Clinical Outcomes and Vaccine Effectiveness for SARS-CoV-2 Infection in People Attending Advanced CKD Clinics

A Retrospective Provincial Cohort Study

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Abstract

Background People with advanced CKD are at high risk of mortality and morbidity from coronavirus disease 2019 (COVID-19). We measured rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe outcomes in a large population attending advanced CKD clinics during the first 21 months of the pandemic. We examined risk factors for infection and case fatality, and we assessed vaccine effectiveness in this population.

Methods In this retrospective cohort study, we analyzed data on demographics, diagnosed SARS-CoV-2 infection rates, outcomes, and associated risk factors, including vaccine effectiveness, for people attending a province-wide network of advanced CKD clinics during the first four waves of the pandemic in Ontario, Canada.

Results In a population of 20,235 patients with advanced CKD, 607 were diagnosed with SARS-CoV-2 infection over 21 months. The case fatality rate at 30 days was 19% overall but declined from 29% in the first wave to 14% in the fourth. Hospitalization and intensive care unit (ICU) admission rates were 41% and 12%, respectively, and 4% started long-term dialysis within 90 days. Significant risk factors for diagnosed infection on multivariable analysis included lower eGFR, higher Charlson Comorbidity Index, attending advanced CKD clinics for more than 2 years, non-White ethnicity, lower income, living in the Greater Toronto Area, and long-term care home residency. Being doubly vaccinated was associated with lower 30-day case fatality rate (odds ratio [OR], 0.11; 95% confidence interval [CI], 0.03 to 0.52). Older age (OR, 1.06 per year; 95% CI, 1.04 to 1.08) and higher Charlson Comorbidity Index (OR, 1.11 per unit; 95% CI, 1.01 to 1.23) were associated with higher 30-day case fatality rate.

Conclusions People attending advanced CKD clinics and diagnosed with SARS-CoV-2 infection in the first 21 months of the pandemic had high case fatality and hospitalization rates. Fatality rates were significantly lower in those who were doubly vaccinated.

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Introduction

CKD is a strong risk factor for severe coronavirus disease 2019 (COVID-19)–related outcomes including hospitalization and all-cause mortality.[1–10] People on maintenance dialysis and with kidney transplants were identified early in the pandemic as subgroups at higher risk for severe outcomes and were prioritized in global vaccination efforts.[11,12]

People with nondialyzed CKD also have high COVID-19 case fatality rates compared with the general population, although systematic reviews suggest that both infection risk and fatality rates are lower overall compared with those in people receiving maintenance dialysis.[5–7] However, early papers from Italy and Turkey reported that fatality rates were similarly high in people with CKD stages 3–5.[10,11] In general, studies in this area have been small, have had varying proportions of people with CKD stages 3–5, and cannot always distinguish risk of infection from risk of fatality, making interpretation difficult. The subset of patients with CKD who are not on maintenance dialysis but who have CKD stage 5 or high-risk proteinuric CKD stages 3b or 4 have received less focused attention.[8] This subgroup, referred to here as patients with advanced CKD, have not always been prioritized for vaccination, despite these concerns about high case fatality rates.[7,10,11,13]

Recent studies have shown that vaccination, despite a decreased serologic response, is associated with lower rates of infection and of severe outcomes in maintenance dialysis patients.[8,14,15] One vaccine effectiveness study found that COVID-19 vaccines were

associated with less incident infection, hospitalizations, and death among non–dialysis-dependent patients with CKD.[16] Another retrospective cohort study found that vaccination was associated with a lower mortality risk, but both these studies looked at people with a wide range of severity of CKD.[8,16]

In Ontario, Canada, there are specially funded province-wide advanced CKD clinics for people with CKD stage 5 and high-risk proteinuric CKD stages 3b and 4.[17] We have analyzed rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe outcomes, including case fatality, in this population during the first 21 months of the pandemic and have looked at risk factors for infection and severe outcomes, and in particular at vaccine effectiveness with regard to these outcomes.

Methods

Setting and Population

The Ontario Renal Network, a part of Ontario Health, is a provincial government agency that funds and manages advanced CKD and maintenance dialysis services working with 27 hospital-based Nephrology Programs in the Canadian province of Ontario.[1,18,19] Advanced CKD Clinics in Ontario are funded by a single payer—the provincial government—operating through the Ontario Renal Network.[1,18,19]

All adult patients attending advanced CKD clinics for at least 30 days and registered in a provincial nephrology database between March 1, 2020, and November 30, 2021, were included in the study population. This comprised both prevalent patients as of March 1, 2020, and incident patients during the study period. Eligibility for these clinics required people to have either an eGFR <15 ml/min per 1.73 m^2 or a 2-year risk of requiring maintenance dialysis >10% on the basis of the Kidney Failure Risk Equation, which takes into account eGFR, urine albumin-creatinine ratio (UACR), age, and sex.[17] eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, without race adjustment.

