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Original Article

ORIGINAL ARTICLE

Mortality associated with the COVID-19 pandemic in the Swiss dialysis population beyond SARS-CoV-2 infection

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ABSTRACT

Background. While SARS-CoV-2 infection has direct obvious consequences on patients undergoing dialysis, the COVID-19 pandemic also had an indirect impact on health systems. Therefore, we aimed to determine whether the COVID-19 era itself was associated with adverse consequences in the Swiss dialysis population as compared to the pre-COVID-19 era, while accounting for direct impact of SARS-CoV-2 infection.
Methods. We retrospectively included all patients recorded in the Swiss dialysis registry from January 2014 to December 2022. The pre-COVID-19 era and the COVID-19 era were defined based on the cut-off date of January 2020. Cox proportional hazard model was used with all-cause mortality as the primary outcome.
Results. The cohort consisted of 7837 patients from 97 dialysis centres. Median age was 68.6 years with 66.1% men. Crude mortality rates were 11.6% (11.0% to 12.2%) and 14.2% (13.4% to 14.9%) person-years for the pre-COVID-19 era and the COVID-19 era, respectively. In multivariable analysis, SARS-CoV-2 infection was associated with an increased risk of mortality (HR 4.26, 95% CI 3.65 to 4.97, $P < .001$) while the COVID-19 era itself was not (HR 0.98, 95% CI 0.88 to 1.08, $P = .687$).
Conclusions. The COVID-19 era was not associated with an excess of mortality in the Swiss dialysis population as compared to the pre-COVID-19 era when accounting for the direct effect of SARS-CoV-2 infection. This suggests that control measures established during the pandemic did not have a negative impact on dialysis patients at the national level. These results could inform health policy makers in the eventuality of future pandemics.

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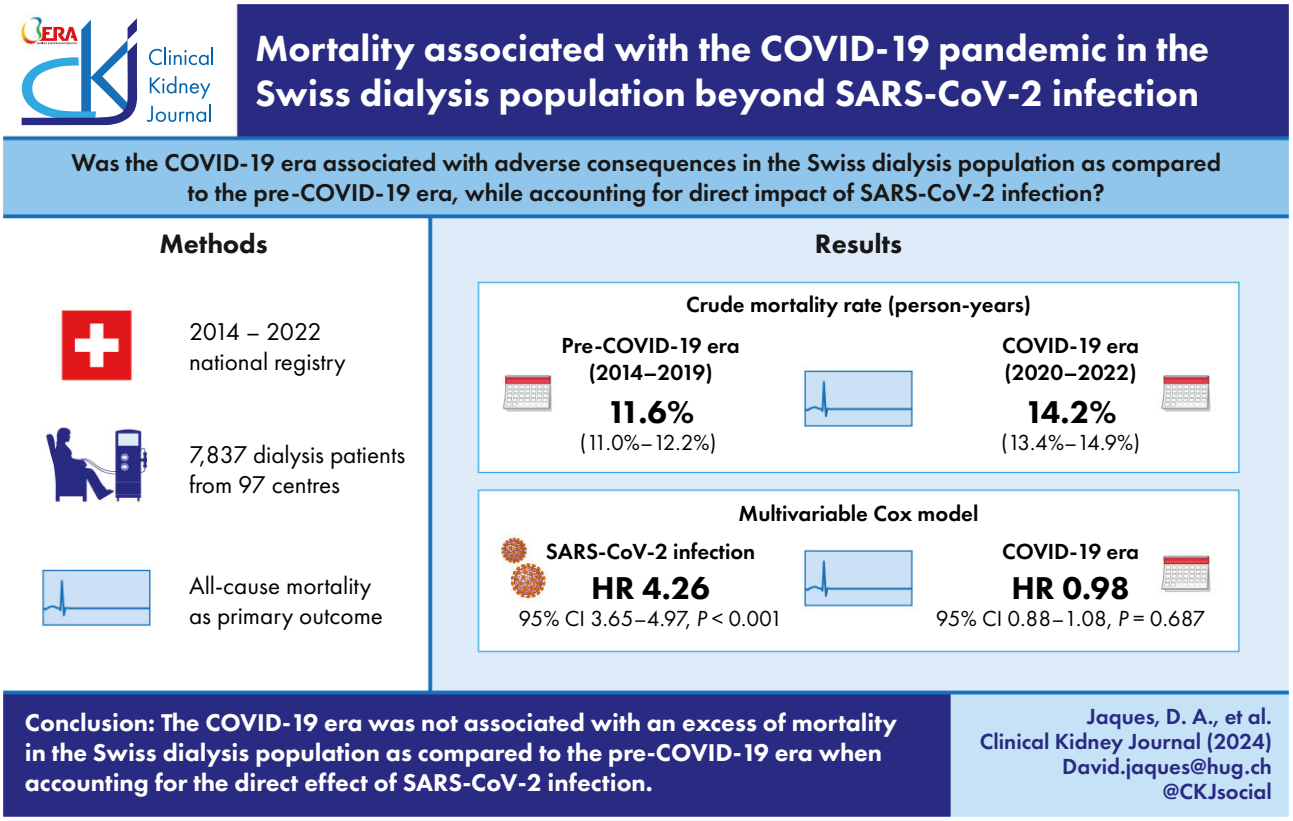
GRAPHICAL ABSTRACT



