Research

Severity of COVID-19 among solid organ transplant recipients in Canada, 2020–2021: a prospective, multicentre cohort study

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Abstract

Background: Severe COVID-19 appears to disproportionately affect people who are immunocompromised, although Canadian data in this context are limited. We sought to determine factors associated with severe COVID-19 outcomes among recipients of organ transplants across Canada.

Methods: We performed a multicentre, prospective cohort study of all recipients of solid organ transplants from 9 transplant programs in Canada who received a diagnosis of COVID-19 from March 2020 to November 2021. Data were analyzed to determine risk factors for oxygen requirement and other metrics of disease severity. We compared outcomes by organ transplant type and examined changes in outcomes over time. We performed a multivariable analysis to determine variables associated with need for supplemental oxygen.

Results: A total of 509 patients with solid organ transplants had confirmed COVID-19 during the study period. Risk factors associated with needing (n = 190), compared with not needing (n = 319), supplemental oxygen included age (median 62.6 yr, interquartile range [IQR] 52.5–69.5 yr v. median 55.5 yr, IQR 47.5–66.5; $p < 0.001$) and number of comorbidities (median 3, IQR 2–3 v. median 2, IQR 1–3; $p < 0.001$), as well as parameters associated with immunosuppression. Recipients of lung transplants (n = 48) were more likely to have severe disease with a high mortality rate (n = 15, 31.3%) compared with recipients of other organ transplants, including kidney (n = 48, 14.8%), heart (n = 1, 4.4%), liver (n = 9, 11.4%) and kidney–pancreas (n = 3, 12.0%) transplants (p = 0.02). Protective factors against needing supplemental oxygen included having had a liver transplant and receiving azathioprine. Having had 2 doses of SARS-CoV-2 vaccine did not have an appreciable influence on oxygen requirement. Multivariable analysis showed that older age (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.02–1.07) and number of comorbidities (OR 1.63, 95% CI 1.30–2.04), among other factors, were associated with the need for supplemental oxygen. Over time, disease severity did not decline significantly.

Interpretation: Despite therapeutic advances and vaccination of recipients of solid organ transplants, evidence of increased severity of COVID-19, in particular among those with lung transplants, supports ongoing public health measures to protect these at-risk people, and early use of COVID-19 therapies for recipients of solid organ transplants.

Recipients of solid organ transplants take life-long immunosuppressive agents to prevent rejection. In Canada, an estimated 3000 transplant procedures are performed annually and 40 000 people are living with a transplant. Early studies from Europe and the United States suggested that transplant recipients were at greater risk of severe COVID-19, with a two- to five-fold greater mortality than the general population.[1–3] It is unclear whether the increased risk is owing to multiple comorbidities, immunosuppression or a combination of both factors.

Initial trials of therapeutics for SARS-CoV-2, including remdesivir, dexamethasone and tocilizumab, did not formally include transplant recipients.[4–6] Similarly, pivotal studies of the SARS-CoV-2 vaccines did not include immunocompromised populations.[7,8] Therefore, the use of COVID-19 therapeutics and SARS-CoV-2 vaccines in the transplant population has been extrapolated from the general population. Commonly used COVID-19 therapies such as dexamethasone and tocilizumab may place transplant recipients at risk of overimmunosuppression,

which may result in secondary infections. In addition, withdrawal of standard immunosuppression may result in organ rejection.

Previous cohort studies of transplant recipients with COVID-19 have primarily focused on the early phase of the pandemic, when therapeutics and vaccinations were limited.[2,9,10] These have generally been single-centre studies with short-term follow-up. Canadian data may differ from that of other countries owing to differences in timing and strategy of vaccine rollouts, as well as use and availability of certain therapeutics. Moreover, current data are limited with regard to longer-term outcomes of COVID-19 in transplant recipients up to 90 days postinfection, especially for the development of graft rejection.

We sought to determine factors associated with severe COVID-19 outcomes, to estimate the impact of available therapeutics on COVID-19 severity and to determine whether disease severity changed over the course of the pandemic among recipients of solid organ transplants from 9 centres in Canada.

Methods

Study design and setting

We performed a multicentre, prospective registry study of recipients of solid organ transplants recruited from 9 tertiary care transplant programs in Canada. We included all transplant patients, including inpatients and outpatients, with symptomatic SARS-CoV-2 infection (any severity) confirmed by polymerase chain reaction (PCR), from Mar. 1, 2020, to Nov. 30, 2021. At each participating site, patients were identified prospectively by referral from their transplant care team or retrospectively if the transplant program became aware of the patients after recovery or death from COVID-19. Data were collected and entered into the registry from the time of diagnosis of SARS-CoV-2 infection to 90 days after diagnosis.