The exclusion criteria for this study were missing health card numbers, non-Ontario residents, eGFR ≥45 ml/min per 1.73 m^2, age younger than 18 years, and incomplete demographic data. Patients with a diagnosis of SARS-CoV-2 infection were defined as testing positive on RT-PCR.[20]

The study period from March 1, 2020, to November 30, 2021, included the first four waves of the COVID-19 pandemic in Ontario but not the period where the Omicron strain of SARS-CoV-2 became dominant.[21] The dates defining these waves are provided in Table 1.

Data Sources

SARS-CoV-2 infection was confirmed by a positive RT-PCR reported in the Ontario Laboratories Information System. This is a comprehensive database that has recorded all SARS-CoV-2 PCR tests in Ontario since the pandemic began. Hospital admissions were identified using the Canadian Institute for Health Information's Discharge Abstract Database, which also allowed determination of medical histories, including comorbidities such as diabetes, cardiac disease, cancer, and previous transplantation, on the basis of the International Classification of Diseases 10 diagnostic codes. Each chronic condition was defined based on 5 years of look-back data from the date of SARS-CoV-2 reporting.[18]

The other datasets used were the (*1*) Ontario Renal Reporting System (ORRS), which identifies all individuals registered with advanced CKD clinics and their age, sex, eGFR, and UACR—ethnicity information is reported in ORRS at the time of patient registration, on the basis of charting by clinical staff who may ask patients or relatives to self-identify ethnicity but are not mandated to do so[1]; (*2*) Ontario Registered Persons Database, which identified all deaths in the province; (*3*) Ontario Health Insurance Plan, containing insurance claims for physicians' billing codes, including long-term care services[1]; (*4*) Statistics Canada Postal Code Conversion File, linking postal codes to standard geographic areas to derive neighborhood income and other socioeconomic indicator quintiles; and (*5*) Ontario COVAX database for vaccination data.[15]

Outcomes

Severe outcomes of SARS-CoV-2 infection were determined using the aforementioned databases and comprised case fatality rate (death within 30 days and 60 days of SARS-CoV-2 positivity), hospitalization (admission within 14 days of SARS-CoV-2 positivity or where testing was positive in the first 3 days after admission), intensive care unit admission, mechanical ventilation or acute dialysis during these hospitalizations, and initiation of long-term outpatient dialysis within 90 days of SARS-CoV-2 positivity.

Statistical Analyses

Patient characteristics at the time of entry into the study cohort were summarized using frequency (percentages) for categorical variables and means (SD) or medians (with interquartile ranges [IQR]). Unadjusted baseline differences between patients with a diagnosis of SARS-COV-2 infection and those without infection were compared using the Chi-squared test for categorical and Student *t* test for continuous variables.

To explore risk factors associated with SARS-CoV-2 infection, a multivariable log-binomial model was used to estimate the incidence rate ratios. There were no missing data among study participants, and no participants were lost to follow-up.

In a subgroup analysis, we performed logistic regression models to assess the association of SARS-CoV-2–related severe outcomes with vaccination status among those diagnosed with infection between December 15, 2020, the start of the vaccine rollout in Ontario, and November 30, 2021. We used the method described by Ashby *et al.* for assessing vaccine effectiveness.[24,25] This compares outcomes in patients on the basis of their vaccination status on the day they are diagnosed with infection. It therefore avoids the same patients contributing both unvaccinated and vaccinated time to the analysis as occurs with time-dependent cohort methodology. It does not, by its nature, allow estimates of protection against the actual infection as only infected people enter the analysis. It is particularly useful in a disease such as COVID-19, where avoiding severe outcomes when infected may be equally or more

Table 1. Severe outcomes in patients with advanced CKD and COVID-19 infection by wave of COVID-19

Wave and Dates	Dominant SARS-CoV-2 Strain[22]	Double Vaccination Proportion among Patients with Advanced CKD,[23] *N* (%)[a]	Patients with SARS-CoV-2 Infection, *n* (% of Patients with Advanced CKD)	30-Day Mortality, *n* (% of Positive Cases)	60-Day Mortality, *n* (% of Positive Cases)	Hospital Admission, *n* (% of Positive Cases)	ICU Admission, *n* (% of Positive Cases)	Mechanical Ventilation, *n* (% of Positive Cases)	Long-Term Outpatient Dialysis within 90 days, *n* (% of Positive Cases)
Wave 1: March 1, 2020–August 31, 2020	N501Y-/E484K- (wild type)	0 (0)	58 (0.3)	17 (29)	20 (34)	25 (43)	<6 (<10)[b]	<6 (<10)[b]	<6 (<10)[b]
Wave 2: September 1, 2020–February 28, 2021	N501Y-/E484K (wild type)	405 (2)	275 (1)	54 (20)	61 (22)	103 (38)	27 (10)	18 (7)	11 (4)
Wave 3: March 1, 2021–July 31, 2021	N501Y-/E484K (wild type) and N501Y+/ E484K+ (Alpha)	17,200 (85)	222 (1)	40 (18)	44 (20)	99 (45)	35 (16)	31 (14)	6 (3)
Wave 4: August 1, 2021–November 30, 2021	N501Y+/ E484K+ (Alpha) and N501Y-/ E48K- (Delta)	18,616 (92)	52 (0.3)	7 (14)	7 (14)	23 (44)	<6 (<11)[b]	<6 (<11)[b]	<6 (<11)[b]
All waves: March 1, 2020–November 30, 2021	—	18,616 (92)	607 (3)	118 (19)	132 (22)	250 (41)	72 (12)	57 (9)	21 (4)
Vaccination era: December 15, 2020–November 30, 2021		18,616 (92)	440 (2)	84 (19)	90 (20)	187 (43)	57 (13)	33 (8)	14 (3)