Keywords: control measures, COVID-19, dialysis, mortality, SARS-CoV-2 infection

KEY LEARNING POINTS

What was known:

- Chronic dialysis patients are vulnerable to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19).
- Beyond direct consequences of SARS-CoV-2 infection, the COVID-19 pandemic also imposed major strains on health systems with a considerable decrease in overall care.
- The overall impact of the COVID-19 pandemic on the outcomes of the chronic dialysis population is largely unknown.

This study adds:

- Using a Swiss national registry over a 9-year time span, we confirm that SARS-CoV-2 infection markedly increased mortality risk in dialysis patients.
- However, the COVID-19 era itself (January 2020 to December 2022) was not associated with an excess of mortality as compared to the pre-COVID-19 era (January 2014 to December 2019) when accounting for the direct effect of viral infection.

Potential impact:

- This suggests that global control measures established during the COVID-19 pandemic did not negatively impact the prognosis of dialysis patients at the national level.
- Those results could inform health policy makers and regulatory agencies in the eventuality of future pandemics to provide equitable and appropriate care to patients requiring chronic dialysis.

INTRODUCTION

The first case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19) in Switzerland was confirmed on 24 February 2020. The number of cases in the Swiss general population steeply increased thereafter with the Federal Council declaring a complete lockdown on 16 March 2020 [1]. Incidence rates of

confirmed SARS-CoV-2 infection rose from 3.7 to 44.3 cases per 100 000 person-days in the Swiss general population during the first and second waves, respectively [1]. Numerous studies worldwide have illustrated that chronic dialysis patients are at increased risk of severe COVID-19, thus translating into high fatality rates [2, 3]. Moreover, observational studies suggest a 4-fold increase of mortality in this population as compared to dialysis-free patients, even after adjustment for clinical and demographical confounders [4]. Overall, the proportion of SARS-CoV-2 infection is estimated to range mostly from 5% to 50% and case fatality rate from 0% to 30% in the worldwide dialysis population [5–11]. Among the main reasons for this poor overall prognosis are the high prevalence of comorbidities in dialysis patients such as cardiovascular diseases and immunocompromised status [12]. Also, with many countries instituting nationwide lockdown, dialysis patients represent a particularly vulnerable group with increased exposure to potential viral transmission owing to frequent transportation to and from dialysis facilities as well as regular contacts with other patients and health workers [13]. Beyond direct consequences of SARS-CoV-2 infection, the COVID-19 pandemic also imposed major strains on global health systems with a considerable decrease in overall care [14]. Consequently, the full impact of the pandemic probably goes much beyond what is indicated by the sheer number of deaths caused by SARS-CoV-2 infection alone [15]. Facing the pandemic, dialysis centres had to rapidly dedicate significant resources to infection control and prevention policies while maintaining essential routine care [16]. In this regard, a recent collaborative survey illustrated that the COVID-19 pandemic had a wide-scale impact on dialysis centres worldwide with important variations in infection rates, resources allocations, and structural adaptations [11].

