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ORIGINAL ARTICLE

COVID-19 among kidney transplant recipients: evaluating risk factors during the initial phase of the pandemic

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ABSTRACT

Background. Current knowledge about risk factors for severe COVID-19 among kidney transplant recipients stem from meta-analyses of small or regional studies.

Methods. All kidney transplant recipients in Sweden as of 1 January 2020 ($n = 5824$) were followed during the first 2 years of the pandemic. Data from the Swedish Renal Registry and linked health care registries were analyzed by multivariable adjusted logistic regression to identify risk factors for severe COVID-19, defined as hospitalization or death due to COVID-19.

Results. Male sex increased the risk of severe COVID-19. While many comorbidities were associated with increased risk, their significance diminished after adjustment for other factors. Kidney transplant recipients of working age, 49–58 years adjusted odds ratio (aOR) 2.32 (95% CI 1.53–3.51) and 59–68 years aOR (1.92; 1.26–2.91) had the highest risk compared to the youngest age group (18–38 years). Compared to recently (<1 year) transplanted patients, those transplanted >5 years ago had a lower risk of severe COVID-19 (aOR 0.52; 0.36–0.75 for 6–10 years; aOR 0.57; 0.41–0.79 for >10 years). Longer pre-transplant dialysis vintage ($aOR_{1\text{-year}}$ 1.04; 1.01–1.06) and deceased donor kidneys (aOR 1.41; 1.09–1.84) increased the risk. Immunosuppression with mycophenolate mofetil (aOR 1.47, 95% CI 1.08–1.99) and proton pump inhibitor use (aOR 1.58, 95% CI 1.24–2.01) were strongly associated with severe COVID-19.

Conclusions. While kidney transplant recipients share risk factors with the general population, working age groups were at the highest risk, unlike in the general population. These findings emphasize the need for targeted prevention and treatment strategies for kidney transplant recipients in future pandemics.

Keywords: COVID-19, epidemiology, kidney transplantation, proton pump inhibitor, working age

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KEY LEARNING POINTS

What was known:

- COVID-19 presents higher mortality and morbidity rates in kidney transplant recipients than in the general population.
- Kidney transplant recipients are vulnerable to COVID-19 due to their ongoing immunosuppressive therapy, impaired vaccine response, and presence of comorbidities.
- Data on risk factors for COVID-19 in kidney transplant recipients derive from small or regional cohort studies.

This study adds:

- Our study addresses a critical gap by analyzing COVID-19 risk factors among kidney transplant recipients nationally, utilizing comprehensive data from the Swedish Renal Registry, which covers >97% of patients undergoing kidney replacement therapy in Sweden.
- Kidney transplant recipients of working age (49–68 years) had higher risk for severe COVID-19 infection than patients of both higher and lower ages, a trend possibly shaped by Sweden's distinct public health strategies during the pandemic.
- Apart from transplantation-related factors (donor type, kidney transplant, and dialysis vintage, immunosuppression), we found a strong risk relation between the use of proton pump inhibitors and severe COVID-19.

Potential impact:

- Our findings offer critical insights for improving the management of kidney transplant recipients in face of future health crises.
- Our study underscores the need for further research on kidney transplant recipients and the observed association between proton pump inhibitor use and increased risk of severe COVID-19.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to unprecedented challenges to healthcare systems worldwide. The pandemic rapidly disseminated throughout the world after the first reported case of COVID-19 in Wuhan, China, in late December 2019, leading the World Health Organization (WHO) to declare it a global pandemic on 11 March 2020 [1]. As of April 2024, the pandemic has caused >770 million infections and 7 million confirmed deaths [2], making it one of the deadliest pandemics in history [3]. Since the initial phase, substantial progress in clinical research has led to a better understanding of SARS-CoV-2, and multiple medical therapies to treat the disease have emerged [4–6]. The introduction of COVID-19 vaccines in 2021 and booster vaccine programs have influenced the COVID-19 pandemic, reducing hospitalizations and altering the course of SARS-CoV-2 infection [7]. The WHO declared an end to the COVID-19 public health emergency in May 2023 [8]. Nevertheless, immunocompromised kidney transplant recipients (KTRs) are still at high risk of developing severe COVID-19 [9, 10], partly due to an impaired vaccine response in many of these patients [11].

KTRs are vulnerable to infections due to their ongoing immunosuppressive therapy, presence of other comorbidities, and in some cases impaired kidney function. Although previous studies have suggested risk factors for severe COVID-19 among KTRs [12], there are limited data on risk factors and outcomes of COVID-19 in KTRs at a national level, where regional or center-related factors play a lesser role. Risk factor identification is important in this population since the risk factors for severe infection may be different from the general population. Identifying modifiable risk factors that increase the susceptibility to severe COVID-19 can help target prevention and treatment strategies, thus improving future outcomes in this population. In this study, we aimed to investigate risk factors for severe COVID-19 by analyzing retrospective data on COVID-19 outcomes, as well as demographic, clinical, and drug-related risk factors for hospitalizations and deaths attributed to COVID-19, in a nationwide cohort of all Swedish KTRs during the first 2 years of the pandemic.

