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Kidney Transplantation in Times of Covid-19: Decision Analysis in the Canadian Context

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic impacted transplant programs across Canada.

Objective: We evaluated the implications of delays in transplantation among Canadian end-stage kidney disease (ESKD) patients to allow pretransplant vaccination.

Design: We used a Markov microsimulation model and ESKD patient perspective to study the effectiveness (quality-adjusted life years [QALY]) of living (LD) or deceased donor (DD) kidney transplantation followed by 2-dose SARS-CoV-2 vaccine versus delay in LD ("Delay LD") or refusal of DD offer ("Delay DD") to receive 2-dose SARS-CoV-2 vaccine pretransplant.

Setting: Canadian dialysis and transplant centers.

Patients: We simulated a 10000-waitlisted ESKD patient cohort, which was predictively modeled for a lifetime horizon in monthly cycles.

Measurements: Inputs on patient and graft survival estimates by patient, LD or DD characteristics, were extracted from the Treatment of End-Stage Organ Failure in Canada, Canadian Organ Replacement Register, 2009 to 2018. In addition, a literature review provided inputs on quality of life, SARS-CoV-2 transmissibility, new variants of concern, mortality risk, and antibody responses to 2-dose SARS-CoV-2 mRNA vaccines.

Methods: We conducted base case, scenario, and sensitivity analyses to illustrate the impact of patient, donor, vaccine, and pandemic characteristics on the preferred strategy.

Results: In the average waitlisted Canadian patient, receiving 2-dose SARS-CoV-2 vaccine post-transplant provided an effectiveness of 22.32 (95% confidence interval: 22.00-22.7) for LD and 19.34 (19.02-19.67) QALYs for DD. Delaying transplants for 6 months to allow 2-dose SARS-CoV-2 vaccine before LD and DD transplant yielded effectiveness of 22.83 (21.51-23.14) and 20.65 (20.33-20.96) QALYs, respectively. Scenario analysis suggested a benefit to short delays in DD transplants to receive 2-dose SARS-CoV-2 vaccine in waitlisted patients ≥55 years. Two-way sensitivity analysis suggested decreased effectiveness of the strategy prioritizing 2-dose SARS-CoV-2 vaccine prior to DD transplant the longer the delay and the higher the Kidney Donor Risk Index of the eventual DD transplant. When assessing the impact of SARS-CoV-2 variants of concern (infection rates ≥10-fold and associated mortality ≥3-fold vs base case), we found short delays to allow 2-dose SARS-CoV-2 vaccine administration pretransplant to be preferable.

Limitations: Risks associated with nosocomial exposure of LDs were not considered. There was uncertainty regarding input parameters related to SARS-CoV-2 infection, new variants, and COVID-19 severity in ESKD patients. Given rollout of population-level SARS-CoV-2 vaccination, we assumed a linear decrease in infection rates over 1 year. Proportions of patients mounting an antibody response to 2-dose SARS-CoV-2 mRNA vaccines were considered in lieu of data on vaccine efficacy in dialysis and following transplantation. Non-age-stratified annual mortality rates were used for waitlisted candidates.

Conclusions: Our analyses suggest that short delays allowing pretransplant vaccination offered comparable to greater effectiveness than pursuing transplantation without delay, proposing transplant candidates should be prioritized to receive at least 2 doses of SARS-CoV-2 vaccine. Our scenario and sensitivity analyses suggest that caution must be exercised when declining DD offers in patients offered low risk DD and who are likely to incur significant delays in access to transplantation. While population-level herd immunity may decrease infection risk in transplant patients, more data are required on vaccine

efficacy against SARS-CoV-2 and variants of concern in ESKD, and how efficacy may be modified by a third vaccine dose, maintenance immunosuppression and timing of induction and rejection therapies.

Keywords
COVID-19, kidney transplantation, end-stage kidney disease, Markov model, real-world data, SARS-CoV-2 vaccine

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to have a significant impact on health care systems in Canada and around the world.[1-4] While transplant activities continued uninterrupted in some hospitals throughout the pandemic,[5] many hospitals, transplant programs, and organ procurement organizations experienced disruptions in transplant activities due to increased demands on health care resource utilization. Moreover, concerns that newly transplanted patients on immunosuppression may be at increased risk of mortality following SARS-CoV-2 infection, and the perception that kidney transplantation is a "semi-elective" procedure and transplant candidates can be stably maintained on dialysis, were also observed.[6,7]

End-stage kidney disease (ESKD) patients represent a vulnerable population at increased risk of death while waitlisted for transplantation.[8-10] Under normal circumstances, kidney transplantation offers significantly better survival and quality of life (QOL), accompanied by reduced health care costs, making it the preferred renal replacement therapy.[11,12] During the first wave of the pandemic, a higher risk of complications and deaths attributable to COVID-19 were observed among ESKD patients, including transplant recipients,[9,13-25] leading some to wonder about the survival advantage associated with transplantation.