While the direct impact of SARS-CoV-2 infection is now well described both in Switzerland and around the globe, the overall impact of the COVID-19 pandemic on the outcomes of the chronic dialysis population is unknown [1]. Consequently, we conducted the present study to determine whether the COVID-19 era itself was associated with an increased mortality in the Swiss chronic dialysis population as compared to the pre-COVID-19 era, while accounting for the direct effect of SARS-CoV-2 infection.

MATERIALS AND METHODS

Participants and setting

In Switzerland, all patients undergoing dialysis for at least 3 months are captured in the Swiss Renal Registry and Quality Assessment Program (SRRQAP). This national registry has been established by the Swiss Society of Nephrology on a voluntary basis since 2006 and on a legal obligation since 2013. The SRRQAP includes all medical establishments from Switzerland (both public and private) providing chronic peritoneal (PD) or haemodialysis (HD) treatment and consists in basic demographical, clinical, and biological data. The registry is completed at the beginning of each year by medical staff of respective dialysis centres with data collected during the previous elapsed calendar year. Data are input electronically in a central SecuTrial® database common to all dialysis centres. In the present study, we retrospectively included all incident patients recorded in the SRRQAP who started dialysis from 1 of January 2014 to the 31 December 2022. No exclusion criteria were applied. As stated, patients on dialysis for <3 months were not considered.

In Switzerland, dialysis centres rapidly implemented structural-level policies in face of the COVID-19 pandemic. Such measures were not reported in the SRRQAP. However, authors (R.G., B.P., and P.A.) were active in the National Dialysis Registry and National Dialysis Commission during the pandemic. Based on those information, implemented protocols throughout dialysis centres in Switzerland mainly included the following measures: (i) systematic screening of chronic dialysis patients for SARS-CoV-2 infection, (ii) measurement of body temperature before each dialysis session, (iii) distancing between dialysis stations of >1 m, (iv) systematic hand and respiratory hygiene measures, (v) use of full protective equipment when caring for patients with confirmed SARS-CoV-2 infection, and (vi) dedicated shifts for SARS-CoV-2 infected patients.

Variables

The COVID-19 era was defined as the period ranging from January 2020 to December 2022. The pre-COVID-19 era was defined as the period ranging from January 2014 to December 2019. Body mass index (BMI) was calculated and expressed as kg/m^2. The presence of diabetes and hypertension were defined on the presence of related medications. Charlson comorbidity score was calculated according to its original definition [17]. Standard laboratory analyses were performed at respective dialysis centres or affiliated clinical laboratories on fresh samples. A SARS-CoV-2 infection was defined as a positive reverse transcriptase polymerase chain reaction (RT-PCR) test on a sample obtained from the upper respiratory tract by nasopharyngeal or oropharyngeal swab, regardless of the presence or absence of symptoms.