MATERIALS AND METHODS

Study design and population

We included all living adult KTRs with a functioning renal graft enrolled in the Swedish Renal Registry (SRR) between 1 January 2020 and 31 December 2021, and analyzed risk factors for hospitalization and mortality due COVID-19 among all those who were alive on 1 January 2020 ($n = 5824$). The SRR is a nationwide registry, with almost complete coverage (>97%) of patients with kidney replacement therapy since 1991 in Sweden, including KTRs [13]. Data from the SRR was linked to other healthcare data sources at the National Board of Health and Welfare using the Swedish personal identification number and was then anonymized. The data sources used for this linkage were the National Patient Register [International Classification of Diseases 10th revision (ICD-10) codes, dates for specialized out-patient and all in-hospital care]; the National Prescribed Drug Register (all prescribed and dispensed drugs from Swedish pharmacies); and the National Cause of Death Register (main and contributing causes of deaths) [14]. Individual consent is not necessary according to the Swedish regulations, but all patients were informed about their participation in the SRR and had the possibility to opt out. The study adheres to the Declaration of Helsinki and was approved by the Ethical Review Committee in Stockholm (Dnr 2018/1591-31/2, 2020-04778, 2021-00675).

Outcomes

The main outcome was COVID-19 related death or hospitalization due to COVID-19, hereafter defined as 'severe COVID-19'. All cause-mortality and death or hospitalization from other causes than COVID-19 were not examined. Information on COVID-19 mortality was obtained from the National Cause of Death Register and defined as a laboratory-verified diagnosis of COVID-19 as the main or contributing cause of death (ICD-10 code U071).

COVID-19 related hospitalization was defined similarly using the ICD-10 code U071 as the main diagnosis in the National Patient Register. A grace period of 90 days was applied between two hospitalization periods for the computation of hospitalization rates.

Variables

The SRR collects information on date and type of kidney transplantation, clinical characteristics, primary kidney disease, and changes between kidney replacement therapy modalities. Comorbidity history at baseline included hypertension, cerebrovascular disease, coronary artery disease, heart failure, chronic obstructive pulmonary disease (COPD), connective tissue disorder, diabetes mellitus, hematological cancer, solid organ cancer, hospitalization for severe infection within the past 12 months, and kidney transplant rejection within the past 12 months. The comorbidities were defined by any prior ICD-10 code for the specific condition in the National Patient Registry, and information on drug use was obtained from the National Prescribed Drug Registry. A patient was considered to use a specific drug if he or she had at least one drug dispensation from a pharmacy within 6 months preceding the baseline. The ICD-10 codes and anatomic therapeutic chemical codes used for classification of comorbidities and current medications are presented in Supplementary Table 1. Abbreviations are listed in Supplementary Material 2.

Statistical analysis

For descriptive purposes, the follow-up period was divided into four semestral periods 1 January 2020, until 30 June 2020 (first wave), 1 July 2020, until 31 December 2020 (second wave), 1 January 2021, until 30 June 2021 (third wave), and 1 July 2021, until 31 December 2021 (fourth wave, after first two vaccinations). In the descriptive analysis, we constructed four different cohorts; each cohort consisted of all KTR alive with a functioning kidney graft at the start of the period (thus accounting also for incident KTR and graft losses during the follow-up). For the analyses of risk factors associated with severe COVID-19, we instead used the defined KTR cohort alive with a functioning graft on 1 January 2020. Patients were followed from inclusion until either death, start of dialysis, or end of follow-up (31 December 2021), whichever occurred first.

The characteristics of the KTR population as per 1 January 2020, were described using descriptive statistics. For continuous variables, median and interquartile range (IQR) were used, while proportions were used for categorical variables. We then computed the crude COVID-19 related hospitalization and mortality rates, as well as the absolute cumulative incidence of COVID-19 related hospitalization and mortality, over each follow-up period.

The association models and criteria were determined based on literature and clinical expertise. Associations between our *a priori* decided risk factors and the primary outcome were analyzed using binary logistic regression. The linear assumption for continuous variables was investigated through spline models and found to be satisfactorily met for our investigated exposures. Subsequently, multivariable analyses were undertaken, adjusting for covariates that were suspected or known confounders (age, sex, primary kidney disease, COPD, heart failure, hypertension, diabetes mellitus, cardiovascular disease, proton pump inhibitor, antiplatelet therapy, hospitalization for severe infection in the previous 12 months, and number of years since kidney transplantation) for the risk association investigated. We then further adjusted for dialysis vintage and donor type, when appropriate.

Each risk factor was assessed independently, since confounders could have influenced the risk factors differently; thus, separate models were used for the adjustments as was deemed appropriate and specified in Table 3 for each analysis. Finally, an unadjusted sensitivity analysis was performed using the cohort of the fourth semestral period for the most important risk factors to evaluate the potential impact of vaccination on the risk associations (Supplementary Table 3). There was no missing data and all statistical analyses were thus performed on complete cases using SAS software version 9.4.

RESULTS

Demographics and clinical characteristics

The main study cohort included 5824 prevalent KTRs who were alive with a functioning graft on 1 January 2020. The characteristics of this cohort at inclusion are presented in Table 1. Their median age was 58 years, 64% were men, 18% had received a preemptive kidney transplantation, and 40% a living-donor-kidney transplant. The median time from transplantation was 7 years and for those patients who had previously undergone dialysis, the median dialysis vintage was 1 year. The most common primary kidney diseases were glomerulonephritis (37%), polycystic kidney disease or hereditary kidney disease (20%), and diabetic nephropathy (13%) while the most prevalent comorbidity was hypertension (95%), followed by diabetes mellitus (30%).

Maintenance immunotherapy consisted of corticosteroids in 81% of patients, calcineurin inhibitors in 95% (tacrolimus 79% and ciclosporin 16%), and mycophenolate mofetil (MMF) in 73%. Almost two thirds (61%) of the cohort were treated with three immunosuppressants as maintenance therapy, while approximately one third (34%) were on two immunosuppressants. The most frequently used drugs, other than immunosuppressants, were betablockers (60%), statins (57%), renin–angiotensin–aldosterone system inhibitors (56%), calcium channel blockers (51%), and proton pump inhibitors (PPI) (51%).