Data collection

At each site, data were systematically collected from the hospital's electronic medical records or outpatient clinic records and entered into an electronic database using REDCap, which was housed at the central site (University Health Network, Toronto). We queried sites for any missing data to optimize complete data collection. We did not exclude patients with missing data. For all patients, we determined date of diagnosis by the first date of SARS-CoV-2 PCR positivity from nasopharyngeal swabs, endotracheal aspirates or bronchoalveolar lavage specimens. If data were available in microbiological records, we distinguished between wild-type SARS-CoV-2 or variants of concern, in particular the Alpha (lineage B.1.1.7) and Delta (lineage B.1.617.2) variants, which were predominant in Canada during the study period.[11] We collected data on patient demographics, comorbidities, vaccination status, immunosuppressive medications and occurrence of complications, including organ rejection.

Outcomes

The predefined primary outcome was patient requirement for supplemental oxygen, which is indicative of moderate COVID-19 severity and consistent with the World Health Organization clinical progression scale.[12] Other outcomes of interest included need for hospital admission, length of stay, admission to the intensive care unit (ICU), need for mechanical ventilation, use of extracorporeal membrane oxygenation and death. The occurrence of pneumonitis was based on compatible symptoms and radiological evidence, including plain chest radiography or computed tomography of the chest.

Sites documented use of therapeutics, including dexamethasone, remdesivir, tocilizumab or SARS-CoV-2-specific monoclonal antibody therapy. The use of therapeutics was decided by the treating physician; however, the approach was generally harmonized across the country, since all transplant centres met virtually each month via a Canadian Blood Services forum to discuss issues related to COVID-19. Complications, such as superimposed bacterial infection and invasive fungal infection, needed to be microbiologically confirmed for inclusion. Sites noted reduction of immunosuppression and the degree of reduction. We defined acute rejection as proven by biopsy or as clinically diagnosed and treated. We defined acute kidney injury according to RIFLE (risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function and end-stage kidney disease) criteria.[13]

Statistical analysis

We analyzed demographics using descriptive statistics. We compared categorical variables using the χ^2 test or Fisher exact test, and compared continuous variables using the Mann–Whitney *U* test. For our primary outcome of oxygen requirement, we performed a multivariable analysis using binary logistic regression including variables that had a *p* value of less than 0.05 on univariate analysis. We used the number of comorbidities rather than individual comorbidities and we excluded prednisone dose because of collinearity with prednisone treatment. We generated 2 models. The first model included all significant covariates, as follows: number of comorbidities, receipt of a lung transplant, receipt of a liver transplant, lymphocyte count, prednisone use, mycophenolate use, tacrolimus trough level and azathioprine use. These variables reflect known parameters that affect response to viral infections and vaccines following transplantation.[2,9,14–17] The second model excluded lymphocyte count and tacrolimus trough since these variables required that the patient have recent bloodwork and missing data were substantial. To compare COVID-19 severity outcomes over time, we categorized the date of diagnosis in 4 different time periods (Mar. 1–June 30, 2020; July 1–Dec. 31, 2020; Jan. 1–June 30, 2021; July 1–Nov. 30, 2021), coinciding with SARS-CoV-2 waves in Canada.[13] We defined statistical significance at the level of *p* less than 0.05. We performed all statistical analyses using IBM SPSS version 28.0 and Stata version 15.1 (StataCorp). We prepared figures using Prism version 9 (GraphPad Software).

Ethics approval

The study received ethics approval from the University Health Network Research Ethics Board (consent waiver), Centre hospitalier universitaire de Québec Ethics Committee (consent waiver),