COVID-19, coronavirus disease 2019; SARS-CoV-2, acute respiratory syndrome coronavirus 2; ICU, intensive care unit.
[a]Double vaccinated was defined as those who received at least two doses. Rates were determined at the end of each wave or time period.
[b]Counts <6 are suppressed for privacy reasons.

important than avoiding infection in the first place. Patients' vaccination status was defined on the date that their first positive test was recorded. They were considered doubly vaccinated 7 days after receipt of a second dose of COVID-19 vaccine, vaccinated once 14 days after the first dose, and all remaining patients were considered unvaccinated. Covariates for these models were chosen on the basis of general literature on risk factors for COVID-19 incidence and mortality and on our clinical interest.[5,7,9,26] We used variance inflation factor to screen for multicollinearity. We considered values of 10 or higher to be strong evidence of multicollinearity, but no such values were found.

All statistical analyses were performed using SAS statistical software, with statistical significance set at two-sided $P < 0.05$.

Table 2. Characteristics of patients enrolled in advanced CKD clinics in the Ontario Renal Network, a part of Ontario Health, from March 1, 2020, through November 30, 2021, overall and according to development of a positive diagnostic test for SARS-CoV-2 infection during follow-up

Characteristic	Overall, n=20,235	Tested Positive, n=607	No Positive Test[a], n=19,628
Follow-up time during the study period			
Mean, d (SD)	391 (225)	278 (148)	395 (226)
Demographics			
Female (%)	8130 (40)	280 (46)	7850 (40)
Age group, yr			
18–39 (%)	740 (4)	31 (5)	709 (4)
40–69 (%)	7248 (36)	231 (38)	7017 (36)
70–79 (%)	5967 (29)	154 (25)	5813 (30)
80+ (%)	6280 (31)	191 (31)	6089 (31)
Mean age, yr (SD)	71 (14)	70 (16)	71 (14)
Ethnicity			
Black (%)	986 (5)	65 (11)	921 (5)
East Asian (%)	1272 (6)	40 (7)	1232 (6)
Indian subcontinent (%)	1395 (7)	75 (12)	1320 (7)
Other non-White (%)	1712 (9)	98 (16)	1614 (8)
Unknown/not given (%)	1669 (8)	42 (7)	1627 (8)
White (%)	13,201 (65)	287 (47)	12,914 (66)
CKD-EPI[b] stage			
G3b[c] (%)	1165 (6)	43 (7)	1122 (6)
G4[c] (%)	12,132 (60)	304 (50)	11,828 (60)
G5[d] (%)	6875 (34)	260 (43)	6615 (34)
Missing/unknown (%)	63 (0.3)	0 (0)	63 (0.3)
Mean eGFR,[e] ml/min per 1.73 m^2 (SD)	18.3 (6.7)	17.5 (7.3)	18.4 (6.7)
Mean UACR,[f] mg/g (SD)	159 (263)	170 (222)	159 (264)
Time spent attending advanced CKD clinics, yr			
≤2 (%)	15,196 (75)	371 (61)	14,825 (76)
>2 (%)	5039 (25)	236 (39)	4803 (24)
Resident of long-term care home			
Yes (%)	436 (2)	54 (9)	382 (2)
Patient location			
GTA[g] (%)	9945 (49)	407 (67)	9536 (49)
Comorbid conditions			
Diabetes mellitus	8370 (41)	290 (48)	8080 (41)
Cancer	1438 (7)	31 (5)	1407 (7)
Cardiac disease	4708 (23)	171 (28)	4537 (23)
Previous transplant	399 (2)	11 (2)	388 (2)
Mean CCI[h] score (SD)	2 (2)	3 (3)	2 (2)
Income quintiles[i]			
1–2 (lowest)	9573 (47)	340 (56)	9232 (47)
3–5 (highest)	10,460 (52)	259 (43)	10,200 (52)
Missing/unknown	204 (1)	8 (1)	196 (1)