Several reports, focusing on the risks and benefits of pursuing transplantation during the pandemic versus interrupting transplant activities, demonstrated the superiority of transplantation,[9,26-32] lending support to the resumption of transplant activities during the second wave of the pandemic. The rollout of SARS-CoV-2 vaccines, though much-anticipated, introduced new considerations for waitlisted ESKD patients. While evidence suggests improvement in anti-spike antibody responses in dialysis and transplant recipients after 2 doses of mRNA vaccines, it appears immune suppression compromises the ability to mount an antibody response, and a substantial proportion of ESKD patients are likely to remain at risk for COVID-19, with this being more pronounced among transplant recipients in comparison to dialysis.[33-37]

Here, we outline the implications of COVID-19 from an ESKD patient's perspective in the context of Canada's publicly funded health care system. To our knowledge, this is the first decision analysis integrating real-world Canadian inputs with the latest COVID-19 data to inform on the survival and quality of life implications of the timing of SARS-CoV-2 mRNA vaccine administration. More specifically, we assess the impact of proceeding with living (LD) and deceased donor (DD) transplants during the pandemic and receiving the vaccine posttransplant in comparison to delaying transplantation to allow pretransplant 2-dose vaccination. To assist with decision making, we illustrate through scenario and sensitivity analyses how the decision may be influenced by pertinent patient, donor, vaccine, and pandemic characteristics given current and emerging viral variants.

Methods

Model Design

Using a Markov model, we applied microsimulations to estimate strategy effectiveness, providing patient-level flexibility and memory. Created with TreeAge Pro Healthcare software version 2021 (TreeAge Software, Inc, Williamstown, MA), the model was designed to predict the long-term impact of suspending kidney transplants for ESKD patients. We simulated a 10 000-patient cohort which followed patients over the lifetime horizon in monthly cycles. Figure 1 presents the

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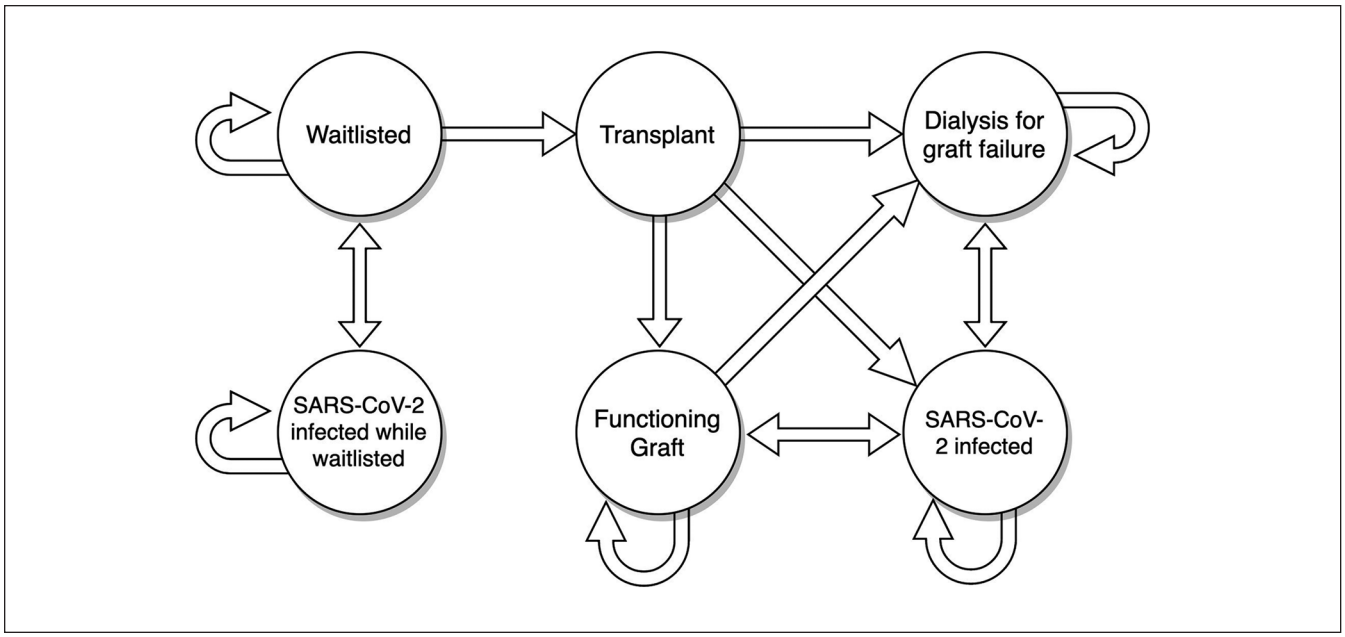

Figure 1. Health states and transitions.
Note. The structure used to model kidney transplants during the COVID-19 pandemic was built around the following main health states: "Waitlisted," "Transplant," "Functioning Graft," "Graft Failure," and "SARS-CoV-2 infected." Arrows represent transitions between health states or patients remaining in the same health state. Patients can transition from all health states to the death health state (omitted for visualization clarity purposes).

model structure, health states considered, and transitions between them.