Table 1: Demographics of transplant recipients with COVID-19

Characteristic	No. (%) of patients*			p value
	All patients n = 509	No oxygen requirement n = 319	Oxygen requirement n = 190	
Sex, male	333 (65.4)	210 (65.8)	123 (64.7)	0.8
Age, yr, median (IQR)	57.5 (47.5–66.5)	55.5 (43.5–63.5)	62.6 (52.5–69.5)	< 0.001
Time from transplant, yr, median (IQR)	6.22 (2.50–12.4)	6.22 (2.23–12.8)	6.32 (3.12–12.1)	0.8
No. of comorbidities, median (IQR)	2 (1–3)	2 (1–3)	3 (2–3)	< 0.001
Organ type				
Kidney	325 (63.9)	204 (63.9)	121 (63.7)	0.95
Kidney–pancreas	25 (4.9)	12 (3.8)	13 (6.8)	0.1
Heart	23 (4.5)	16 (5.0)	7 (3.7)	0.5
Lung	48 (9.4)	19 (6.0)	29 (15.3)	< 0.001
Liver	79 (15.5)	64 (20.1)	15 (7.9)	< 0.001
Other†	9 (1.8)	4 (1.2)	5 (2.6)	0.3
Vaccination status				
Never vaccinated	427 (83.9)	268 (84.0)	159 (83.7)	0.9
1 dose	26 (5.1)	15 (4.70)	11 (5.8)	0.6
2 doses	53 (10.4)	33 (10.3)	20 (10.5)	0.95
3 doses	3 (0.6)	3 (0.9)	0	0.2
Vaccine type‡				
mRNA-1273	20 (3.9)	9 (2.82)	11 (5.79)	0.1
BNT162b2	54 (10.6)	38 (11.9)	16 (8.42)	0.2
AstraZeneca	5 (1.0)	2 (0.6)	3 (1.6)	0.3
Immunosuppression				
Lymphocyte count at diagnosis, × 10^9/L, median (IQR)‡	0.80 (0.41–1.40)	0.975 (0.60–1.5)	0.635 (0.40–1.0)	< 0.001
Treatment for rejection in preceding 3 mo	14 (2.8)	8 (2.5)	6 (3.2)	0.7
ATG in preceding 6 mo	10 (2.0)	7 (2.2)	3 (1.6)	0.6
Prednisone	411 (80.7)	237 (74.3)	174 (91.6)	< 0.001
Prednisone daily dose, mg, median (IQR)	5 (5–6.25)	5 (0–5)	5 (5–7.5)	< 0.001
Mycophenolate mofetil or mycophenolate sodium	370 (72.7)	218 (68.3)	152 (80)	0.004
Mycophenolate sodium daily dose, mg, median (IQR)§	720 (0–1080)	720 (0–1080)	720 (360–1080)	0.1
Tacrolimus	413 (81.1)	260 (81.5)	153 (80.5)	0.8
Tacrolimus trough level, ng/mL, median (IQR)‡	7.0 (5.1 – 10.5)	6.3 (4.675–7.625)	6.9 (5.1–9.6)	0.002
Cyclosporine	63 (12.4)	35 (11.0)	28 (14.7)	0.2
Azathioprine	31 (6.1)	25 (7.8)	6 (3.2)	0.03
Sirolimus	19 (3.7)	14 (4.4)	5 (2.6)	0.3
SARS-CoV-2 variant				
No variant of concern detected	281 (55.2)	176 (55.2)	105 (55.3)	0.98
Alpha	76 (14.9)	40 (12.5)	36 (18.9)	0.05
Delta	20 (3.9)	15 (4.7)	5 (2.6)	0.2
Unknown	128 (25.1)	87 (27.3)	41 (21.6)	0.1
Other	4 (0.8)	1 (0.31)	3 (1.6)	0.1

Note: ATG = antithymocyte globulin, IQR = interquartile range.
*Unless otherwise indicated.
†Other includes 6 patients who received kidney–liver transplants, 2 who received a heart–lung transplant and 1 who received an islet cell transplant.
‡Three patients were missing vaccine type and 221 were missing lymphocyte count. Tacrolimus level was missing in 97 of the 413 patients recorded as receiving tacrolimus.
§Doses of mycophenolate mofetil were converted to the equivalent dose of mycophenolate sodium for analysis.

Comité d'éthique de la recherche de l'Université de Montréal (consent waiver), Centre hospitalier de l'Université de Montréal Research Ethics Board (consent waiver), the University of Saskatchewan Research Ethics Board (written consent), the University of Alberta Health Research Ethics Board (written consent), the Conjoint Health Research Ethics Board at University of Calgary (written consent) and the Unity Health Toronto Research Ethics Board (written consent).