Covid-19 related outcomes over the first two pandemic years

The follow-up period was divided into 6-month intervals for descriptive purposes. At the beginning of each semestral period, we defined a new cohort of KTR alive with a functioning graft. During the following semestral periods, there were 5856 (1 July until 31 December 2020), 5916 (1 January 2021, until 30 June 2021), and 5959 (1 July 2021, until 31 December 2021) KTRs, respectively. Table 2 shows the cumulative incidence of hospitalizations and deaths due to COVID-19 per each semestral period among the KTRs in Sweden. Over the entire 2-year follow-up period, 385 KTRs were hospitalized due to COVID-19, 10 of these patients twice, with a total of 395 hospitalization events. The hospitalization rates during the first and second semester were 0.76 and 0.77/10 000 person-years, respectively, peaking at a rate of 1.58/10 000 person-years in the third semester.

During the entire study period, 64 KTRs died due to COVID-19, seven of whom died without having been admitted to hospital. The semestral cumulative incidence of COVID-19 deaths was highest in the third semester (0.5%) with a mortality rate of 0.29/10 000 person-years, followed by the first semester (0.3%). The COVID-19 mortality rate during the fourth semester (0.08/10 000 person-years), following two COVID-19 vaccinations,

Table 1: Baseline characteristics of KTRs in Sweden at the start of the COVID-19 pandemic (1 January 2020).

Characteristics	Category	Number (%) Median (IQR)
Total number		5824 (100)
Men		3718 (64)
Age, years (median, IQR)		58 (47–67)
	18–38	740 (13)
	39–48	832 (14)
	49–58	1403 (24)
	59–68	1543 (27)
	>68	1306 (22)
Preemptive transplant		1045 (18)
Primary kidney disease		
	Glomerulonephritis	2123 (37)
	Diabetic nephropathy	759 (13)
	Hypertensive/renovascular	442 (8)
	Polycystic kidney disease/hereditary	1169 (20)
	Tubulointerstitial disease	674 (12)
	Other specified kidney disease	74 (1)
	Unknown kidney disease	583 (10)
Years since kidney transplantation (median, IQR)		7 (3–14)
	align="center"≤1	844 (15)
	align="center"2–5	1488 (26)
	align="center"6–10	1384 (24)
	align="center"≥10	2108 (36)
Years on dialysis before kidney transplant, (median, IQR)		1 (0–3)
Comorbidity	Hypertension	5513 (95)
	Cerebrovascular disease	430 (7)
	Coronary artery disease	514 (9)
	Heart failure	519 (9)
	COPD	124 (2)
	Connective tissue disorder	228 (4)
	Diabetes mellitus	1756 (30)
	Hematological cancer	127 (2)
	Solid organ cancer	575 (10)
	Hospitalization for severe infection previous 12 months	568 (10)
	Kidney transplant rejection previous 12 months	8 (0.1)
Current medication		
Immunosuppression	Systemic corticosteroids	4713 (81)
	Cyclosporine	905 (16)
	Tacrolimus	4601 (79)
	Mycophenolate mofetil	4246 (73)
	Azathioprine	357 (6)
	Everolimus	263 (5)
	Sirolimus	33 (0.6)
	Number of immunosuppressants	
	≤1	211 (4)
	2	1985 (34)
	3–4	3627 (62)
Antihypertensive treatment	Renin–angiotensin–aldosterone inhibitors	3195 (56)
	Betablocker	3463 (60)
	Calcium channel blocker	2987 (51)
	Alfa receptor antagonist	585 (10)
	Diuretic	1783 (30)
	Number of antihypertensives	
	0	731 (13)
	1–2	2942 (51)
	3	1347 (23)
	4–5	804 (14)
Anticoagulation	Antiplatelet inhibitor	1639 (28)
	Warfarin/DOAC	681 (12)
Antidiabetic drugs	Blood glucose lowering drugs, excluding insulins	670 (12)
	Insulin	1021 (18)
Antidepressant		779 (13)
Statin		3309 (57)
Proton pump inhibitor		2947 (51)

Table 2: Semestral mortality and hospitalization due to COVID-19 among KTRs in Sweden.

Period	COVID-19 hospitalizations (number, %)	Hospitalization rate (per 10 000 person-years)	COVID-19 mortality (number, %)	Mortality rate per 10 000 person-years
1 January 2020–30 June 2020	80 (1.4)	0.76	15 (0.3)	0.14
1 July 2020–31 December 2020	82 (1.4)	0.77	9 (0.2)	0.08
1 January 2021–30 Jun 2021	161 (2.7)	1.58	31(0.5)	0.29
1 July 2021–31 December 2021	72 (1.2)	0.69	9 (0.2)	0.08

Number of people re-hospitalized in the period between 2020 and 2021, $n = 10$ (2 in the second semester, 3 in the third semester, 5 in the fourth semester).

was similar to the second semester (0.08/10 000 person-years) before any vaccines were available.

Risk factors for severe COVID-19

Demographic risk factors and comorbidity

Women had a lower risk of severe COVID-19 in both the unadjusted and adjusted analyses [adjusted odds ratio (aOR) 0.74, 95% confidence interval (CI) 0.59–0.92] (Table 3). Our results did not suggest an association between increasing age and risk of severe COVID-19. However, compared to those aged 18–38 years, we found that KTRs between 49 and 68 years were at higher risk, with the highest point estimate for patients aged 49–58 years (aOR 2.32, 95% CI 1.53–3.51). When investigating the risk in relation to the primary kidney disease, we found that as compared to patients with glomerulonephritis, those with hypertensive or renovascular kidney disease (aOR 1.57, 95% CI 1.03–2.40) had an increased risk of severe COVID-19, whereas the risk associated with diabetic nephropathy dropped below significance level after the adjustment for dialysis vintage and donor type. As for other concomitant comorbidities, our results identified hypertension, heart failure, COPD, and diabetes mellitus as risk factors in the unadjusted, but not in the multivariable adjusted models. Patients with a history of hospitalization for severe infection during the previous 12 months also had an increased risk for severe COVID-19 (aOR 1.59, 95% CI 1.15–2.19).