[a]This includes patients who tested negative for acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or did not have a SARS-CoV-2 test.
[b]Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
[c]Moderately to severely decreased kidney function, eGFR 15–44 ml/min per 1.73 m^2.
[d]Kidney failure, eGFR <15 ml/min per 1.73 m^2.
[e]eGFR, as calculated by the CKD-EPI formula.
[f]Urine albumin-creatinine ratio (UACR) (mg/g).
[g]Greater Toronto Area (GTA).
[h]Charlson Comorbidity Index (CCI).
[i]Income quintile is a measure of neighborhood socioeconomic status that divides the population into five income groups of equal size. Group 1 lives in the neighborhoods with the lowest incomes and group 5 in those with the highest incomes.[18]

Ethics Approval

Ontario Renal Network, part of Ontario Health, is a provincial agency that funds and manages services for patients with CKD. The data collection was in accordance with Ontario Health's legislative authority under the Ontario Personal Health Information Protection Act, 2004. This study followed the principles of the Declaration of Helsinki.

Results

During the study period, there were 20,235 patients with advanced CKD followed for a total of 21,676 patient-years and a mean of 391 days (Table 2). Patient selection and reasons for nonparticipation are displayed in Figure 1. The mean age of the cohort was 71 years, and 60% were male. The median eGFR was 18 (IQR, 14–23) ml/min per 1.73 m^2, 91% of patients had moderate-to-severe proteinuria as defined by a UACR ≥266 mg/g (30 mg/mmol), and 34% had CKD stage 5. Baseline comorbidities included diabetes in 41% of patients, cardiac disease in 23%, previous cancer in 7%, and previous kidney transplant in 2%. During the study period, 607 (3%) tested positive for SARS-CoV-2 infection, equivalent to an infection rate of 2.8 per 100 patient-years of follow-up. These cases followed a similar time and wave distribution to the cases in the general population of Ontario (Supplemental Figure 1). Cumulative PCR-diagnosed infection rates in the general Ontario population in the same time period were approximately 4%.[21]

Risk Factors for COVID-19

We compared the characteristics of the 607 patients who were diagnosed with SARS-CoV-2 infection with the 19,628 who were not (Table 2). On multivariable analysis, risk factors for diagnosed infection included older age; non-White ethnicity including Black, Indian subcontinent, and other non-White ethnicities; duration of time attending advanced CKD clinics >2 years; residency in a long-term care home; living in the Greater Toronto Area; lower income quintiles; eGFR <15 ml/min per 1.73 m^2; and higher comorbidity by Charlson Comorbidity Index (CCI) score (Table 3).

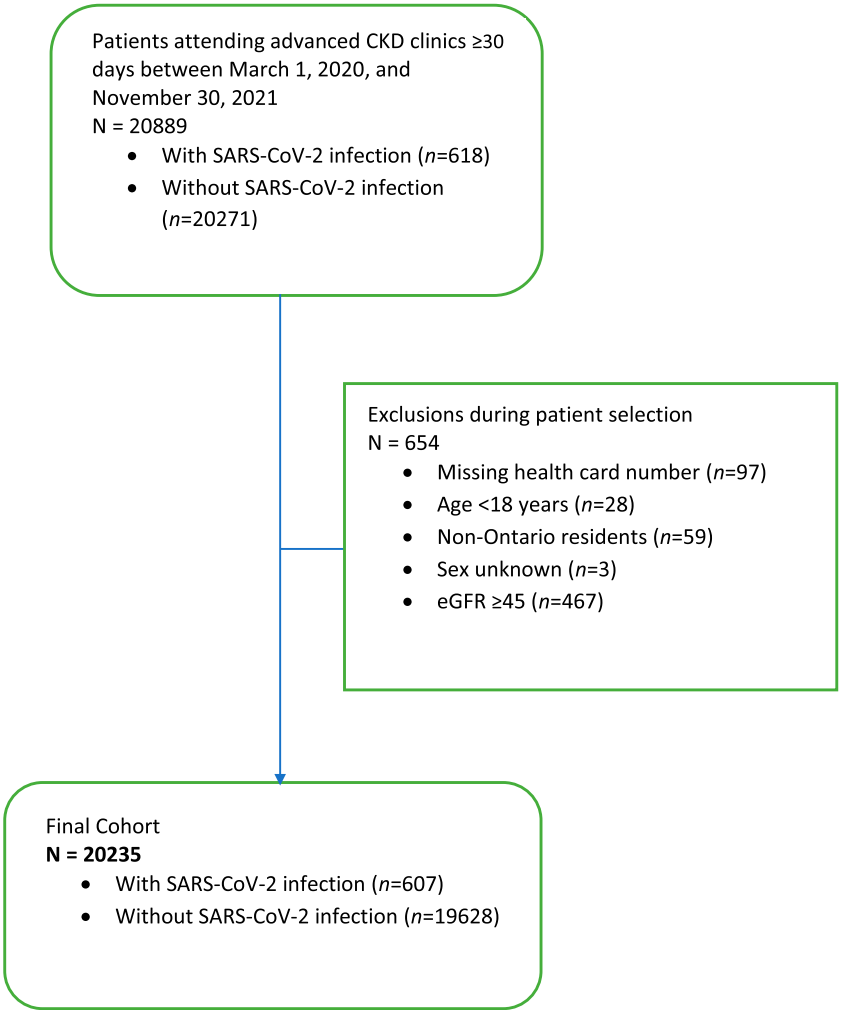

Figure 1. Flow diagram of patient selection. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2. Figure 1 can be viewed in color online at www.cjasn.org.