Results

A total of 509 recipients with solid organ transplants had confirmed COVID-19 during the study period. The demographics and baseline characteristics for all participants are shown in Table 1 and by clinical centre in Appendix 1, Supplementary Table 1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.220620/tab-related-content. Most were male (65.4%), with a median age of 57.5 years. Most patients in the cohort (63.9%) had kidney transplants. The most frequently detected variant of concern was of the Alpha lineage, in 76 (14.9%) patients, followed by the Delta variant in 20 (3.9%) patients. Only 14 (2.8%) patients had received treatment for organ rejection in the 3 months before the COVID-19 diagnosis. Reduction of immunosuppression occurred in 302 (59.3%) patients. Four patients in this group had acute rejection, whereas 4 patients who did not have a reduction of immunosuppression also had acute rejection. A total of 82 (16.1%) patients had received 1 or more doses of vaccine, 53 (10.4%) had received 2 doses and 3 (0.6%) had received 3 doses of vaccine against SARS-CoV-2. The predominant vaccine type was BNT162b2, which was administered to 54 (10.6%) participants. The frequency of SARS-CoV-2 infection in transplant recipients, as shown in Figure 1, reflected the epidemic curve of the general population in Canada.[18]

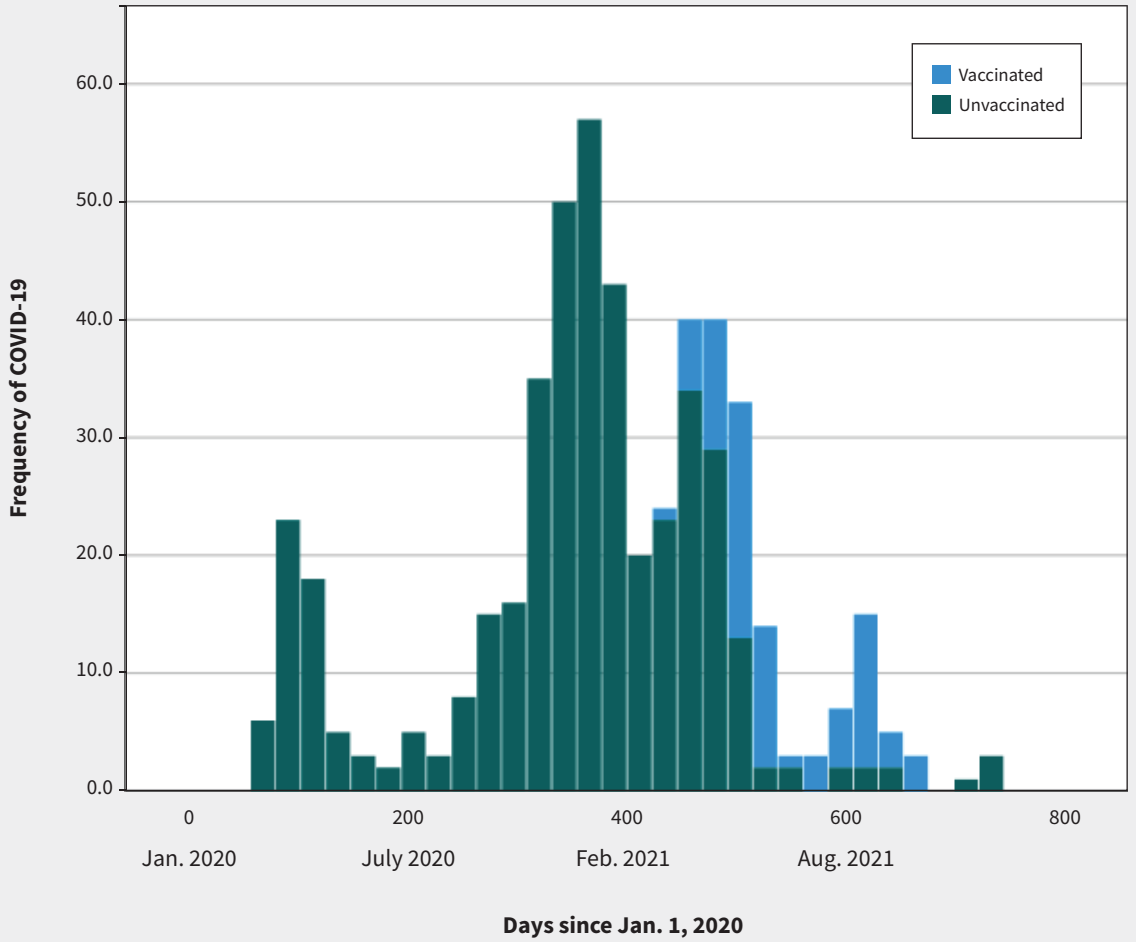

Figure 1: Frequency of COVID-19 over the study period, by vaccination status. Vaccinated participants included any patient who had received 1 or more doses of an approved SARS-CoV-2 vaccine and a confirmed SARS-CoV-2 infection more than 7 days after the first vaccine dose. The x-axis represents days since Jan. 1, 2020, and the y-axis represents the number of participants with COVID-19. In Canada, SARS-CoV-2 vaccines first became available in December 2020, with health care workers and older adults being the first priority groups. Patients who were immunosuppressed, including solid organ transplant recipients, were eligible to be vaccinated as of March 2021.

Table 2: Multivariable analysis of oxygen requirement, using both clinical characteristics and laboratory parameters*

Variable	OR (95% CI)
Age, yr	1.04 (1.02–1.07)
No. of comorbidities	1.63 (1.30–2.04)
Lung transplant	2.44 (0.76–7.89)
Liver transplant	0.41 (0.15–1.19)
Prednisone use	1.95 (0.72–5.31)
Mycophenolate use	0.86 (0.41–1.82)
Azathioprine use	0.13 (0.014–1.29)
Tacrolimus level	1.20 (1.09–1.31)
Lymphocyte count	1.02 (1.0003–1.032)

Note: CI = confidence interval, OR = odds ratio.