Kidney transplantation-related risk factors

We identified several kidney transplantation-related factors that were associated with an increased risk of severe COVID-19 (Table 3). A KTR with a deceased donor graft (versus a living donor graft) was at higher risk of COVID-19 hospitalization or death (aOR 1.41, CI 95% 1.09–1.84). Moreover, the risk of severe COVID-19 was also increased in those with a more recent kidney transplantation procedure. Every year that had passed since transplantation lowered the risk for severe COVID-19 by 3% (aOR 0.97, 95% CI 0.95–0.98). Compared to KTR who were transplanted <1 year ago, those who had received their transplant 6–10 years ago or >10 years ago had an about 50% lower risk of being hospitalized or die from COVID-19 (aOR 0.52, CI 95% 0.36–0.75 and aOR 0.57, CI 95% 0.41–0.79, respectively). Longer duration of chronic dialysis treatment prior to kidney transplantation was another important risk factor associated with an increased risk for COVID-19 hospitalization and death [aOR 1.04, CI 95% 1.01–1.06 (per 1 year increase)]. Among the other factors specific for KTR, we found that maintenance immunosuppressant treatment with MMF, was associated with an elevated risk for severe COVID-19 (aOR 1.47, CI 95% 1.08–1.99) while other immunosuppressants (tacrolimus, ciclosporin, corticosteroids, azathioprine, everolimus, sirolimus) were not independently associated with this outcome.

Drug-related risk factors

In our analyses, we could demonstrate an increased risk for severe COVID-19 for some of the antihypertensive drugs commonly used in the KTR population; calcium channel blockers (aOR 1.38, CI 95% 1.09–1.75), alfa receptor antagonists (aOR 1.44, CI 95% 1.03–1.98), and diuretics (aOR 1.44, CI 95% 1.13–1.84) were all associated with a higher risk in the multivariate analysis, but treatment with RAASi was not associated with a higher risk (aOR 1.23, 95% CI 0.97–1.56). The number of antihypertensive drugs used by patients was also important; the use of four or more antihypertensive drugs was associated with an increased risk compared to up to one drug (aOR 1.87, CI 95% 1.32–2.64). Use of insulin was also associated with an increased risk (aOR 1.84, CI 95% 1.22–2.79) whereas other blood glucose lowering drugs were not. Finally, there was a strong association between the use of PPI and the risk of severe COVID-19 in both the unadjusted and adjusted analyses (OR 1.88, 95% CI 1.52–2.33 and aOR 1.58, 95% CI 1.24–2.01, respectively). We found no significant associations for severe COVID-19 with anticoagulation therapy, antidepressants, or statin treatments.

In a sensitivity analysis, we investigated whether the risk associations for our main exposures were similar during the fourth semester when most KTR in Sweden had been offered two vaccinations with an mRNA vaccine. Due to the low number of events, we only performed an unadjusted analysis in which the results were in line with our main analysis, although with lower precision (Supplementary Table 3).

DISCUSSION

This nationwide observational study of characteristics, adverse outcomes, and risk factors among KTRs over the first 2 years of the COVID-19 pandemic in Sweden, reveals that some previously identified risk factors for severe COVID-19 in the general population, such as male gender, and antihypertensive medication also played a significant role among KTRs, while others, such as comorbidity status were not independent risk factors in our adjusted analyses [15–18]. In contrast to results in general population studies, we did not find a linear relationship between severe COVID-19 and increasing age among KTRs [16, 19, 20]. Instead, we identified specific age groups that appeared to have an elevated risk. In our cohort, individuals aged 49 to 68 years exhibited an increased risk of severe COVID-19, with the highest risk observed among those aged 49 to 58 years.

Sweden's public health policy regarding COVID-19 significantly differed from lockdown measures implemented in other countries. In Sweden, employers were recommended to

Table 3: Risk factors for COVID-19 hospitalization or death in KTRs.