Inputs

Inputs for transplant strategies were extracted from the Treatment of End-Stage Organ Failure in Canada, Canadian Organ Replacement Register (CORR), 2009 to 2018.[38] CORR provides data on incidence, prevalence, wait time, as well as graft and ESKD patient survival in Canada. Data from British-Columbia, Alberta, Saskatchewan, Manitoba, Ontario, New-Brunswick, Nova-Scotia, Prince-Edward-Island, and Newfoundland from 2009 to 2018 were included in CORR. For some measures (eg, incident ESKD), data were also provided for the territories of Yukon, Nunavut, and the North-Western Territories, but this was inconsistent in the entire publicly available report. Data from Quebec were not included in CORR data tables because of significant underreporting between 2011 and 2018.

A literature review was performed to obtain inputs not available in CORR (eg, COVID-19 related survival). Supplemental Appendix 1 outlines the search strategy, with references updated on a weekly basis. As of May 2, 2021, Canadian SARS-CoV-2 infection rates were estimated at 3247 per 100 000 individuals who were tested for SARS-CoV-2, ranging from 2515 to 4408 per 100 000 in British-Columbia and Alberta, respectively.[39] Raw infection rates can be found in Supplemental Appendix 2. Utilities (minimum-to-maximum) associated with each health state were assigned the following values: Transplant: 0.78 (0.63-0.93)[40]; Functioning graft: 1 (1-1)[41]; Waitlisted: 0.61 (0.54-0.68)[40]; Dialysis: 0.61 (0.54-0.61)[40]; SARS-CoV-2 infected: 0.64 (0.49-0.77).[42,43] To account for disparities in utility associated to the functioning graft health state, we also considered utilities reported by Wyld et al.[44]

The population was composed of adult (≥18-year-old) Canadian ESKD patients. When available, published hazard ratios (HR) were applied onto CORR survival data. Rates were transformed to monthly probabilities using internal formulae in TreeAge. Table 1 presents the various inputs incorporated in the model. Supplemental Appendices 2 to 5 present time-varying age-specific inputs, donor risk profiles, and Canadian infection rates.

Outcome and Analyses

"Effectiveness" was measured in months of mean patient survival and reported in quality-adjusted life years (QALY). The 95% confidence intervals surrounding the mean effectiveness estimates, calculated as $\pm 2 \times$ (Variance/Sample size)$^{1/2}$, were constructed to determine the presence of statistically significant differences between delaying versus proceeding with transplantation.

We compared effectiveness of four different strategies. The status quo scenario of proceeding with transplantation (and receiving 2-dose vaccine posttransplant), represented by the LD and DD strategies, was compared with delaying transplantation to allow 2-dose SARS-CoV-2 vaccine administration

Table 1. Model Inputs Used for Base Case Scenario.

Health state	Name	Probability / rate / value	Low	High	Reference
Waitlisted	Time on waiting list for deceased donor (months)	46.00	18.00	74.00	38
	Time on waiting list for living donor (months)	17.70	3.00	32.70	38
	Proportion of patients on hemodialysis	0.77	—	—	38
	Proportion of patients on peritoneal dialysis	0.23	—	—	38
	Annual death rate while waitlisted	2.50%	2.20%	3.20%	38
Transplant	HR of dying in the first 30 days after deceased donor transplant[a]	1.43	1.30	1.57	45
	HR of dying in the first 30 days after living donor transplant[a]	0.64	0.53	0.74	45
Functioning graft	HR of dying with functioning deceased donor graft[a]	0.46	0.43	0.49	45
	HR of dying with functioning living donor graft[a]	0.23	0.21	0.25	45
	Graft survival estimates		Supplemental Appendix 4		38
COVID-19 specific	SARS-CoV-2 infection rate in Canada[b]	3247	2515	4408	39
	Length of SARS-CoV-2 infection (months)	1.00[c]	1.00[c]	2.00	30,46
	COVID-19 monthly death probability while on dialysis (age 18-64)	0.08	0.07	0.10	13,38
	COVID-19 monthly death probability while on dialysis (age 65-74)	0.20	0.17	0.22	
	COVID-19 monthly death probability while on dialysis (age 75+)	0.30	0.27	0.32	
	COVID-19 monthly death probability with functioning graft (age 18-64)	0.12	0.10	0.15	
	COVID-19 monthly death probability with functioning graft (age 65-74)	0.29	0.24	0.35	
	COVID-19 monthly death probability with functioning graft (age 75+)	0.44	0.35	0.52	
	HR of dying from COVID-19 disease with new viral variants[d]	1.50	1.00	3.00	47,48
	Dialysis patients' response to SARS-CoV-2 vaccine	0.91	0.87	0.96	34,36,37
	Transplant patients' response to SARS-CoV-2 vaccine	0.49	0.47	0.50	33,35

Note. HR = hazard ratio.
[a]Reference: patient survival while on dialysis. Also see Supplemental Appendix 5.
[b]Per 100 000 tested for SARS-CoV-2.
[c]Markov model requires that patients spend at least one cycle within a particular health state.
[d]COVID-19 survival without variants of concern (VOC).

pretransplant ("Delay LD" and "Delay DD," respectively). In the latter, for the base-case scenario, LD or DD transplant were expected to occur within 6 months from the decision to delay transplantation and the pandemic was expected to last for 1 year following this decision.