*Patients with missing data for tacrolimus level and lymphocyte count are not included in this model.

Table 3: Multivariable analysis of oxygen requirement, using clinical characteristics and excluding laboratory parameters*

Variable	OR (95% CI)
Age, yr	1.03 (1.02–1.05)
No. of comorbidities	1.53 (1.29–1.81)
Lung transplant	2.83 (1.42–5.65)
Liver transplant	0.53 (0.24–1.17)
Prednisone use	2.36 (1.13–4.93)
Mycophenolate use	1.16 (0.68–1.98)
Azathioprine use	0.27 (0.09–0.83)

Note: CI = confidence interval, OR = odds ratio.
*Includes all 509 patients.

Disease severity

Patient characteristics that were significantly associated with need for supplemental oxygen and hospital admission on univariate analysis are reported in Table 1 and Appendix 1, Supplementary Table 2, respectively.

On multivariable analysis (Table 2), factors associated with need for supplemental oxygen were age, number of comorbidities, higher tacrolimus level and lower lymphocyte count. Since tacrolimus level and lymphocyte count were only available for those patients who had current laboratory values, there was considerable missing data. Therefore, we generated a second model that excluded these variables (Table 3). Age and number of comorbidities remained consistent associations; however, having a lung transplant and being on prednisone at baseline were also associated with need for supplemental oxygen. The need for oxygen was associated with other complications in recipients of solid organ transplants with COVID-19 (Table 4), including a longer median length of hospital stay (14 d, interquartile range [IQR] 7–27 d v. 6 d, IQR 3–11.75 d; $p < 0.001$) and a greater proportion of fungal infections (6.3% v. 0%, $p < 0.001$) among those that required supplemental oxygen than among those who did not.

Hospital admission occurred in 276 (54.2%) patients, with 190 (37.3%) patients needing supplemental oxygen. Admission to ICU and mechanical ventilation were needed for 94 (18.5%) and 76 (14.9%) patients, respectively. Overall, 57 (11.2%) patients died within 28 days of COVID-19 diagnosis, with an additional 21 deaths that occurred up to 90 days postdiagnosis. Among vaccine breakthrough infections, 90-day all-cause mortality was 3 of 26 (11.5%), 4 of 53 (7.6%) and 0 of 3 (0%) of patients that had 1, 2 and 3 doses of vaccine, respectively.

A longitudinal analysis of the overall cohort over the 4 study periods indicated that there was no significant change over time in the proportion of patients requiring oxygen ($p = 0.1$), ICU admission ($p = 0.8$) or ventilatory support ($p = 0.5$), or the proportion of those who died ($p = 0.2$).