Table 3. Factors associated with SARS-CoV-2 infection after multivariable adjustment among patients with advanced CKD

Patient Characteristic	Number with Infection, *N* (% of Positive Cases)	Adjusted Rate Ratio (95% CI)
Demographics		
Female	280 (46)	1.14 (0.96 to 1.34)
Male	327 (54)	1.00 (Ref.)
Age, yr	—	0.99 (0.98 to 1.00)
Ethnicity		
Black	65 (11)	2.13 (1.61 to 2.82)
East Asian	40 (7)	1.08 (0.76 to 1.52)
Indian subcontinent	75 (12)	2 (1.53 to 2.62)
Other non-White	98 (16)	2.32 (1.84 to 2.94)
Unknown/missing	42 (7)	1.12 (0.80 to 1.57)
White	287 (47)	1.00 (Ref.)
Kidney function (eGFR, ml/min per 1.73 m^2)		
15–44	347 (57)	0.64 (0.54 to 0.76)
<15	260 (43)	1.00 (Ref.)
Time spent in advanced CKD, yr		
>2	236 (39)	1.41 (1.20 to 1.67)
≤2	371 (61)	1.00 (Ref.)
Long-term care residence		
Yes	54 (9)	4.58 (3.41 to 6.16)
No	553 (91)	1.00 (Ref.)
Geographic location		
GTA	407 (67)	1.81 (1.51 to 2.18)
Non-GTA	200 (33)	1.00 (Ref.)
Charlson Comorbidity Index (per unit increase in score)	—	1.07 (1.04 to 1.11)
Income quintile[a]		
3–5	259 (43)	0.81 (0.69 to 0.95)

Adjustment was for the covariates of age, sex, ethnicity, eGFR, time attending clinics, long-term care residency, living in Greater Toronto Area (GTA), comorbidity score, and income quintile. SARS-CoV-2, acute respiratory syndrome coronavirus 2; CI, confidence interval; Ref., reference group.
[a]Income quintile is a measure of neighborhood socioeconomic status that divides the population into five income groups of equal size. Group 1 lives in the neighborhoods with the lowest incomes and group 5 in those with the highest incomes.[18]

Outcomes

COVID-19 Outcomes, Risk Factors, and Impact of Vaccination

The 30-day and 60-day case fatality rates of the 607 patients who tested positive for SARS-CoV-2 were 19% and 22%, respectively, (Table 1). The 60-day fatality rate was highest at 34% in the first wave, when none of the patients were vaccinated, and was still very high in waves two (22%) and three (20%). The overall hospitalization rate was 41%, while 12% were admitted to the intensive care unit (ICU), 9% received ventilation, and 2% received acute dialysis during their admission. The proportion of patients who started outpatient maintenance dialysis within 90 days of testing positive for SARS-CoV-2 was 4% (Table 1).

Among the 440 patients who were diagnosed with SARS-CoV-2 infection between December 15, 2020, the date the vaccine rollout began in Ontario, and the end of our study period, we compared those who were doubly vaccinated with those who were not. The only significant difference was in age (Supplemental Table 1). On multivariable analysis, being doubly vaccinated was associated with markedly lower 30-day case fatality (odds ratio [OR], 0.11; 95% confidence interval [CI], 0.03 to 0.52). Older age (OR, 1.06 per year; 95% CI, 1.04 to 1.08) and higher CCI score (OR, 1.11 per unit; 95% CI, 1.01 to 1.23) were associated with a higher risk of case fatality (Supplemental Table 2). A single vaccination was not associated with significantly lower fatality. Sex, ethnicity, eGFR, comorbid states, location of residence, COVID-19 wave, and income quintiles were not significant predictors of fatality. In a separate analysis, there was no difference in case fatality between people receiving the two different mRNA vaccines (Supplemental Table 3). There were no significant differences in COVID-19–related hospitalization, ICU admissions, ventilation, and dialysis initiation, when examined separately, between those who were doubly vaccinated at the time of diagnosed infection and those who were not (Table 4).

