healthcare contacts) and earlier diagnosis (and treatment) of COVID-19 [35, 36]. In KTRs however, the SMR increased to a higher baseline level throughout the follow-up, as well as after vaccinations were introduced (SMR 2.11 in 2019, 2.20 in 2020 and 2.47 in 2021).

During the COVID-19 pandemic, Sweden had a policy based on voluntary restrictions, unlike most other European countries [6]. Nevertheless, in relation to the period before the pandemic, outcomes in the KRT patients in the present study were in general comparable to outcomes reported from other countries [29, 30, 37, 38]. It is possible that the spread of the infection may have been too rapid to control among at-risk populations, considering the large outbreak in the community during the first two waves [39]. On the other hand, positive effects of early strict lockdown during the first wave have been reported from Austria, where only 10 of 5512 KTRs were diagnosed with SARS-CoV-2 [40]. The Swedish approach could thus have impacted the results during the early phase of the pandemic. A similar outbreak in a country with less-developed or accessible healthcare might have resulted in higher mortality rates and outcomes may also have differed without the rapid vaccination campaign prioritizing risk groups.

The major strength of this study is the inclusion of a nationwide cohort of KRT patients and complete follow-up without losses due to the complete coverage of healthcare registries in Sweden. This study is the first nationwide report of outcomes in KRT patients before and after vaccination for COVID-19. Another strength of our study is that all-cause mortality during the pandemic is reported along with COVID-19 mortality and hospitalization rates. The pandemic affected the healthcare system on many different levels and all-cause mortality reflects the pandemic's overall impact on KRT patients. Also, COVID-19 may have gone undiagnosed, especially in the beginning of the pandemic when testing capacity was lower, and although few patients in our study died of COVID-19 outside of a hospital, this might have influenced COVID-19 outcomes, but not all-cause mortality. Another strength is the analysis of the SMR, which considers the influence of the pandemic in the underlying population. There were some limitations. We did not have data on COVID-19 hospitalization rates in the general population nor information on positive test results or individual vaccinations. Vaccination coverage in Sweden for SARS-CoV-2 is overall high, with 86.1% of the adult population having received two doses of vaccine. One might assume that at-risk populations (such as KRT patients)

prioritized for vaccination early during the vaccination campaign probably had an even higher vaccination rate. Thus, differences in vaccine coverage could have impacted our results, especially the SMR, where comparisons with the general population are made.

In conclusion, the COVID-19 pandemic in Sweden resulted in increased mortality and hospitalization rates among KRT patients. Both absolute and relative mortality rates were substantially higher in dialysis patients during the first two COVID-19 waves compared with transplanted patients. Following the vaccine rollout, there was a distinct reduction in hospitalization and mortality rates among dialysis patients that was not reflected among the KTRs, who at this time surpassed the dialysis patients in COVID-19 mortality and hospitalization rates. Compared with the general population in Sweden, the monthly SMRs were several times higher but relatively stable in dialysis patients during the follow-up period. In contrast, the SMR for KTRs showed an increasing trend. These results could help guide future healthcare planning if new virulent SARS-CoV-2 strains emerge.

SUPPLEMENTARY DATA

Supplementary data is available at *ndt* online.

ACKNOWLEDGEMENTS

We thank the SRR and the participating clinics for sharing their data and the nephrology healthcare workers for their work providing care to patients with kidney disease.

FUNDING

This study was supported by grants from the Westman Foundation, Njurfonden and the Gelin Foundation. The fund providers took no part in the statistical analyses, interpretation of data or drafting of the manuscript. A.C. was partially funded by the European Union Erasmus traineeship program at the University of Milano-Bicocca.

AUTHORS' CONTRIBUTIONS

M.E. was responsible for data acquisition. M.E., A.C. and J.W. were responsible for the concept and study design. A.C. was responsible for the statistical analysis. J.W. and M.E. were responsible for drafting the manuscript. All authors were responsible for interpretation of the results, critically revising and evaluating the content and final approval.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

B.L. has been employed by Baxter Healthcare and received grants from Baxter Healthcare to Karolinska Institutet not related to the work submitted. None of the other authors have any financial disclosures to declare in relation to the work submitted.