Characteristic	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (7) (95% CI)	*P* value
Age, per year[a]	1.01 (1.00–1.02)	.053	1.01 (1.00–1.01)	.11	n/a	
18–38	Ref.					
39–48	1.37 (0.85–2.21)	.20	1.36 (0.84–2.19)	.21		
49–58	2.36 (1.56–3.57)	<.001	2.32 (1.53–3.51)	<.001		
59–68	1.94 (1.28–2.94)	.002	1.92 (1.26–2.91)	.002		
>68	1.62 (1.05–2.50)	.03	1.60 (1.04–2.47)	.03		
Women[b]	0.73 (0.59–0.92)	.01	0.74 (0.59–0.92)	.01		
Primary kidney disease[c]						
Glomerulonephritis	Ref.			Ref.		Ref.
Diabetes nephropathy	1.86 (1.36–2.54)	<.001	1.50 (1.03–2.21)	.03	1.35 (0.89–2.04)	.16
Hypertensive/renovascular	1.77 (1.21–2.59)	.003	1.70 (1.15–2.51)	.01	1.57 (1.03–2.40)	.04
Polycystic kidney disease/hereditary	1.29 (0.96–1.74)	.10	1.34 (0.99–1.81)	.05	1.31 (0.94–1.82)	.11
Tubulointerstitial disease	1.12 (0.77–1,64)	.54	1.22 (0.83–1.78)	.31	1.10 (0.72–1.68)	.65
Other specified kidney disease	2.22 (1.04–4,74)	.04	2.41 (1.12–5.25)	.02	2.01 (0.88–4.57)	.09
Unknown kidney disease	1.61 (1.13–2.29)	.09	1.68 (1.18–2.41)	.004	1.66 (1.12–2.46)	.01
Years on dialysis before kidney transplantation[c]	1.04 (1.02–1.07)	<.001	1.04 (1.01–1.07)	.004	1.04 (1.01–1.06)	.008
Years since kidney transplantation[c]	0.97 (0.95–0.98)	<.001	0.97 (0.95–0.98)	<.001	0.97 (0.95–0.98)	<.001
≤1 year		Ref.				
2–5 years	0.75 (0.56–1.01)	.06	0.74 (0.55–0.99)	.05	0.74 (0.53–1.03)	.07
6–10 years	0.50 (0.36–0.70)	<.001	0.49 (0.35–0.68)	<.001	0.52 (0.36–0.75)	<.001
>10 years	0.54 (0.40–0.72)	<.001	0.55 (0.41–0.74)	<.001	0.57 (0.41–0.79)	<.001
Deceased donor (vs live donor)[c]	1.74 (1.39–2.18)	<.001	1.59 (1.26–2.01)	<.001	1.41 (1.09–1.84)	<.001
Comorbidity[d]						
Hypertension	2.01 (1.09–3.70)	.02	1.39 (0.74–2.59)	.31	1.43 (0.70–2.99)	.33
Cerebrovascular disease	0.81 (0.53–1.24)	.33	0.70 (0.46–1.09)	.12	0.74 (0.47–1.16)	.19
Coronary artery disease	1.02 (0.71–1.46)	.91	0.80 (0.55–1.17)	.24	0.86 (0.58–1.28)	.46
Heart failure	1.72 (1.27–2.32)	<.001	1.50 (1.09–2.06)	.01	1.34 (0.96–1.88)	.09
COPD	2.11 (1.24–3.60)	.006	1.85 (1.07–3.2)	.03	1.72 (0.95–3.11)	.07
Connective tissue disorder	0.84 (0.47–1.48)	.54	0.91 (0.51–1.64)	.77	0.97 (0.53–1.79)	.93
Diabetes mellitus	1.42 (1.15–1.76)	.001	1.29 (1.04–1.61)	.02	1.22 (0.96–1.55)	.10
Solid cancer	0.83 (0.58–1.21)	.33	0.80 (0.55–1.17)	.25	0.70 (0.46–1.05)	.08
Hematological cancer	0.57 (0.23–1.39)	.21	0.56 (0.23–1.38)	.21	0.60 (0.24–1.50)	.28
Hospitalization for severe infection previous 12 months	1.56 (1.17–2.12)	.003	1.55 (1.14–2.11)	.01	1.59 (1.15–2.19)	.01
Immunosuppressive Medication[d]						
Systemic corticosteroids	1.47 (1.07–1.97)	.01	1.33 (0.99–1.80)	.05	1.25 (0.90–1.73)	.18
Cyclosporine	0.71 (0.52–0.98)	.04	0.78 (0.55–1.10)	.15	0.80 (0.55–1.16)	.24
Tacrolimus	1.41 (1.07–1.86)	.02	1.28 (0.94–1.74)	.11	1.37 (0.98–1.93)	.06
Mycophenolate mofetil	1.72 (1.32–2.25)	<.001	1.53 (1.14–2.01)	.004	1.47 (1.08–1.99)	.01
Azathioprine	0.55 (0.32–0.95)	.03	0.75 (0.43–1.30)	.31	0.82 (0.45–1.50)	.53
Everolimus	0.66 (0.36–1.18)	.16	0.64 (0.35–1.15)	.14	0.59 (0.31–1.13)	.11
Sirolimus	0.90 (0.21–3.77)	.88	1.07 (0.25–4.58)	.92	1.11 (0.26–4.78)	.88
Other immunosuppressants	0.66 (0.37–1.16)	.15	0.67 (0.36–1.14)	.13	0.62 (0.33–1.14)	.13
≥3 immunosuppressant	1.68 (1.33–2.11)	<.001	1.50 (1.17–1.93)	.001	1.48 (1.13–1.95)	.001
Antihypertensive medication[c]						
RAASi	1.28 (1.04–1.58)	.02	1.20 (0.96–1.49)	.09	1.23 (0.97–1.56)	.08
Betablocker	1.33 (1.07–1.65)	.01	1.15 (0.91–1.45)	.22	1.09 (0.85–1.40)	.50
Calcium channel blocker	1.49 (1.21–1.84)	<.001	1.38 (1.11–1.72)	.004	1.38 (1.09–1.75)	.007
Alfa receptor antagonist	1.74 (1.30–2.31)	<.001	1.57 (1.17–2.11)	.002	1.44 (1.03–1.98)	.003
Diuretic	1.67 (1.36–2.06)	<.001	1.49 (1.19–1.87)	<.001	1.44 (1.13–1.84)	<.001
Number of antihypertensive drugs	1.28 (1.18–1.38)	<.001	1.22 (1.11–1.33)	<.001	1.22 (1.11–1.33)	<.001
≥1 antihypertensive	Ref.		Ref.		Ref.	
2 antihypertensive	1.23 (0.93–1.64)	.15	1.11 (0.83–1.50)	.47	1.13 (0.82–1.56)	.46
3 antihypertensive	1.64 (1.23–2.18)	<.001	1.43 (1.06–1.92)	.02	1.35 (0.97–1.88)	.07
≥4 antihypertensive	2.35 (1.74–3.18)	<.001	1.95 (1.40–2.69)	<.001	1.87 (1.32–2.64)	<.001
Anticoagulation[e]						
Antiplatelet inhibitor	1.16 (0.93–1.45)	.19	0.93 (0.74–1.18)	.56	0.98 (0.76–1.27)	.89
Warfarin/DOAC	1.15 (0.85–1.56)	.38	1.02 (0.74–1.41)	.97	1.03 (0.73–1.46)	.84