Treatment characteristics

Participants managed as outpatients were not treated with any specific therapy (including monoclonal antibodies, which had not been implemented during the study period). Therefore, we

Table 4: Clinical outcomes of overall cohort of recipients of solid organ transplants with COVID-19, by oxygen requirement

Outcome	No. (%) of patients*		*p* value
	No oxygen requirement *n* = 319	Oxygen requirement *n* = 190	
Length of hospital admission, d, median (IQR)†	6 (3–11.75)	14 (7–27)	< 0.001
Fungal infection	0	12 (6.3)	< 0.001
Acute rejection	7 (2.2)	1 (0.5)	0.1
ICU admission	4 (1.2)	90 (47.4)	< 0.001
All-cause mortality within 28 d of COVID-19 diagnosis	2 (0.6)	55 (28.9)	< 0.001
All-cause mortality within 90 d of COVID-19 diagnosis	9 (2.8)	69 (36.3)	< 0.001

Note: ICU = intensive care unit, IQR = interquartile range.
*Unless otherwise indicated.
†Among the 276 (54.2%) patients required hospital admission, including the 190 patients who required supplemental oxygen.

examined treatment characteristics in only the 190 patients admitted to hospital and requiring oxygen (Table 5). Of these, 136 (71.6%) received dexamethasone, 68 (35.8%) received remdesivir and 34 (17.9%) received tocilizumab. Remdesivir use (Table 5) was associated with a greater survival at 90-day follow-up (p = 0.04). Probable or proven invasive fungal infections occurred in 12 (6.3%) participants and 27 (14.2%) participants had culture-positive bacterial infections.

Type of organ transplant

Clinical severity was also related to type of organ transplant (Table 6). Recipients of lung transplants (n = 48) had a significantly higher rate of hospital admission related to COVID-19, (n = 34, 70.8%, p = 0.002) and cytomegalovirus viremia (n = 7, 14.6%, p < 0.001) compared with recipients of other organ types. They also had significantly higher rates of ICU admission and ventilator requirement, and had the highest all-cause mortality rate within 90 days of COVID-19 diagnosis (Figure 2).

Interpretation

We conducted a prospective, multicentre cohort study to assess risk factors for disease severity and outcomes among recipients of solid organ transplants with COVID-19 over the course of the pandemic in Canada. Within an immunosuppressed group, age and comorbidities, as well as transplant-related factors such as tacrolimus levels and lymphopenia, were significantly associated with the need for supplemental oxygen. We also observed that use of remdesivir in patients who needed supplemental oxygen was associated with lower mortality. The overall number of cases reported waned over the study period; however, ICU admission and mortality did not change appreciably over time. Although all transplant patients are at increased risk of severe COVID-19 compared with the general population, the risk factors determined in our study could be used to prioritize patients for various preventive and early therapeutic interventions.

Table 5: Treatment characteristics in subgroup of participants receiving oxygen therapy (n = 190) by mortality outcome

	No. (%) of patients		
Treatment	Alive n = 121	Deceased n = 69	p value
Dexamethasone	88 (72.7)	48 (69.6)	0.6
Remdesivir	50 (41.3)	18 (26.1)	0.04
Tocilizumab	23 (19.0)	11 (15.9)	0.6
Antibiotics (any)	97 (80.2)	48 (69.6)	0.1
Reduction in calcineurin inhibitor (any)	31 (25.6)	18 (26.1)	0.9
Reduction in antimetabolite (any)	86 (71.1)	44 (63.8)	0.3

Table 6: Outcomes of COVID-19 by type of transplant

	No. (%) of patients						
Outcomes	Kidney n = 325	Heart n = 23	Lung n = 48	Liver n = 79	Kidney–pancreas n = 25	Other n = 9	p value*
Hospital admission related to COVID-19	182 (56.0)	9 (39.1)	34 (70.8)	29 (36.7)	17 (68.0)	5 (55.6)	0.002
Pneumonitis	147 (45.2)	8 (34.8)	31 (64.6)	19 (24.1)	16 (64.0)	5 (55.6)	< 0.001
Acute rejection	3 (0.9)	2 (8.7)	1 (2.1)	1 (1.3)	1 (4.0)	0	0.09
Cytomegalovirus viremia	9 (2.8)	0	7 (14.6)	1 (1.3)	0	0	< 0.001
Acute kidney injury (any)	70 (21.5)	3 (13.0)	14 (29.2)	9 (11.4)	4 (16.0)	2 (22.2)	0.2
ICU	64 (19.7)	1 (4.4)	16 (33.3)	8 (10.1)	4 (16.0)	1 (11.1)	0.01
Ventilator	53 (16.3)	1 (4.4)	13 (27.1)	6 (7.6)	2 (8.0)	1 (11.1)	0.03
All-cause mortality within 28 d of diagnosis	33 (10.2)	1 (4.4)	12 (25.0)	4 (5.1)	1 (4.0)	1 (11.1)	0.002
All-cause mortality within 90 d of diagnosis	48 (14.8)	1 (4.4)	15 (31.3)	9 (11.4)	3 (12.0)	2 (22.2)	0.02

Note: ICU = intensive care unit.
*Test of significance across the 6 organ transplant subgroups.