Statistical analysis

Continuous variables are expressed as median and interquartile range. Categorical variables are expressed as number and relative frequencies (%). Baseline characteristics were compared between patients starting dialysis during the pre-COVID-19 era or during the COVID-19 era. Between-groups comparison was conducted using a *t*-test as well as chi-square for continuous and categorical variables, respectively. We conducted survival analyses with all-cause mortality as the primary outcome and COVID-19 era as the main predictor. The last follow-up date was the 31 of December 2022. For univariable analyses, we used an extended Kaplan–Meier survival function. For multivariable analyses, we used a time-varying multivariable Cox proportional hazard model. We adjusted for the following potential confounders that were a priori specified: age, gender, BMI, Charlson comorbidity score, dialysis mode (HD as opposed to PD), SARS-CoV-2 infection, and SARS-CoV-2 vaccination [17]. COVID-19 era, SARS-CoV-2 infection, and SARS-CoV-2 vaccination were time-dependent variables. SARS-CoV-2 infection was assumed to have an influence on the outcome of death during the 90 days following a positive RT-PCR test as advocated by previous studies [18, 19]. Date of vaccination against SARS-CoV-2 was not reported in the national registry. Consequently, vaccination against SARS-CoV-2, if administered, was considered to have taken place on the 19 of December 2020, when vaccination first became available in Switzerland. Patients transplanted during follow-up were censored. Complete case analysis was conducted. Proportional hazard assumption was tested using log–log plots. *P* values <.05 were considered significant. Statistical analyses were conducted using R version 4.2.3.

Table 1: Baseline characteristics at dialysis initiation according to period of dialysis initiation (pre-COVID-19 era as opposed to COVID-19 era) ($n = 7'837$).

	Pre-COVID-19 era (2014–2019) ($n = 5399$)	COVID-19 era (2020–2022) ($n = 2438$)	*P* value
Age (years)	68.4 (56.8–76.9)	69.3 (57.3–77.8)	.058
Gender (men)	3578 (66.2%)	1604 (65.7%)	.678
BMI (kg/m^2)	25.3 (22.2–29.3)	25.5 (22.3–29.4)	.192
Ethnicity (White)			.380
- White	4975 (92.8%)	2238 (91.8%)	
- African	142 (2.6%)	78 (3.3%)	
- Asian	170 (3.2%)	80 (3.3%)	
- Other	76 (1.4%)	42 (1.7%)	
Diabetes	1996 (36.9%)	906 (37.1%)	.871
Hypertension	4398 (81.5%)	2016 (82.7%)	.072
ESKD cause			
- Diabetes	1085 (20.1%)	471 (19.3%)	.854
- Vascular disease	1256 (23.2%)	579 (23.7%)	
- Glomerulonephritis	812 (15.0%)	374 (15.3%)	
- Other	2246 (41.6%)	1014 (41.5%)	
Charlson score	4 (2–5)	4 (2–5)	.929
Dialysis treatment (HD)	4618 (85.6%)	2137 (87.6%)	**.014**
AVF	2278 (49.3%)	904 (42.3%)	**<.001**
Haemoglobin (g/l)	109 (99–119)	109 (99–119)	.698
Calcium (mmol/l)	2.21 (2.10–2.32)	2.21 (2.11–2.33)	.390
Phosphate (mmol/l)	1.57 (1.30–1.89)	1.58 (1.30–1.93)	**.039**

Abbreviations: BMI, body mass index; ESKD, end-stage kidney disease.
Bold values indicate $P < .05$.

Ethics

All patients included after January 2021 in the SRRQAP provided informed consent for their coded data to be used for quality control and clinical research purposes. For patients included before the year 2021, use of their data was granted retrospectively by the local ethics committee of the canton of Zurich, Switzerland (KEK-ZH) (number 2020-02401) based on article 34 HFG, which regulates handling of data obtained without consent and information. This study was approved by the local ethics committee of the canton of Zurich and performed according to the declaration of Helsinki.

RESULTS

Baseline characteristics

The entire cohort consisted of 7837 patients from 97 dialysis centres with 5399 (68.8%) starting dialysis during the pre-COVID-19 era (January 2014 to December 2019) and 2438 (31.1%) starting during the COVID-19 era (January 2020 to December 2022). Median age was 68.6 (57.1–77.2) years with 5182 (66.1%) men. Baseline characteristics of patients according to period of dialysis initiation are described in Table 1. Compared to patients starting dialysis during the pre-COVID-19 era, those starting during the COVID-19 era were more likely to undergo HD (as opposed to PD), less likely to bear an arteriovenous fistula (AVF), and had higher serum phosphate. Other baseline characteristics were similar between groups.