Table 3: Continued

Characteristic	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (7) (95% CI)	*P* value
Antidiabetic drugs[c]						
Blood lowering drugs, excluding insulins	1.29 (0.96–1.73)	.10	1.01 (0.71–1.44)	.95	1.01 (0.74–1.57)	.66
Insulin	1.77 (1.39–2.24)	<.001	1.70 (1.17–2.47)	.005	1.84 (1.22–2.79)	.004
Antidepressant[c]	0.95 (0.70–1.29)	.74	0.94 (0.69–1.29)	.69	0.97 (0.69–1.35)	.94
Statin[c]	1.35 (1.09–1.68)	.01	1.17 (0.93–1.47)	.18	1.10 (0.86–1.40)	.46
Proton pump inhibitor[e]	1.88 (1.52–2.33)	<.001	1.69 (1.36–2.11)	<.001	1.58 (1.24–2.01)	<.001

[a]Adjusted for gender.
[b]Adjusted for age (categorical).
[c]Adjusted for age (categorical), gender, COPD, heart failure, hypertension, diabetes mellitus, coronary artery disease, hospitalization for severe infection previous 12 months.
[d]Adjusted for age (categorical), gender, COPD, heart failure, hypertension, diabetes mellitus, coronary artery disease, hospitalization for severe infection previous 12 months, and years since transplantation.
[e]Adjusted for age (categorical), gender, COPD, heart failure, hypertension, diabetes mellitus, coronary artery disease, hospitalization for severe infection previous 12 months, proton pump inhibitor.
[f]Adjusted for age (categorical), gender, COPD, heart failure, hypertension, diabetes mellitus, coronary artery disease, hospitalization for severe infection previous 12 months, antiplatelet inhibitor.
[g]Additionally adjusted for time on dialysis, donor type.

facilitate remote work for employees, but there was no outright closure of workplaces. All businesses and social services in Sweden operated as usual, except for recommendations to maintain a physical distance between individuals. However, while individuals aged 70 years and older were asked to self-isolate [21], working age individuals in Sweden may have encountered challenges in effectively isolating themselves since there was no formal lockdown. Additionally, patients between the ages of 49 and 58 may have had more extensive social interactions, including living with children of school age, and working spouses, compared to older patients. All these factors likely have influenced the risk of SARS-CoV-2 infection in this group.

Although many comorbid conditions (diabetes mellitus, hypertension, heart failure, and COPD) were associated with severe COVID-19 in the unadjusted analysis, we did not observe an independent association between a diagnosis of hypertension or other comorbid conditions and severe COVID-19 among KTRs [20, 22, 23]. This is not surprising since 95% of the cohort in this study had hypertension as a comorbidity. However, patients treated with three or more antihypertensive medications did have an increased risk. One potential explanation is that the use of multiple antihypertensive drugs reflects more severe hypertension and is a marker for severe comorbidity burden. Resistant hypertension is defined by the American Heart Association as above-goal elevated blood pressure in a patient despite the concurrent use of three antihypertensive drug classes at maximum or maximally tolerated daily doses or ≥4 antihypertensive medications [24]. Although our study did not include data on blood pressure, it is plausible to assume that the use of multiple antihypertensives reflects a more difficult-to-treat hypertension and thereby a risk factor for severe COVID-19. Similarly, the use of insulin, but not other blood glucose lowering agents or a diagnosis of diabetes mellitus was associated with severe COVID-19. Since insulin itself is unlikely to increase the risk of severe COVID-19, it may be seen as a marker of diabetes severity, emphasizing the importance of assessing the total comorbidity burden and disease severity in the risk assessment for KTRs.

Previous studies have shown that immunosuppressive treatment in organ transplant recipients increases the risk of infections, including COVID-19 [25, 26]. Despite the success of vaccination programs in the general population, the COVID-19 vaccines are less immunogenic in KTRs [11, 27–29]. Our study showed that the use of MMF was associated with an increased risk of severe COVID-19.

Our investigation took place mostly before vaccinations for COVID-19 started in Sweden. Although it is difficult to draw firm conclusions of the risk associations after the vaccination program was launched, our sensitivity analysis in the final semestral period after the vaccinations started in Sweden suggests similarly elevated risks for MMF users. Also, previous results from our group indicate that KTRs exhibited elevated risk of severe COVID-19 also after the introduction of vaccines [30]. This is in line with previous reports where MMF therapy has been associated with a reduced immune response to repeated vaccinations. In a German multicenter study, MMF treatment was the strongest predictor of a reduced response to SARS-CoV-2 vaccination in KTRs [31]. Additionally, a French liver transplant center reported that MMF was a major determinant of impaired seroconversion and optimal response to COVID-19 vaccination [32]. Furthermore, a German single center study suggested that pausing MMF before the fourth COVID-19 vaccination increased the serological response rate in KTRs [27]. In view of these data, it is plausible to assume that a reduced vaccine response due to MMF treatment may have increased the risk of severe COVID-19 in KTRs. With respect to other frequently used maintenance immunosuppressive medications in KTRs (calcineurin inhibitors, mTor inhibitors, and corticosteroids), we did not identify any risk association with severe COVID-19 outcomes.