As in other cohorts, we found the number of comorbidities and age to be associated with the need for supplemental oxygen among recipients of solid organ transplants.[2,9,19,20] Recipients of lung transplants were at the greatest risk of severe disease and death. This is likely owing to increased levels of immunosuppression, an aberrant local immune response in the transplanted lungs and varying degrees of baseline chronic lung allograft dysfunction.[9] In contrast, recipients of liver transplants were less likely to have severe disease, reflecting their relatively lower degrees of immunosuppression.[21] High tacrolimus levels and lymphopenia were also associated with severe disease and reflect higher immunosuppression. In contrast to Heldman and colleagues,[16] we did not find any significant improvements over time in disease severity outcomes, including ICU admission and death.[16] The lack of change in our cohort may be owing to the longer study time period, the advent of more severe variants of SARS-CoV-2 in 2021 and the availability of therapeutics across all studied time periods.

We observed a high rate of hospital admissions related to COVID-19 among transplant patients (54.2%), as well as long hospital stays (median 5 d, IQR 5–19 d). This is consistent with findings from the United States and France.[19,20] We also noted that the proportion of patients admitted to hospital tended to be higher than the proportion that needed supplemental oxygen (37.3%), likely because a significant proportion of patients are admitted for predominantly gastrointestinal symptoms, also shown in international cohorts.[20,22]

Therapies given to transplant patients with COVID-19 mirrored those used in the general population. We found an association between remdesivir therapy and a lower mortality rate. However, remdesivir is recommended for use in patients requiring supplemental oxygen, but has been shown to have limited benefit in those on mechanical ventilation, which suggests that our finding that a greater proportion of patients alive at the end of the study had received remdesivir may reflect its use in patients who are not as severely ill, rather than its generally beneficial effects on mortality among transplant patients.[5,23]

A unique aspect to COVID-19 management in transplantation is modulation of immunosuppression. Immunosuppressive drugs, especially antimetabolites, were reduced by clinicians in more than two-thirds of patients who required oxygen in our study. No specific data suggest that reducing immunosuppression drugs is a helpful strategy in managing COVID-19, although it is commonly described in other reports related to immunosupressed patient populations.[9,16,19,20,22,24,25] Of note, however, many transplant patients with more severe disease in our cohort received augmented immunosuppression in the form of dexamethasone and tocilizumab.[4] Therefore, it remains unclear whether the additive immunosuppression of dexamethasone