Discussion

In this study of 20,235 patients attending a province-wide network of advanced CKD clinics, we found that more advanced CKD, more comorbidities, non-White ethnicity, lower income, living in the Greater Toronto Area, and residency in a long-term care home were all significant risk factors on multivariable analysis for diagnosed SARS-CoV-2 infection. We observed a very high 60-day case fatality rate of 22% over the first four waves of the pandemic. The case fatality rate did, however, decline in successive waves. Hospitalization rates and ICU admission rates were also high at 41% and 12%, respectively, over the four waves, and 4% started long-term dialysis within 90 days of testing positive. Being doubly vaccinated was associated with markedly lowercase fatality, while older age and comorbidity were associated with a higher case fatality.

Three related but separate questions arise when considering the interaction between CKD and COVID-19 in the pre-Omicron period. The first is whether people with CKD were more likely to be infected with SARS-CoV-2. This was clearly the case for people on maintenance dialysis, as shown by Chung *et al.* in a systematic review.[5] For those with advanced CKD, this is less clear. Gilbertoni *et al.* found a markedly higher risk of diagnosed infection in those with CKD stages 3 and 4 compared with the general population in a region of Italy during the first 5 months of the pandemic, but there may have been major underdiagnosis in the general population because of less comorbidity and milder symptoms and the difficulty of getting tested at that time.[11] Our study, in contrast, found a cumulative infection rate in the first 21 months of the pandemic in our advanced CKD cohort that was slightly less than that in the Ontario general population, and we would argue that underdiagnosis is more likely in the general population where the disease is typically milder than in a CKD cohort. This lower infection rate in advanced CKD might also reflect deliberate self-isolation by a vulnerable population. It should be noted that overall

Table 4. Associations of COVID vaccination with severe outcomes among advanced CKD patients with SARS-CoV-2 infection

Outcome	Number with Outcome/COVID-19 Cases (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
COVID-19 30-day mortality[a]			
Double vaccinated[b]	<6/41 (<5)	0.19 (0.05 to 0.82)	0.11 (0.03 to 0.52)
Vaccinated once[c]	15/81 (19)	0.85 (0.46 to 1.59)	0.51 (0.25 to 1.05)
Unvaccinated[d]	67/318 (21)	1.00 (Ref.)	1.00 (Ref.)
COVID-19 hospital admission			
Double vaccinated	14/41 (34)	0.69 (0.35 to 1.37)	0.50 (0.23 to 1.06)
Vaccinated once	37/81 (46)	1.13 (0.69 to 1.84)	0.75 (0.43 to 1.32)
Unvaccinated	136/318 (43)	1.00 (Ref.)	1.00 (Ref.)
COVID-19 ICU admission			
Double vaccinated	<6/41 (<5)	0.31 (0.07 to 1.33)	0.23 (0.05 to 1.01)
Vaccinated once	10/81 (12)	0.85 (0.41 to 1.78)	0.65 (0.29 to 1.47)
Unvaccinated	45/318 (14)	1.00 (Ref.)	1.00 (Ref.)
COVID-19 ventilation[e]			
Double vaccinated	<6/41 (<5)	0.60 (0.07 to 2.64)	0.32 (0.07 to 1.47)
Vaccinated once	10/81 (12)	0.94 (0.37 to 2.37)	0.53 (0.19 to 1.44)
Unvaccinated	45/318 (14)	1.00 (Ref.)	1.00 (Ref.)

COVID-19, coronavirus disease 2019; SARS-CoV-2, acute respiratory syndrome coronavirus 2; OR, odds ratio; CI, confidence interval; Ref., reference group; ICU, intensive care unit.
[a]COVID-19 mortality, hospital admission, and COVID-19 ICU admission models adjusted for age, Charlson comorbidity score, sex, ethnicity (White versus non-White), eGFR, and pandemic waves.
[b]Patients were double vaccinated 7 days after receipt of a second dose of COVID-19 vaccine.
[c]Patients were considered vaccinated once 14 days after the first dose.
[d]Patients who did not meet the criteria for the double-vaccinated or vaccinated-once groups were considered unvaccinated.
[e]COVID-19 ventilation model adjusted for sex, age, Charlson comorbidity score, and pandemic waves.

population infection rates have been lower in Canada than in many of the countries where other studies come from, including Italy and the United States.[27]

A second question is whether case fatality rates were higher for people with CKD than in the general population. This was clearly so for people on maintenance dialysis and was also the case in the study by Gilbertoni where it was ten times higher at 45% in people with CKD stages 3–5 compared with the general population.[1,5,11] A study from Turkey showed a seven times higher case fatality rate of 28% in CKD stages 3–5 than in the general population, but this study only looked at hospitalized patients.[10] Similarly, our cohort had a case fatality rate of 22% at 60 days, far in excess of the rate in the general population of Ontario which was < 0.15% and which fell in successive waves.[28]

A third question is whether case fatality in the CKD population differed with severity of CKD or whether it was mainly driven by nonrenal comorbidities. Gilbertoni noted a lower case fatality rate in CKD stage 3 compared with stages 4 and 5.[11] We found no difference between those with eGFR above and below 15 ml/min per 1.73 m^2 in our cohort, but almost all had at least CKD stage 4, so the results are not contradictory. Williamson *et al.*, in a large UK population study from the first pandemic wave, found a three times higher COVID-19 mortality for those with eGFR <30 compared with those between 30 and 60 ml/min per 1.73 m^2, but this study looked at overall mortality and could not distinguish case fatality from infection risk.[7] This all suggests that, across the broad eGFR range, CKD severity and other comorbidities are associated with increased case fatality, but the influence of eGFR is less apparent once eGFR is <30. Further investigation is needed.