Interestingly, our analysis revealed a strong association between the use of PPIs and an increased risk of severe COVID-19. This is particularly noteworthy considering that PPIs are typically prescribed post-transplantation as prophylaxis against ulcers and to prevent gastroesophageal reflux [33]. Despite their generally favorable safety profile, increasing evidence over the past decade has shown that PPI use is associated with various long-term clinical complications, including cardiovascular diseases, kidney and liver diseases, and infections [34, 35]. Furthermore, there is concern about pharmacological interactions between PPIs and immunosuppressive drugs in transplant patients, which could further exacerbate the risk of infections [36].

The major strengths of our study were the use of a nationwide, well-characterized cohort of KTRs within a universally funded healthcare system where patients had similar access to hospital care (and vaccination) and no missing KTR cohort data or loss to follow-up due to the linkages to Swedish national healthcare registers. However, we also acknowledge certain limitations. Like all observational studies, it is not possible to confer causality for our risk associations. Also, the SRR does not continuously record clinical variables such as glomerular filtration rate, blood pressure, and body mass index in KTRs, which may have resulted in some degree of residual confounding. Swedish legislation does not allow registration of ethnicity. A further limitation is thus that generalizability to other populations may therefore be limited.

In conclusion, our study presents several key findings related to the risk of experiencing severe COVID-19 among KTRs in Sweden. Notably, it underscores a heightened risk among individuals of working age, which may be attributed to the increased risk of virus transmission within the context of Sweden. This observation serves as a valuable lesson drawn from the COVID-19 pandemic, offering insights that should be considered when preparing for potential future pandemics. Additionally, our study suggests that it is likely the severity of comorbidities that constitutes an increased risk for severe disease rather than the comorbidity itself. Furthermore, our research highlights the potential significance of PPI therapy and suggests its possible role as a modifiable risk factor relevant to the management of COVID-19.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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CONFLICT OF INTEREST STATEMENT

None declared.

AUTHORS' CONTRIBUTIONS

M.E. was responsible for data acquisition; M.E., A.N., and J.W. were responsible for the concept and study design; A.C. did the statistical analysis; all authors interpreted the results; A.N., J.W., and M.E. drafted the manuscript; all authors critically revised and evaluated the content; and all authors conducted the final approval.

DATA AVAILABILITY STATEMENT

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

REFERENCES

1. Organization WH. *WHO Director-General's opening Remarks at the Media Briefing on COVID-19–11 March 2020*. https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 (10 April 2020, date last accessed).
2. Organization WH. *Coronavirus Disease (COVID-19)—Numbers at a Glance*. https://www.who.int/emergencies/diseases/novel-coronavirus-2019?adgroupsurvey=%7badgroupsurvey%7d&gclid=EAIaIQobChMIscXagO_0gAMVR5RoCR1q-QILEAAYASAAEgKuMfD_BwE (1 April 2024, date last accessed).
3. Wikipedia. *List of Epidemics and Pandemics*. https://en.wikipedia.org/wiki/List_of_epidemics_and_pandemics (1 April 2024, date last accessed).
4. Wong CKH, Lau KTK, Au ICH *et al*. Clinical improvement, outcomes, antiviral activity, and costs associated with early treatment with Remdesivir for patients with coronavirus disease 2019 (COVID-19). *Clin Infect Dis* 2021;**74**:1450–8. https://doi.org/10.1093/cid/ciab631
5. The RECOVERY Collaborative Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022;**399**:665–76. https://doi.org/10.1016/s0140-6736(22)00163-5
6. Dhand A, Okumura K, Wolfe K *et al*. Sotrovimab for treatment of COVID-19 in solid organ transplant recipients. *Transplantation* 2022;**106**:e336–7. https://doi.org/10.1097/tp.0000000000004136
7. Watson OJ, Barnsley G, Toor J *et al*. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022;**22**:1293–302. https://doi.org/10.1016/S1473-3099(22)00320-6
8. World Health Organization (WHO). *Statement on the Fifteenth Meeting of the IHR (2005) Emergency Committee on the COVID-19 Pandemic*. https://www.who.int/news/item/05-05-2023-statement-on-the-fifteenth-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-coronavirus-disease-(covid-19)-pandemic?adgroupsurvey=%7badgroupsurvey%7d&gclid=EAIaIQobChMI3KbFvqrl_gIVAuuyCh0x-wMPEAAYASABEgKR-fD_BwE (10 May 2023, date last accessed).
9. Cristelli MP, Rissoni RAP, Viana LA *et al*. How did the omicron surge affect kidney transplant recipients compared with a cohort from the general population? *Transplantation* 2022;**106**:e382–3. https://doi.org/10.1097/tp.0000000000004193
10. Hamm SR, Rezahosseini O, Møller DL *et al*. Incidence and severity of SARS-CoV-2 infections in liver and kidney transplant recipients in the post-vaccination era: real-life data from Denmark. *Am J Transplant* 2022;**22**:2637–50. https://doi.org/10.1111/ajt.17141
11. Nowak A, Hemmingsson P, Evans M *et al*. Serological response to Nuvaxovid (NVX-CoV2373) vaccine given as a fifth dose in non- and low-responder kidney transplant recipients. *Nephrol Dial Transplant* 2023;**38**:1564–6. https://doi.org/10.1093/ndt/gfad010