(See related article by Messchendorp and Gansevoort. Vaccinated kidney transplant recipients are yet not sufficiently protected against COVID-19. *Nephrol Dial Transplant* 2023; 38: 2423–2425)

REFERENCES

1. Nacif LS, Zanini LY, Waisberg DR *et al.* COVID-19 in solid organ transplantation patients: a systematic review. *Clinics* 2020;**75**:e1983. https://doi.org/10.6061/clinics/2020/e1983
2. Shimada N, Shimada H, Itaya Y *et al.* Novel coronavirus disease in patients with end-stage kidney disease. *Ther Apher Dial* 2021;**25**:544–50. https://doi.org/10.1111/1744-9987.13599
3. Goicoechea M, Sanchez Camara LA, Macias N *et al.* COVID-19: clinical course and outcomes of 36 hemodialysis patients in Spain. *Kidney Int* 2020;**98**:27–34. https://doi.org/10.1016/j.kint.2020.04.031
4. Krisinformation.se [Emergency information from Swedish authorities]. The first confirmed coronavirus case in Sweden 2020. https://www.krisinformation.se/en/news/2020/january/who-classes-the-outbreak-of-the-corona-virus-as-an-international-threat-to-human-life2
5. Socialstyrelsen [The National Board of Health and Welfare]. Statistik om Covid-19. https://www.socialstyrelsen.se/statistik-och-data/statistik/statistik-om-covid-19/
6. Ludvigsson JF. The first eight months of Sweden's COVID-19 strategy and the key actions and actors that were involved. *Acta Paediatr* 2020;**109**:2459–71. https://doi.org/10.1111/apa.15582
7. Schon S, Ekberg H, Wikstrom B *et al.* Renal replacement therapy in Sweden. *Scand J Urol Nephrol* 2004;**38**:332–9. https://doi.org/10.1080/00365590410033380
8. Hodcroft EB. CoVariants: SARS-CoV-2 mutations and variants of interest. https://covariants.org/
9. Patone M, Thomas K, Hatch R *et al.* Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. *Lancet Infect Dis* 2021;**21**:1518–28. https://doi.org/10.1016/S1473-3099(21)00318-2
10. Lauring AS, Tenforde MW, Chappell JD *et al.* Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. *BMJ* 2022;**376**:e069761. https://doi.org/10.1136/bmj-2021-069761
11. Twohig KA, Nyberg T, Zaidi A *et al.* Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis* 2022;**22**:35–42. https://doi.org/10.1016/S1473-3099(21)00475-8
12. Mlcochova P, Kemp SA, Dhar MS *et al.* SARS-CoV-2 B.1.617.2 delta variant replication and immune evasion. *Nature* 2021;**599**:114. https://doi.org/10.1038/s41586-021-03944-y
13. Hirabara SM, Serdan TDA, Gorjao R *et al.* SARS-COV-2 variants: differences and potential of immune evasion. *Front Cell Infect Microbiol* 2022;**11**:781429. https://doi.org/10.3389/fcimb.2021.781429
14. Jager KJ, Kramer A, Chesnaye NC *et al.* Results from the ERA-EDTA Registry indicate a high mortality due to COVID-19 in dialysis patients and kidney transplant recipients across Europe. *Kidney Int* 2020;**98**:1540–8. https://doi.org/10.1016/j.kint.2020.09.006
15. Smolander J, Bruchfeld A. The COVID-19 epidemic: management and outcomes of hemodialysis and peritoneal dialysis patients in Stockholm, Sweden. *Kidney Blood Press Res* 2021;**46**:250–6. https://doi.org/10.1159/000514268
16. SNR [Svenskt Njurregister]. Årsrapporter (Swedish Renal Register Annular Reports) 2013-2022. https://www.medscinet.net/snr/arsrapporter.aspx