While a subsequent DD transplant offer may be realized within 6 months in unsensitized blood group A patients, for example, declining DD offers by candidates with other blood groups and/or history of sensitization could result in more protracted delays in access to transplantation. These were explored in scenario analyses outlining various delay periods. In addition, we conducted sensitivity analysis considering various patient age groups, pandemic characteristics (ie, SARS-CoV-2 infection, SARS-CoV-2 variants of concern [VOCs], and length of pandemic), and information on donor quality defined according to the Kidney Donor Risk Index (KDRI, see Supplemental Appendix 3). The KDRI incorporates 10 donor factors (age, height, weight, ethnicity, history of hypertension, history of diabetes, cause of death, serum creatinine, hepatitis C virus status, and donation after circulatory death) demonstrating modest predictive value for long-term graft survival. Since its derivation using the US Scientific Registry of Transplant Recipients, KDRI has also been studied in several Canadian populations (ie, Ontario, BC, Alberta, and Quebec).[49-53] Two-way sensitivity analyses with 1000 trials and a 10-year horizon were performed to assess how different combinations of recipient, donor, and pandemic characteristics, including emerging SARS-CoV-2 variants, may impact effectiveness and modify the preferred strategy.

Also, we estimated the effectiveness in patients refusing to undergo vaccination altogether. For these analyses, we considered the following strategies: patients opting to pursue LD or DD when offered versus to "Delay LD" or "Delay DD" and consider transplantation only upon resolution of the pandemic. In this analysis, the pandemic was expected to last for 1 year following the patient's decision. We conducted scenario analyses to represent potential changes in

Table 2. Two-Way Sensitivity Analysis, Impact of Delay Period, and Donor Kidney Donor Risk Index Category on Deceased Donor Strategy Effectiveness.

Kidney Donor Risk Index		Effectiveness (quality-adjusted life year)[a]				
		Transplant DD	6-month delay DD	12-month delay DD	24-month delay DD	36-month delay DD
1	Q1 (0.63-0.95)	7.81	8.38	8.43	8.00	7.63
2	Q2 (0.96-1.13)	7.67	8.25	8.31	7.95	7.56
3	Q3 (1.14-1.32)	7.49	8.15	8.21	7.87	7.50
4	Q4 (1.33-1.60)	7.57	8.21	8.26	7.90	7.54
5	Q5 (1.61-3.15)	7.21	7.96	7.98	7.70	7.37

Note. DD = deceased donor; Q1 = Quintile.
[a]Time horizon: 10 years.

effectiveness should declining an offer result in various delays in eventual access to transplantation.

Finally, to account for disparities in utility associated with graft function,[44] we conducted a scenario analysis estimating the utility associated with the functioning graft health state at 0.82 (minimum to maximum: 0.74-0.90).

Assumptions

The COVID-19 pandemic was assumed to last for an additional 1-year period (12 cycles). Community and nosocomial SARS-CoV-2 infection rates were considered equivalent and lasting for up to 2 months. Waitlisted patients with SARS-CoV-2 infection were put on hold, until they were free of infection (within 1-2 months) and reactivated on the waiting list. COVID-19 was assumed to affect LD and DD similarly. Based on published literature, COVID-19 was assumed to have no significant impact on graft failure.[54] As ESKD patients are considered a population at risk, we assumed that they were offered vaccination as a priority group with 2 doses administered within 3 months. In the vaccination scenario, community infection rates were assumed to decrease to null in a linear fashion over a period of 6 months after the beginning of the vaccination campaign. Furthermore, an effective vaccine was considered to negate survival and QOL-related effects of COVID-19. In lieu of efficacy data on SARS-CoV-2 vaccines and their impact on survival of ESKD patients, we considered data on immunogenicity of the vaccines in dialysis and kidney transplant recipients. As the study relied on published data, research ethics board approval was not required.

Results

Using microsimulations, the Markov model illustrates the effectiveness of pursuing kidney transplantation (LD and DD strategies) followed by 2-dose SARS-CoV-2 vaccine versus remaining on the waiting list to receive 2-doses SARS-CoV-2 vaccine pretransplant (Table 2). The model outputs for the base case, representing the average waitlisted Canadian ESKD patient, established that continuing LD and DD provided an effectiveness of 22.32 (22.00-22.7) versus 19.34 (19.02-19.67) QALYs, respectively. Delaying transplantation to receive 2-dose SARS-CoV-2 vaccine yielded similar effectiveness of 22.83 (21.51-23.14) and slightly greater effectiveness of 20.65 (20.33-20.96) QALYs for "Delay LD" and "Delay DD" transplants, respectively.

Scenario analysis evaluating the impact of recipient age on the preferred strategy established that the effectiveness of "Delay LD" and "Delay DD" decreased as a function of recipient age, with benefit observed with short delays in DD transplants to allow pretransplant 2-dose SARS-CoV-2 vaccine in patients 55 years of age and older (Figure 2).