In this study, we found that the 30-day case fatality rate declined as the pandemic progressed. We hypothesize that these lower fatality rates are related to several factors, including better management of COVID-19 as the pandemic progressed, a higher proportion of vaccinated patients, the death of more vulnerable patients in the earlier waves, and perhaps variant strains that cause less severe infection. The study period, however, preceded the appearance of the less pathogenic Omicron variant as the dominant SARS-CoV-2 strain.

Our study shows that double-dose mRNA vaccination is associated with a substantially lower fatality rate among advanced CKD patients with diagnosed SARS-CoV-2 infection. It is also associated with a 50% lower hospitalization rate, but this did not reach statistical significance, perhaps because of relatively small numbers of people being double vaccinated during much of the time period studied and consequent reduced statistical power. It may also be because in this highly comorbid population, hospitalization does not distinguish more severe from less severe degrees of illness as strongly as mortality does. This finding is not inconsistent with a recent British Columbia vaccine effectiveness study that found that COVID-19 vaccines were effective in preventing a composite of hospitalization and death in a CKD population.[16] The studies differed in methodology in that the British Columbia study used a composite of mortality and hospitalization rather than two separate end points and looked at a much broader CKD population with a mean eGFR of 30 as compared with 18 in our study. In both studies, however, the lowering in ORs for severe outcomes associated with double vaccination were of broadly similar magnitude.

In this study, we used the method described by Ashby *et al.* to assess vaccine effectiveness in the maintenance

dialysis population.[25] Although this methodology, by its nature, cannot assess protection from SARS-CoV-2 infection, it does permit a much simpler analysis and answers what may be a more clinically important question in this population, which is whether vaccination is associated with lower rates of case fatality and other severe outcomes in infected people.

Within our advanced CKD cohort, we found that older age, more comorbidities, and lower eGFR were associated with a higher risk of diagnosed SARS-CoV-2 infection, which is consistent with other studies.[7,8,11,29] A potential confounder to these relationships is that older patients with more comorbidities may be more likely to get tested because of more symptomatic illness or more frequent hospitalization.[5,6] We found that non-White ethnicity, lower income, and residency in long-term care homes were associated with a higher risk of infection, as has been previously reported in the maintenance dialysis population.[1] This emphasizes the importance of socioeconomic factors in COVID-19 infection.[1,30,31] Consistently during the first 18 months of the COVID-19 pandemic, disadvantaged populations have been found to suffer higher risk of infection and severe outcomes.[30–32]

This study has a number of strengths. First, our data are from a province of more than 14 million people where a single-payer public funding system and the existence of comprehensive databases makes it possible to report reliably and in detail on the entire population of registered patients with advanced CKD.[11,18] Second, the clearly defined acceptance criteria for these clinics allow us to focus on a very advanced CKD population at particular risk for requiring dialysis, as compared with other studies that include broader CKD populations. Third, we had a large sample size, and this enabled us to measure 30-day and 60-day case fatality rates and provided enough statistical power to perform multivariable analyses on predictors of SARS-CoV-2 infection and mortality. Finally, although maintenance dialysis patients are relatively easily studied, the advanced CKD population are generally less accessible. This study, therefore, provides unique insights into a population that is at high risk for severe illness and death from COVID-19.

This study has some limitations. First, milder cases of SARS-CoV-2 infection may have been missed because patients did not present for PCR testing, and this may explain partly why the case fatality rate is so high. Second, our study may not be generalizable to other jurisdictions because of differences in population characteristics, health care resources, and variant strains of SARS-CoV-2. Third, the results of this study may not be applicable to newer variants of SARS-CoV-2, such as the Omicron strains, which may be less pathogenic, but which also may be more resistant to vaccines—this needs to be investigated. Fourth, we did not have data on immunosuppressive medications or body mass index or of COVID-19 treatments received in our cohort. Finally, we could not definitively say to what degree severe outcomes were caused by, as distinct from associated with, SARS-CoV-2 infection, but this is a challenging issue with all studies on this topic.

In this retrospective cohort study, we describe a high rate of severe outcomes after diagnosed SARS-CoV-2 infection during the first four waves of the pandemic in Ontario, but double-dose vaccination was associated with much lower fatality rates. We advocate that patients with advanced CKD be a priority group in global vaccination and therapeutic efforts against COVID-19.