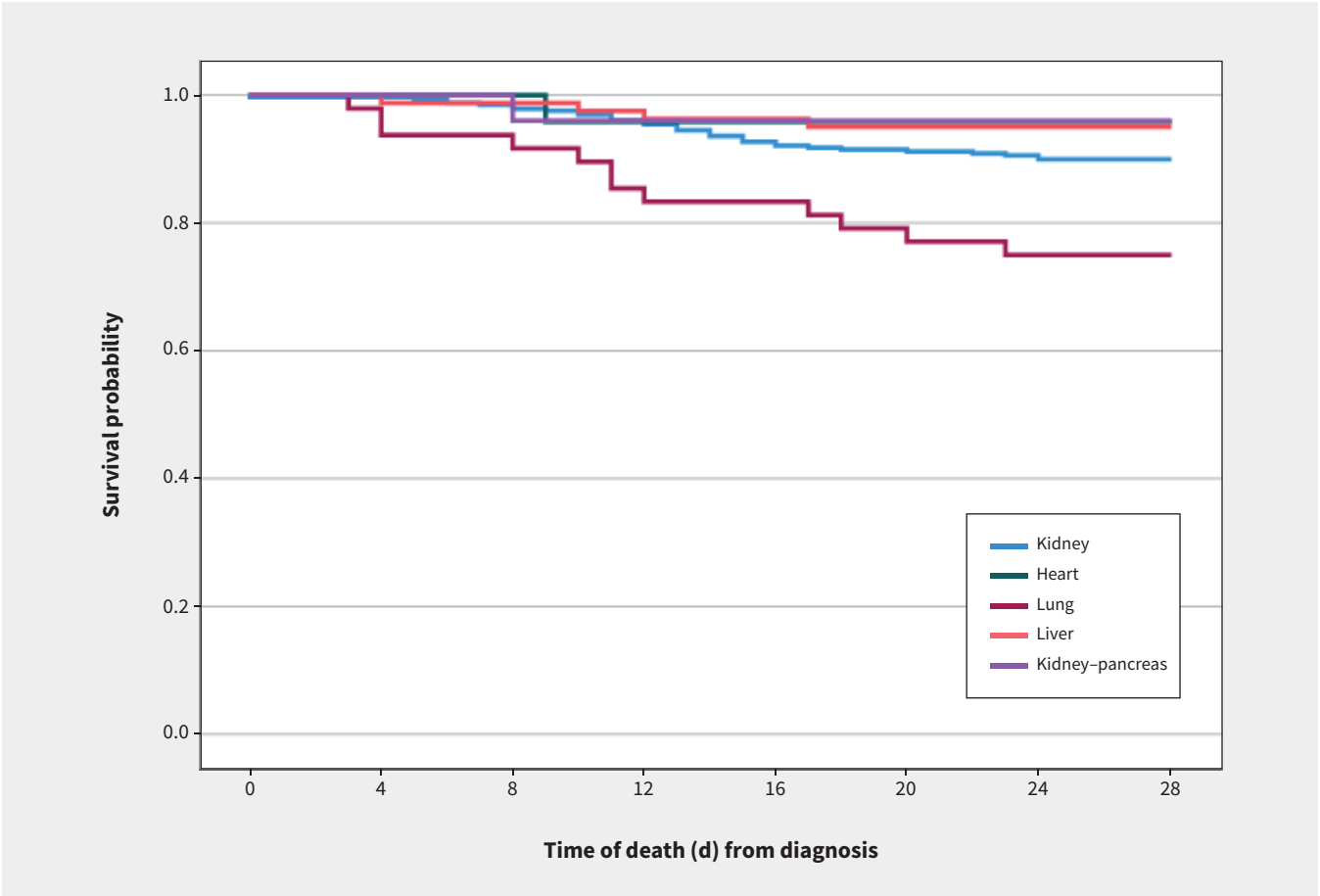

Figure 2: Unadjusted survival by 28 days from diagnosis, according to type of organ transplant (log rank, $p < 0.001$).

and tocilizumab, coupled with reduction of maintenance immunosuppression, is of any benefit, with only limited and descriptive reports from the transplant literature. Despite changes in immunosuppression, organ transplant rejection after COVID-19 was an uncommon occurrence.

Limitations

Although we accessed data for a large number of patients from multiple sites, there may have been a degree of incomplete case ascertainment (e.g., mildly ill patients who do not come to medical attention). This may mean we overestimated the proportion of severely ill patients. The use of targeted therapies was by clinician choice and may have been centre-specific, although therapies were relatively harmonized across the country, informed by regular online educational meetings that were arranged by the Canadian Blood Services for the transplant community. The inclusion of chest radiography as a modality to diagnose pneumonitis is a limitation, as it is neither sensitive nor specific for the diagnosis. Donor-specific antibody was not routinely monitored in transplant recipients after SARS-CoV-2 infection, so acute rejection may have been under-reported. However, most patients were followed for a maximum of 90 days, and so any change in graft function would likely have been detected in this time. Unmeasured confounders include primarily laboratory parameters, such as overall immunoglobulin levels, levels of other immunosuppressives such as mycophenolate, and vaccine-associated neutralizing antibody and T-cell responses. An area of future research is the assessment of vaccine effectiveness, given that we only had a small number of breakthrough infections after a third dose of vaccine. Our study period also ended before the emergence of the Omicron variant and did not include analysis of treatment options with monoclonal antibody therapy or antiviral agents.

Conclusion

We describe COVID-19 severity in a large, prospective cohort of recipients of solid organ transplants in Canada. Despite therapeutic advances, disease severity did not appear to change over time and recipients of lung transplants appear the most vulnerable. Preventive measures, such as additional vaccine doses or passive antibody prophylaxis, should continue to be evaluated, as well as early outpatient management with monoclonal antibody therapy and newly available oral antiviral agents. Our findings highlight the importance of ongoing public health measures for the protection of recipients of solid organ transplants and judicious vaccination of their close and household contacts.

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