Follow-up description

A schematic representation of the follow-up according to study periods is provided in Supplementary Figure S1. Considering the whole cohort, the median follow-up time was 27 (12–47) months, during which 1570 (20.0%) patients received a kidney transplant and 2767 (35.3%) patients died corresponding to a crude annual mortality rate of 12.8% (12.3% to 13.3%) person-years. During the pre-COVID-19 era (2014–2019), 1360 (25.2%) patients died corresponding to a crude annual mortality rate of 11.6% (11.0% to 12.2%) person-years. Major causes of death were cardiovascular and infection diseases with respective annual mortality rates of 3.5% and 2.0%. During the COVID-19 era (2020–2022), 1836 (33.2%) patients had a SARS-CoV-2 infection with a case fatality rate of 9.7%. During this same period, 1407 (25.4%) patients died corresponding to a crude annual mortality rate of 14.2% (13.4% to 14.9%) person-years. Major causes of death were cardiovascular and infection diseases with respective annual mortality rates of 3.8% and 3.6%. The annual cause-specific mortality rate according to study periods is illustrated in Fig. 1.

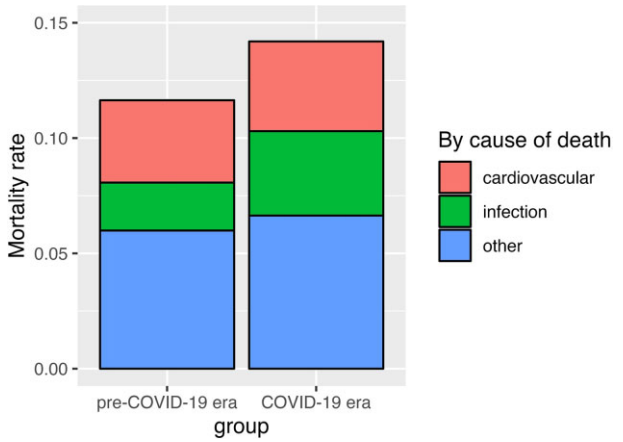


Figure 1: Annual cause-specific mortality rates according to study periods ($n = 7837$).

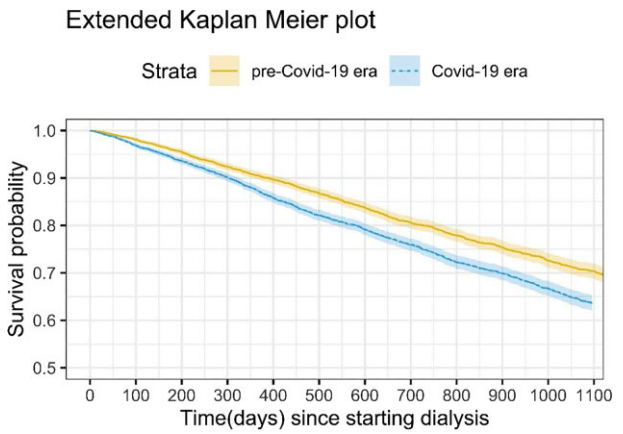


Figure 2: Extended Kaplan–Meier survivor function for all-cause mortality according to study periods ($n = 7837$).

Mortality risk analysis

Extended Kaplan–Meier survivor function allowing estimation of all-cause mortality according to time-varying covariable study periods (COVID-19 era as opposed to the pre-COVID-19 era) is illustrated in Fig. 2. Results from the univariable as well as multivariable Cox model for all-cause mortality are presented in Table 2. In univariable analysis, SARS-CoV-2 infection, age,

Table 2: Cox model for all-cause mortality ($n = 7837$).