Because delaying transplantation, and more so declining DD offers, could result in variable delays in access to transplantation depending on each patient's blood group and degree of sensitization, among others, we conducted scenario analyses. In comparison to the short delays (6-months) in LD and DD transplants to receive 2-dose vaccine as outlined in the base case, the effectiveness of DD transplants (followed by 2-dose vaccine posttransplant) converged as waiting time increased to up to 3 years (Figures 3A and 3B).

Because in addition to delays in access to transplantation, declining a DD offer may result in subsequent donor offers with better or worse risk profiles, we assessed changes to effectiveness considering both length of delay as well as the KDRI score of DD transplant. In this 2-way sensitivity analysis, we found the effectiveness of "Delay DD" to allow 2-dose pretransplant SARS-CoV-2 vaccine decreased the longer the delay in access to transplantation and the higher the KDRI score (Table 2).

When considering the pandemic characteristics, we observed (see Figure 3C and 3D) that the effectiveness of "Delay DD" and "Delay LD" strategies did not noticeably vary as a function of SARS-CoV-2 infection rates. In contrast, we observed decreased effectiveness of the LD and DD strategies the more extreme the infection rates in comparison to the base case.

To assess the impact of SARS-CoV-2 VOCs on the preferred strategy, we explored the impact of infection rates up to 10-fold greater and mortality risk up to 3-fold higher than that estimated for the base case. This 2-way sensitivity

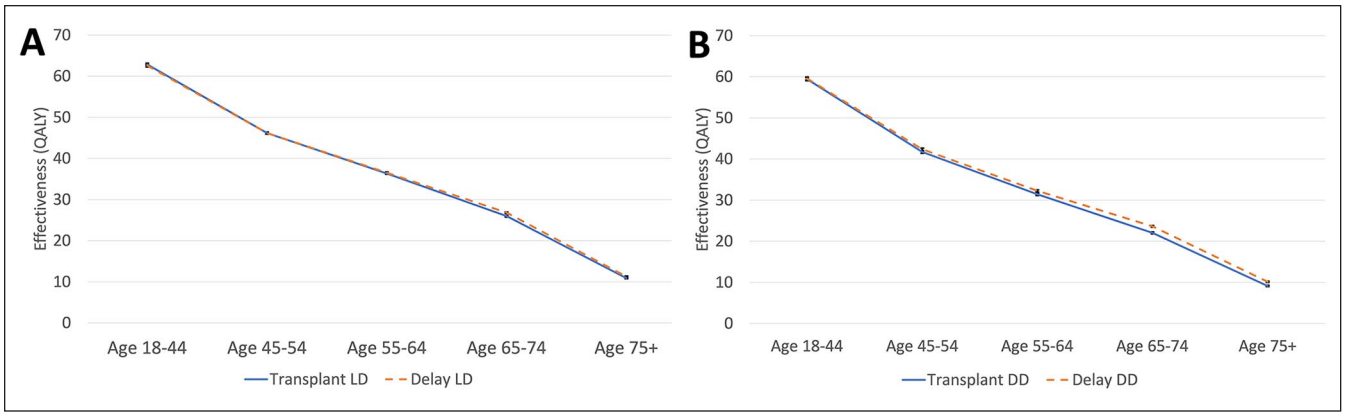

Figure 2. Transplant strategy effectiveness by candidate age group.
Note. Effectiveness in quality-adjusted life years of Transplant LD and "delay LD" (A) as well as Transplant DD and "Delay DD" (B) strategies by candidate age group. Error bars represent 95% confidence intervals. LD = living donor; DD = deceased donor; QALY = quality-adjusted life years.