Disclosures

P.G. Blake reports honoraria from Baxter Global and Otsuka Australia; advisory or leadership role as a contracted Medical Lead of Ontario Renal Network, Ontario Health—this is a paid role; and serving on the Editorial Board of *American Journal of Nephrology*. K.S. Brimble reports serving as a contracted medical lead of Ontario Renal Network, Ontario Health. R. Cooper, J. Ip, Y. Tang, D. Thomas, and A. Yeung are salaried employees of Ontario Renal Network, Ontario Health. M.A. Hladunewich reports consultancy agreements with Alnylam Pharmaceuticals; research funding from Calliditas Therapeutics, Chemocentryx, Ionis, Pfizer, and Roche; advisory or leadership roles for *Kidney International* and UpToDate; and other interests or relationships as medical lead for Glomerular Disease Ontario Renal Network. A. Levin reports employment with BC Provincial Renal Agency and Providence health Care; consultancy agreements with AstraZeneca, Bayer, Boehringer Ingelheim, Chinook Therapeutics, GSK, Janssen, Kidney Foundation of Canada, NIH, Otsuka, and REATA; research funding from AstraZeneca, Boehringer Ingelheim, Canadian Institute of Health Research (CIHR), CITF (Canadian Immunology Task Force), GSK, Health Research BC, Kidney Foundation of Canada, MOH BC, and Shared Care BC; honoraria from AstraZeneca, Bayer, GSK, Janssen, and NIH; advisory or leadership roles for AstraZeneca, Boehringer Ingelheim, CADTH, Chinook Therapeutics, CITF, GSK, KRESCENT (Kidney Scientist Education Research National Training Program), NIDDK, REATA BC Renal (Exec Director), and Steering Committee Chair CURE Consortium; DSMB for NIDDK, Kidney Precision Medicine, U Washington Kidney Research Institute Scientific Advisory Committee; International Society of Nephrology Research Committee; and other interests or relationships as CREDENCE National Coordinator from Janssen - directed to her academic team, NIDDK CURE Chair Steering Committee, International Society of Nephrology, Canadian Society of Nephrology, Kidney Foundation of Canada Steering Committee ALIGN trial, and DSMB Chair RESOLVE Trial (Australian Clinical Trial Network). M.J. Oliver is the sole owner of Oliver Medical Management Inc., which is a private corporation that licenses the Dialysis Measurement Analysis and Reporting (DMAR) software system. Oliver Medical Management Inc. is co-owner of a Canadian Patent for DMAR systems. M.J. Oliver is a contracted medical lead at Ontario Renal Network Ontario Health, reports honoraria from Baxter Healthcare, participated in advisory boards for Amgen and Janssen, and reports other interests or relationships with Ontario Health. All remaining authors have nothing to disclose.

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Author Contributions

P.G. Blake, M.J. Oliver, and D. Thomas conceptualized the study; P.G. Blake, M.J. Oliver, and D. Thomas were responsible for methodology; P.G. Blake and R. Cooper were responsible for project administration; M.J. Oliver was responsible for funding acquisition; J. Ip and D. Thomas were responsible for data curation; P.G. Blake, M.J. Oliver, D. Thomas, and A. Yeung were responsible for investigation; P.G. Blake provided supervision; M.J. Oliver, J. Roushani, and D. Thomas were responsible for visualization; Y. Tang and D. Thomas were responsible for formal analysis; M.J. Oliver and D. Thomas were responsible for validation; P.G. Blake, J. Roushani, and D. Thomas wrote the original draft; and P.G. Blake, R. Cooper, M.A. Hladunewich, J. Ip, A. Levin, M.J. Oliver, J. Roushani, K. Scott Brimble, D. Thomas, and A. Yeung reviewed and edited the manuscript.

Data Sharing Statement

Ontario Health is prohibited from making the data used in this research publicly accessible if they include potentially identifiable personal health information and/or personal information as defined in Ontario law, specifically the Personal Health Information Protection Act and the Freedom of Information and Protection of Privacy Act. Upon request, data deidentified to a level suitable for public release may be provided.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B635.

Supplemental Figure 1. The SARS-CoV-2 cases in the advanced CKD population compared with the SARS-CoV-2 cases in the Ontario population by wave from March 1, 2020, through November 30, 2021.

Supplemental Table 1. Characteristics of the unvaccinated, single-vaccinated, and double-vaccinated patients at baseline on the basis of vaccination status at the time of diagnosis with SARS-CoV-2 infection.

Supplemental Table 2. Risk factors for 30-day mortality among advanced CKD patients with SARS-CoV-2 infection from December 15, 2020, to November 30, 2021.

Supplemental Table 3. Number of advanced CKD patients with the severe outcomes of 30-day mortality, hospital admission, and ICU admission by type of vaccine received or unvaccinated.

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