12. Caillard S, Chavarot N, Francois H *et al*. Is COVID-19 infection more severe in kidney transplant recipients? *Am J Transplant* 2021;**21**:1295–303. https://doi.org/10.1111/ajt.16424
13. Svenskt Njurregister (Swedish Renal Registry). Annual report 2018. Sweden: Länsjukhuset Ryhov. Jönköping. Accessed 20 March 2020, https://www.medscinet.net/snr/rapporterdocs/Svenskt%20Njurregister%202018.pdf, 2020.
14. Wettermark B, Zoega H, Furu K *et al*. The Nordic prescription databases as a resource for pharmacoepidemiological research—a literature review. *Pharmacoepidemiol Drug Saf* 2013;**22**:691–9. https://doi.org/10.1002/pds.3457
15. Leon-Abarca JA, Memon RS, Rehan B *et al*. The impact of COVID-19 in diabetic kidney disease and chronic kidney disease: a population-based study. *Acta Biomed* 2020;**91**:e2020161. https://doi.org/10.23750/abm.v91i4.10380
16. Fang X, Li S, Yu H *et al*. Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis. *Aging* 2020;**12**:12493–503. https://doi.org/10.18632/aging.103579
17. Attaway AA, Zein J, Hatipoğlu US. SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: an analysis of Cleveland Clinic's COVID-19 registry. *EClinMed* 2020;**26**:100515. https://doi.org/10.1016/j.eclinm.2020.100515
18. Bae S, Kim SR, Kim M-N *et al*. Impact of cardiovascular disease and risk factors on fatal outcomes in patients with COVID-19 according to age: a systematic review and meta-analysis. *Heart* 2021;**107**:373–80. https://doi.org/10.1136/heartjnl-2020-317901
19. Pijls BG, Jolani S, Atherley A *et al*. Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies. *BMJ Open* 2021;**11**:e044640. https://doi.org/10.1136/bmjopen-2020-044640
20. Richardson S, Hirsch JS, Narasimhan M *et al*. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;**323**:2052–9. https://doi.org/10.1001/jama.2020.6775
21. Swedish Public Health Autorithy F. The public health agency of Sweden, information about Covid -19 pandemic. https://www.folkhalsomyndigheten.se/smittskydd-beredskap/utbrott/utbrottsarkiv/covid-19-pandemin-2019-2023/nar-hande-vad-under-pandemin/ (19 April 2024, date last accessed).
22. Gao C, Cai Y, Zhang K *et al*. Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. *Eur Heart J* 2020;**41**:2058–66. https://doi.org/10.1093/eurheartj/ehaa433
23. Huang S, Wang J, Liu F *et al*. COVID-19 patients with hypertension have more severe disease: a multicenter retrospective observational study. *Hypertens Res* 2020;**43**:824–31. https://doi.org/10.1038/s41440-020-0485-2
24. Carey RM, Calhoun DA, Bakris GL *et al*. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. *Hypertension* 2018;**72**:e53–90. https://doi.org/10.1161/HYP.0000000000000084
25. Caillard S, Anglicheau D, Matignon M *et al*. An initial report from the French SOT COVID Registry suggests high mortality due to COVID-19 in recipients of kidney transplants. *Kidney Int* 2020;**98**:1549–58. https://doi.org/10.1016/j.kint.2020.08.005
26. Osmanodja B, Mayrdorfer M, Halleck F *et al*. Undoubtedly, kidney transplant recipients have a higher mortality due to COVID-19 disease compared to the general population. *Transpl Int* 2021;**34**:769–71. https://doi.org/10.1111/tri.13881
27. Osmanodja B, Ronicke S, Budde K *et al*. Serological response to three, four and five doses of SARS-CoV-2 vaccine in kidney transplant recipients. *J Clin Med* 2022;**11**:2565. https://doi.org/10.3390/jcm11092565
28. Prendecki M, Willicombe M. SARS-CoV-2 vaccine strategies in kidney transplant recipients. *Lancet Infect Dis* 2023;**23**:263–4. https://doi.org/10.1016/S1473-3099(22)00666-1
29. Ma BM, Tam AR, Chan KW *et al*. Immunogenicity and safety of COVID-19 vaccines in patients receiving renal replacement therapy: a systematic review and meta-analysis. *Front Med* 2022;**9**:827859. https://doi.org/10.3389/fmed.2022.827859
30. Wijkström J, Caldinelli A, Bruchfeld A *et al*. Results of the first nationwide cohort study of outcomes in dialysis and kidney transplant patients before and after vaccination for COVID-19. *Nephrol Dial Transplant* 2023;**38**:2607–16. https://doi.org/10.1093/ndt/gfad151
31. Kantauskaite M, Müller L, Kolb T *et al*. Intensity of mycophenolate mofetil treatment is associated with an impaired immune response to SARS-CoV-2 vaccination in kidney transplant recipients. *Am J Transplant* 2022;**22**:634–9. https://doi.org/10.1111/ajt.16851
32. Meunier L, Sanavio M, Dumortier J *et al*. Mycophenolate mofetil decreases humoral responses to three doses of SARS-CoV-2 vaccine in liver transplant recipients. *Liver Int* 2022;**42**:1872–8. https://doi.org/10.1111/liv.15258
33. Courson AY, Lee JR, Aull MJ *et al*. Routine prophylaxis with proton pump inhibitors and post-transplant complications in kidney transplant recipients undergoing early corticosteroid withdrawal. *Clin Transplant* 2016;**30**:694–702. https://doi.org/10.1111/ctr.12736
34. Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 2011;**56**:931–50. https://doi.org/10.1007/s10620-010-1560-3
35. Yibirin M, De Oliveira D, Valera R *et al*. Adverse effects associated with proton pump inhibitor use. *Cureus* 2021;**13**:e12759. https://doi.org/10.7759/cureus.12759
36. Boonpheng B, Thongprayoon C, Bathini T *et al*. Proton pump inhibitors and adverse effects in kidney transplant recipients: a meta-analysis. *World J Transplant* 2019;**9**:35–47. https://doi.org/10.5500/wjt.v9.i2.35

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