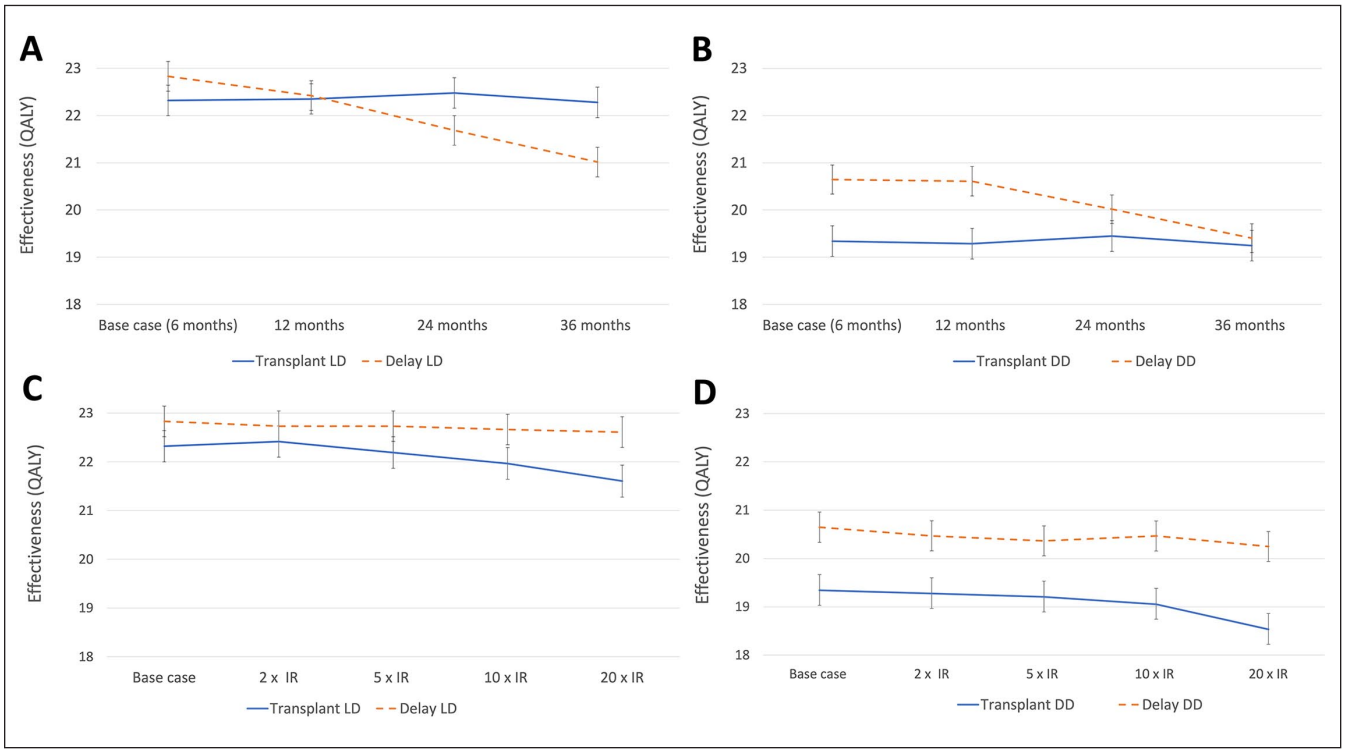

Figure 3. Scenario analyses, impact of transplant delay period and infection rates on effectiveness.
Note. Effectiveness of transplant LD and "Delay LD" (A) as well as Transplant DD and "Delay DD" (B) strategies by delay period to transplantation. Effectiveness of Transplant LD and "Delay LD" (C) as well as Transplant DD and "Delay DD" (D) by SARS-CoV-2 infection rates. Error bars represent 95% confidence intervals. LD = living donor; DD = deceased donor; QALY = quality-adjusted life years; IR = infection rate.

analysis favored the "Delay LD" and "Delay DD" strategies, in which administration of 2-dose SARS-CoV-2 vaccine while waitlisted was followed by LD and DD, respectively, within 6 months (Table 3).

As some ESKD patients might decline vaccination altogether (and some might not mount a protective immune response), we conducted scenario analysis assuming vaccines were refused both pretransplant as well as posttransplant. We compared the effectiveness projections when pursuing LD and DD transplantation without delay during the pandemic versus opting to delay LD transplantation or declining DD offers until resolution of the pandemic (Table 4). In these analyses, we considered different pandemic lengths and found that short delays of up to 1 year in the context of stable waiting list mortality and down trending infection rates appeared to be acceptable and even offer slightly better

Table 3. Two-Way Sensitivity Analysis, Impact of SARS-CoV-2 Variant Infection Rate, and Associated Mortality on Strategy Effectiveness.

Multiplier of SARS-CoV-2 variant infection rate	Multiplier of SARS-CoV-2 variant associated mortality	Effectiveness in quality-adjusted life year[a]			
		Transplant LD	Delay LD	Transplant DD	Delay DD
1	1	9.18	8.99	8.21	8.43
	2	9.17	8.98	8.18	8.43
	3	9.07	9.01	8.11	8.44
3.25	1	8.99	9.01	8.03	8.44
	2	8.96	9.01	8.01	8.45
	3	8.99	9.03	8.00	8.46
5.5	1	8.89	9.03	7.89	8.45
	2	8.89	9.05	7.95	8.44
	3	8.51	9.01	7.59	8.39
7.75	1	9.18	8.99	8.21	8.43
	2	9.17	8.98	8.18	8.43
	3	9.07	9.01	8.11	8.44
10	1	8.99	9.01	8.03	8.44
	2	8.96	9.01	8.01	8.45
	3	8.99	9.03	8.00	8.46

Note. LD = living donor; DD = deceased donor.
[a]Time horizon: 10 years.

Table 4. Scenario Analysis, Unvaccinated Waitlisted Patients Undergoing Transplant Without Delay (Immediate Transplant), or Experiencing Various Delays While Awaiting Pandemic Resolution.

Type of strategy	Effectiveness (quality-adjusted life year)				
	Immediate transplant unvaccinated	6-month delay unvaccinated	12-month delay unvaccinated	24-month delay unvaccinated	36-month delay unvaccinated
Transplant living donor	22.32 (22.00-22.64)	22.68 (22.36-22.99)	20.72 (20.41-21.02)	21.83 (21.52-22.15)	21.17 (20.85-21.49)
Transplant deceased donor	19.35 (19.03-19.68)	20.47 (20.16-20.78)	22.64 (22.33-22.95)	20.07 (19.77-20.38)	19.51 (19.19-19.83)

Note. These scenarios also inform effectiveness in patients who do not mount an antibody response to SARS-CoV-2 vaccines.