17. Akalin E, Azzi Y, Bartash R *et al.* Covid-19 and kidney transplantation. *N Engl J Med* 2020;**382**:2475–7. https://doi.org/10.1056/NEJMc2011117
18. Hilbrands LB, Duivenvoorden R, Vart P *et al.* COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant* 2020;**35**:1973–83. https://doi.org/10.1093/ndt/gfaa261
19. Softeland JM, Friman G, von Zur-Muhlen B *et al.* COVID-19 in solid organ transplant recipients: a national cohort study from Sweden. *Am J Transplant* 2021;**21**:2762–73. https://doi.org/10.1111/ajt.16596
20. Quiroga B, Soler MJ, Ortiz A *et al.* Safety and immediate humoral response of COVID-19 vaccines in chronic kidney disease patients: the SENCOVAC study. *Nephrol Dial Transplant* 2022;**37**:1868–78. https://doi.org/10.1093/ndt/gfab313
21. Galmiche S, Nguyen LBL, Tartour E *et al.* Immunological and clinical efficacy of COVID-19 vaccines in immunocompromised populations: a systematic review. *Clin Microbiol Infect* 2022;**28**:163–77. https://doi.org/10.1016/j.cmi.2021.09.036
22. Sanders JSF, Bemelman FJ, Messchendorp AL *et al.* The RECOVAC immune-response study: the immunogenicity, tolerability, and safety of COVID-19 vaccination in patients with chronic kidney disease, on dialysis, or living with a kidney transplant. *Transplantation* 2022;**106**:821–34. https://doi.org/10.1097/TP.0000000000003983
23. Verleye A, Wijtvliet V, Abrams S *et al.* Seroconversion rate after primary vaccination with two doses of BNT162b2 versus mRNA-1273 in solid organ transplant recipients: a systematic review and meta-analysis. *Nephrol Dial Transplant* 2022;**37**:1566–75. https://doi.org/10.1093/ndt/gfac174
24. Stumpf J, Siepmann T, Lindner T *et al.* Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. *Lancet Reg Health Eur* 2021;**9**:100178.
25. Affeldt P, Koehler FC, Brensing KA *et al.* Immune responses to SARS-CoV-2 infection and vaccination in dialysis patients and kidney transplant recipients. *Microorganisms* 2022;**10**:4. https://doi.org/10.3390/microorganisms10010004
26. Bin Lee ARY, Wong SY, Chai LYA *et al.* Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *Br Med J* 2022;**376**:e068632.
27. Evans M, Rydell H, Prütz K-G *et al.* Association between implementation of novel therapies and improved survival in patients starting hemodialysis; the Swedish Renal Registry 2006–2015. *Nephrol Dial Transplant* 2020;**36**:1298–306. https://doi.org/10.1093/ndt/gfaa142.P1437
28. Segelmark M, Segelmark L, Smolander J *et al.* Mortaliteten hos svårt njursjuka var hög under covid 19-pandemin. *Läkartidningen* 2021;**118**:21051.
29. Massie AB, Werbel WA, Avery RK *et al.* Quantifying excess deaths among solid organ transplant recipients in the COVID-19 era. *Am J Transplant* 2022;**22**:2077–82. https://doi.org/10.1111/ajt.17036
30. Carriazo S, Aparicio-Madre MI, Tornero-Molina F *et al.* Impact of different COVID-19 waves on kidney replacement therapy epidemiology and mortality: REMER 2020. *Nephrol Dial Transplant* 2022;**37**:2253–63. https://doi.org/10.1093/ndt/gfac234
31. Vart P, Jager KJ, Arnol M *et al.* COVID-19 pandemic waves and mortality among patients on kidney replacement therapy. *Kidney Int Rep* 2022;**7**:2091–6. https://doi.org/10.1016/j.ekir.2022.06.007
32. El Karoui K, Hourmant M, Ayav C *et al.* Vaccination and COVID-19 dynamics in dialysis patients. *Clin J Am Soc Nephrol* 2022;**17**:395–402. https://doi.org/10.2215/CJN.10300721
33. Ashby DR, Caplin B, Corbett RW *et al.* Severity of COVID-19 after vaccination among hemodialysis patients an observational cohort study. *Clin J Am Soc Nephrol* 2022;**17**:843–50. https://doi.org/10.2215/CJN.16621221
34. Ashby DR, Caplin B, Corbett RW *et al.* Outcome and effect of vaccination in SARS-CoV-2 Omicron infection in hemodialysis patients: a cohort study. *Nephrol Dial Transplant* 2022;**37**:1944–50. https://doi.org/10.1093/ndt/gfac209
35. Bergman J, Ballin M, Nordstrom A *et al.* Risk factors for COVID-19 diagnosis, hospitalization, and subsequent all-cause mortality in Sweden: a nationwide study. *Eur J Epidemiol* 2021;**36**:287–98. https://doi.org/10.1007/s10654-021-00732-w
36. Ballin M, Bergman J, Kivipelto M *et al.* Excess mortality after COVID-19 in Swedish long-term care facilities. *J Am Med Dir Assoc* 2021;**22**:1574–80.e8. https://doi.org/10.1016/j.jamda.2021.06.010
37. Thaunat O, Legeai C, Anglicheau D *et al.* IMPact of the COVID-19 epidemic on the moRTAlity of kidney transplant recipients and candidates in a French Nationwide registry sTudy (IMPORTANT). *Kidney Int* 2020;**98**:1568–77. https://doi.org/10.1016/j.kint.2020.10.008
38. Ziemba R, Campbell KN, Yang TH *et al.* Excess death estimates in patients with end-stage renal disease – United States, February–August 2020. *MMWR Morb Mort Wkly Rep* 2021;**70**:825–9. https://doi.org/10.15585/mmwr.mm7022e2
39. Pashakhanlou AH. Sweden's coronavirus strategy: the Public Health Agency and the sites of controversy. *World Med Health Policy* 2022;**14**:507–27. https://doi.org/10.1002/wmh3.449
40. Watschinger B, Watschinger C, Reindl-Schwaighofer R *et al.* Impact of timely public health measures on kidney transplantation in Austria during the SARS-CoV-2 outbreak—a nationwide analysis. *J Clin Med* 2020;**9**:3465. https://doi.org/10.3390/jcm9113465

Received: January 27, 2023; Editorial decision: May 15, 2023