	Univariable analysis			Multivariable analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
COVID-19 era (as opposed to pre-COVID-19 era)	1.07	0.98 to 1.12	.119	0.98	0.88 to 1.08	.687
SARS-CoV-2 infection	4.16	3.59 to 4.80	**<.001**	4.26	3.65 to 4.97	**<.001**
SARS-CoV-2 vaccination	1.04	0.96 to 1.14	.334	0.90	0.80 to 1.00	.055
Age (years)	1.05	1.04 to 1.05	**<.001**	1.04	1.03 to 1.04	**<.001**
Gender (woman)	0.89	0.82 to 0.96	**.003**	0.98	0.90 to 1.06	.656
BMI (kg/m^2)	0.97	0.97 to 0.98	**<.001**	0.97	0.96 to 0.97	**<.001**
Charlson score	1.23	1.22 to 1.25	**<.001**	1.19	1.17 to 1.21	**<.001**
HD treatment (as opposed to PD treatment)	1.13	1.01 to 1.26	**.041**	0.81	0.72 to 0.92	**.002**

Abbreviations: HR, hazard ratio; BMI, body mass index; HD, haemodialysis; PD, peritoneal dialysis.
Bold values indicate $P < .05$.

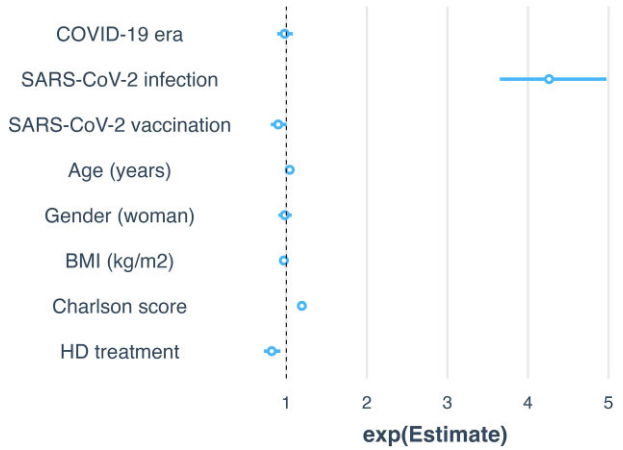


Figure 3: Hazard ratios of multivariable Cox survivor function for all-cause mortality ($n = 7837$).

Charlson comorbidity score, and HD (as opposed to PD) were positively associated with mortality risk, whereas woman gender and BMI were negatively associated with mortality risk. The COVID-19 era itself and SARS-CoV-2 vaccination were not associated with mortality risk. In multivariable analysis adjusting for a priori specified confounders, SARS-CoV-2 infection, age, and Charlson comorbidity score were positively associated with mortality risk, whereas HD (as opposed to PD) and BMI were negatively associated with mortality risk. The COVID-19 era itself, SARS-CoV-2 vaccination, and gender were not associated with mortality risk. Hazard ratios of multivariable Cox model for all-cause mortality are illustrated in Fig. 3.

In sensitivity analysis, PD patients were excluded and the sub-group of 6632 patients on HD was considered. Results from the multivariable Cox model for all-cause mortality further adjusted for the presence of AVF are presented in Supplementary Table 1. Results were similar to the main analysis and the COVID-19 era itself was not associated with mortality risk. The presence of an AVF was negatively associated with mortality risk.

DISCUSSION

In this study, we reported on the mortality of chronic dialysis patients in Switzerland over a 9-year time span, comparing the pre-COVID-19 era (2014 to 2019) to the COVID-19 era (2020 to 2022). While SARS-CoV-2 infection markedly increased mortality risk, the COVID-19 era itself was not associated with an excess of mortality in this population as compared to the pre-COVID-19 era. These results provide new insights into the overall impact of the COVID-19 pandemic on chronic dialysis patients at a national level and could be informative to health care policy makers in the eventuality of future pandemics.