QALYs. However, when longer delays were projected to the next donor offer, DD transplant became the preferred strategy. Finally, scenario analyses results considering utilities reported in Wyld et al 2012[44] did not differ from the base-case analysis and confirmed the main findings (Supplemental Appendix 6).

Discussion

Our analysis is the first of its kind to demonstrate that in the average Canadian ESKD patient waitlisted for transplantation, delaying transplantation to receive 2-dose SARS-CoV-2 vaccine while on the waiting list yielded similar effectiveness to LD and greater effectiveness than DD, if LD transplant and subsequent DD offer and transplant were expected to occur within a short delay. In the case of DD transplant, declining an offer, which resulted in delays exceeding 3 years, and subsequent donor offers with higher KDRI scores, made the DD strategy (with posttransplant vaccination) preferable. While the effectiveness of the "Delay LD" and "Delay DD" strategies did not noticeably vary as a function of SARS-CoV-2 infection rates, higher infection rates led to more pronounced decreases in effectiveness of both LD and DD strategies, with more extreme infection rates than those observed in the base case making delayed transplantation the preferred strategy. Finally, when assessing the impact on the preferred strategy of the SARS-CoV-2 pandemic characteristics as well as the transmissibility and the mortality risk associated with VOCs, we found strategies prioritizing pretransplant 2-dose vaccine administration, albeit with brief delays in transplantation, to be preferable.

Outside of the pandemic, LD and DD transplants are known to offer superior survival and quality of life in comparison to remaining waitlisted. Several publications preceding vaccine rollout similarly suggested the superiority of pursuing transplantation over remaining on the waiting list

during the COVID-19 pandemic. Massie et al[26] used a Markov model with a 5-year horizon to compare outcomes when pursuing immediate transplants or delayed transplants in the United States. Immediate kidney transplantation provided survival benefit in most scenarios except for scenarios with substantially higher case fatality rates (eg, ≥50% fatality). A more recent decision analysis by Vinson et al[55] also relying on US data found that patient life expectancy diminished for both waitlisted and transplant recipients as the pandemic conditions became more unfavorable. However, the overall net benefit of transplantation during the pandemic was preserved. While much like these studies, our analysis of waitlisted Canadian ESKD patients refusing the vaccine appeared to offer comparable effectiveness when LD transplants proceeded without delay, our base-case analysis, using Canadian ESKD survival probabilities, QOL estimates, and a lifetime horizon, suggests that brief delays in transplantation to allow administration of 2-dose SARS-CoV-2 vaccine may offer comparable effectiveness as the LD and greater effectiveness than DD strategy as long as the pretransplant 2-dose SARS-CoV-2 vaccine strategies resulted in rather short delays in access to transplantation.

Importantly, for our base-case model inputs, we relied on immunogenicity data of SARS-CoV-2 mRNA vaccines in lieu of efficacy data on each of the currently available vaccines in ESKD and immunosuppressed kidney transplant recipients.[56,57] The fact that antibody titers are lower than in healthy controls[34,36,37,57,58] may indicate a lower efficacy of vaccines in dialysis patients than the general population. This, in turn, might diminish the projected effectiveness of the "Delay LD" and "Delay DD" strategies. Moreover, our analyses assumed that the level of immunogenicity afforded pretransplant was maintained posttransplant and did not consider scenarios when one dose is administered pretransplant and another posttransplant. While our scenario analyses in patients refusing vaccines can inform on effectiveness in the extreme context of no immunity afforded by the vaccine, it is important to recall the findings arising from this analysis hinge on the assumption that the pandemic will resolve within 1 year thanks to population-level vaccination and herd immunity. To better inform future decision making, more data are required on the actual efficacy of vaccination and whether in the absence of neutralizing antibodies, ESKD patients might still be protected (postvaccination) by a sufficient cellular immune response.[59,60] Data are also needed on how vaccine efficacy may be further modified by maintenance immunosuppression regimens,[61] as well as the timing of induction and rejection therapies.

When considering the characteristics of the pandemic, we found that effectiveness of the "Delay LD" and "Delay DD" strategies did not noticeably vary as a function of SARS-CoV-2 infection rates. Yet, given lower vaccine immunogenicity in the posttransplant context, higher infection rates led to decreased effectiveness in both LD and DD strategies. It is important to mention that the results of the base-case analysis for both transplant and delayed transplant strategies were rather similar and dependent on the considered model assumptions. Some of these assumptions were that patients would be allowed to resume their active status on the waiting list within 1 to 2 months from resolution of SARS-CoV-2 infection and that the pandemic was to last for 1 year following the decision to delay or to proceed with transplantation.