SARS-CoV-2 infection has major direct consequences on patients undergoing chronic dialysis. The International Society of Nephrology (ISN) and the Dialysis Outcomes and Practice Patterns Study (DOPPS) collaborated to characterize those consequences on a worldwide level [6, 11]. Infection rates varied considerably among participating countries, mirroring in part the infection burden in the general population [6]. In Western Europe, the proportion of SARS-CoV-2 infection among chronic HD patients mostly ranged between 5% to 30% [11]. In the present study, we observed a slightly higher proportion of cases with 33% of the Swiss chronic dialysis population positive for SARS-CoV-2 infection at any time during the COVID-19 era. Moreover, we observed a case fatality rate of 9.7% in line with local and worldwide previously published data [1, 11]. This confirms the major vulnerability of dialysis patients in the setting of the COVID-19 pandemic [4, 12, 13]. When comparing time periods before and during the COVID-19 pandemic, we observed a substantial 2.6% increase in overall mortality rates from 11.6% to 14.2% person-years. Infection-related mortality rates largely contributed to this phenomenon increasing from 2.0% in the pre-COVID-19 era to 3.6% in the COVID-19 era. More specifically, SARS-CoV-2 infection was associated with a >4-fold increase in mortality independent of other predictors. Comparable results have been reported in a previous study including 56 chronic HD patients in two Spanish centres [18]. Finally, we did not observe an association between vaccination against SARS-CoV-2 and all-cause mortality in multivariable analysis. However, the diagnosis of SARS-CoV-2 infection was based on a positive PCR test, regardless of the presence of symptoms. Moreover, the direct effect of SARS-CoV-2 infection on mortality was also considered in our model. Consequently, one should not conclude from our results that SARS-CoV-2 vaccination is overall ineffective.

Beyond direct obvious consequences of SARS-CoV-2 infection on patients' health, the COVID-19 pandemic had a major indirect impact on dialysis services posing a challenge to resource allocation, infrastructure organization and overall health care [11]. Consequently, national organizations have issued guidelines on the conduct of in-centre HD treatment during the COVID-19 pandemic [20–22, 23]. Among potential measures, a decrease

in dialysis frequency and/or duration (i.e. incremental HD) has been suggested to decrease time at risk of infection in dialysis centres. This practice has been observed to be safe both in routine clinical care as well as during the COVID-19 pandemic in selected cases [24, 25]. However, such practice could also be associated with poor outcomes when resources are limited [26]. Moreover, adoption of social distancing of >2 m in dialysis stations as well as the implementation of isolation rooms and dedicated shifts for infected patients might have resulted in a decrease of total dialysis sessions provided by centres [27]. Missed HD sessions have also been a challenge for most centres owing to interruption of transportation services, disruption of HD shifts or avoidance of exposure to viral transmission [5]. Finally, pandemic conditions have put an unprecedented pressure on the nephrology workforce of HD centres with some regions reporting more than half of their staff being infected with SARS-CoV-2 [11]. In addition, remaining staff had to face redeployment in other clinical areas as well as the supplemental workload of providing nephrology consult and dialysis treatment to patients with acute kidney injury associated with SARS-CoV-2 infection [28, 29]. Outside nephrology, the COVID-19 pandemic was also associated with a decrease of about one-third in overall healthcare use, affecting not only outpatient visits but also hospital admissions as well as diagnostic and therapeutic procedures [14]. This equally affected emergency, primary, and speciality care with similar consequences for non-COVID-19 patients [30, 31]. Altogether, those indirect consequences of the COVID-19 pandemic might have affected dialysis patients care beyond direct effects of the SARS-CoV-2 infection itself. While major reductions in overall healthcare utilization have been observed during the COVID-19 pandemic, the impact of such constraints on chronic dialysis patients care is largely unknown [14]. Based on large epidemiological datasets, it is usually accepted that the full impact of the COVID-19 pandemic has been significantly greater than reported deaths attributed to SARS-CoV-2 infection alone [15]. In the USA, it has been estimated that 84% of all-cause excess mortality during the COVID-19 pandemic could be statistically attributed to the direct impact of SARS-CoV-2 infection, while the remaining proportion would represent indirect consequences [32]. Similarly, cardiovascular mortality unrelated to SARS-CoV-2 infection was considerably in excess in Norway during 2020–2022 [33]. Conversely, fewer deaths than expected were reported in Switzerland during 2020–2022 once accounting for mortality directly caused by SARS-CoV-2 infection, suggesting indirect positive effects of control measures [34]. In the present study, we observed that the COVID-19 era (2020 to 2022) per se was in fact not associated with an increased risk of mortality in chronic dialysis patients as compared to the pre-COVID-19 era (2014 to 2019) in Swiss dialysis centres once accounting for the direct effect of SARS-CoV-2 infection. We could thus not demonstrate a negative effect from the indirect consequences of the COVID-19 era or the control measures on the mortality of Swiss dialysis patients. This result could serve national policymakers on the guidance to dialysis centres in case of future pandemic hazard.

Among other considered variables, we observed that older age, high Charlson comorbidity score as well as low BMI were associated with an increased risk of mortality during the COVID-19 pandemic in the Swiss dialysis population [35, 36]. Those factors are well-recognized prognostic parameters in this population and our results are in agreement with those clinical associations at the national level. Finally, HD treatment (as opposed to PD treatment), was associated with increased mortality risk in univariable analysis but decreased mortality risk in multivariable analysis. This would suggest that the unfavourable prognosis associated with HD treatment in this setting is mainly mediated by confounding variables such as a higher risk of SARS-CoV-2 infection and/or higher burden of comorbidity. Moreover, differences in SARS-CoV-2 screening strategies between HD and PD patients might account for the apparent protective effect of HD treatment on all-cause mortality. It also must be noted that dialysis modality was defined at treatment initiation and not updated during follow-up. We believe, however, that readers should not overinterpret this finding as treatment modality was integrated in our multivariable analysis to adjust for potential cofounding effects on the primary outcome and not to infer conclusions on this specific clinical parameter. Furthermore, it has previously been shown that home dialysis was associated with a lower burden of SARS-CoV-2 infection, hospitalization and mortality as compared to in-centre HD [37]. Finally, in sensitivity analysis considering only HD patients, the presence of an AVF was associated with a lower risk of mortality as compared to vascular access with a catheter. This observation is in agreement with previous reports on this specific topic [38].

Readers must bear in mind certain limitations of our study. Most important is the fact that data not routinely captured in the SRRQAP registry could not be retrieved a posteriori. Specifically, date of vaccination against SARS-CoV-2 was not reported and had to be imputed. Moreover, details on structural-level policies implemented in each dialysis centre during the COVID-19 pandemic were not available and could not be specifically taken into account in our analyses. We believe, however, that major factors influencing mortality were included in our multivariable analyses thus allowing for robust conclusions to be drawn. Finally, in regard with the follow-up period, longer term consequences of the COVID-19 pandemic could not be excluded. Theoretically, a detrimental impact of the pandemic on patients' prognosis might also have been obscured by a concomitant improvement of health care over time. The main strength of our study is represented by a large and unbiased sample of all patients undergoing dialysis at a national level over several years for which precise and granular data were available.

CONCLUSION

Using a national registry over a 9-year time span, we confirm that SARS-CoV-2 infection markedly increased mortality risk in Swiss dialysis patients. However, the COVID-19 era itself (January 2020 to December 2022) was not associated with an excess of mortality in this population as compared to the pre-COVID-19 era (January 2014 to December 2019) when accounting for the direct effect of viral infection. This suggests that global control measures established during the COVID-19 pandemic did not negatively impact the prognosis of dialysis patients at the national level. Those results could inform health policy makers and regulatory agencies in the eventuality of future pandemics to provide equitable and appropriate care to patients requiring chronic dialysis.

SUPPLEMENTARY DATA

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

FUNDING

This study required no specific source of funding.

AUTHORS' CONTRIBUTIONS

D.A.J. analysed the data, interpreted the results, and wrote the manuscript. L.H. analysed the data and revised the manuscript. R.G. managed the data, interpreted the results, and revised the manuscript. M.K. analysed the data, interpreted the results, and revised the manuscript. B.P. designed the study, interpreted the results, and revised the manuscript. P.A. designed the study, interpreted the results, and revised the manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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