Since the fall of 2020, new SARS-CoV-2 variants have been rapidly emerging. The World Health Organization projects that given the ongoing high rates of transmission globally, SARS-CoV-2 VOCs will continue to evolve over time.[62] Of these variants, 20I/501Y.V1, VOC 202012/01, or B.1.1.7 that was detected first in the United Kingdom has many mutations and appears to be associated with an increased risk of death compared with other variants.[47,48] More recently, the Delta variant has been demonstrating increased transmissibility and secondary attack rate, increased risk of hospitalization, reduction in neutralizing activity, and decreased vaccine efficacy/effectiveness. European projections suggest this variant will rapidly become the dominant circulating lineage over the coming months. Two-way sensitivity analyses considering both the potential for higher case fatality rates related to more severe COVID-19 as well as increased transmissibility with these emerging new variants, suggested brief delays in transplantation to allow 2-dose SARS-CoV-2 vaccine administration as the preferable strategy. This finding highlights the importance of prioritizing waitlisted patients to receive 2-dose vaccine. Yet, more data are required on vaccine efficacy against SARS-CoV-2 and VOCs in ESKD, and the role of a third vaccine and/or vaccines directed against VOCs in preventing infection and disease in ESKD patients pre- and posttransplant.

The COVID-19 pandemic found patients of older age and with significant comorbidity burden more vulnerable to experience worse outcomes.[13,63,64] Our scenario analyses showed that continuing LD and posttransplant vaccination offered comparable effectiveness to pretransplant vaccination across the age groups reported in CORR. Although similar trends were observed for DD transplants, pretransplant vaccination appeared to be the favorable strategy, with a benefit observed when pursuing DD transplants within a short delay to allow pretransplant 2-dose vaccine in patients 55 years of age and older. This population is considered at higher risk of experiencing complications related to SARS-CoV-2 infection. Despite lower suspected immunogenicity of vaccine posttransplant, decreasing infection rates as larger proportions of the general population undergo vaccination in addition to the survival advantage offered by transplantation in comparison to dialysis likely contribute to the similar effectiveness of the two strategies.

In the case of DD transplant, decline of an offer to allow pretransplant vaccination was deemed acceptable, if the delay in access to transplantation did not exceed 3 years. Not surprisingly, however, effectiveness decreased the longer the delay in access to transplantation and the higher the KDRI

score of the eventually offered donor. It is important to note that because CORR survival data do not specify deceased donor KDRI scores, we incorporated HRs extracted from Young et al[53] onto CORR survival estimates, which represent the average kidney transplant recipient rather than those in the referent KDRI category. Consequently, risks associated with KDRI may be overestimated. In addition, while it may appear that cohort survival may not be compromised when DD is delayed for shorter periods of time, it is important to highlight that organ wastage during the pandemic is expected to exacerbate the perpetual gap between organ supply and demand following the pandemic. Moreover, missed opportunities for transplantation may not recur during the lifetime of candidates who are particularly difficult to match with compatible donors. Our analysis provides transplant professionals with the insights required to inform patients when deciding to prioritize receiving 2-dose SARS-CoV-2 vaccine pretransplant versus proceeding with transplantation and receiving 2-dose vaccine following transplantation. Importantly, to further mitigate risk of contracting SARS-CoV-2 and incurring complications related to COVID-19, patients opting to pursue transplantation without delay may always benefit from adhering to public health recommendations on how to minimize risk of exposure. Inevitably, it is only the elimination of SARS-CoV-2 and variants of concerns[47] and development of population-level herd immunity that will secure optimal outcomes for transplant candidates and recipients.

Our article provides the first analysis assessing the risk-benefit balance of pursuing LD and DD transplants in Canada in the context of the COVID-19 pandemic with particular attention to pertinent recipient, donor, vaccine, and pandemic characteristics. Performed during the second wave of the COVID-19 pandemic in Canada, our model can inform decisions on preferred timing of vaccine administration in reference to transplantation as newer and more aggressive strains of SARS-CoV-2 are identified and various SARS-CoV-2 vaccines as well as therapeutic and immunomodulatory strategies are being rolled out. Despite these advantages, several limitations must be noted. First, publicly available survival data in CORR are not stratified by age, do not include time-dependent estimates or information on priority in access to transplantation, and are not limited to adult candidates. Publicly available age-stratified dialysis survival data do not discriminate between waitlisted and non-waitlisted dialysis patients, or those on dialysis pretransplant and following graft failure. For this reason, while utilization of age-stratified dialysis survival data could result in less favorable survival projections, utilization of waitlisted survival data could result in more favorable survival projections than those observed in adult Canadian waitlisted patients. Second, our model inferences are dependent on input parameters related to SARS-CoV-2 infection and COVID-19 in ESKD patients and the uncertainties associated with them. Nonetheless, the scenario and sensitivity analyses conducted (eg, spectrum of infectivity and mortality risk) address some of these uncertainties and inform decision makers on determinants of the preferred strategies. Third, as the model focused on the patient perspective, risks associated with nosocomial exposure of living donors to SARS-CoV-2 were not considered. Yet, in the context of primarily community exposure, the added risk related to nosocomial infection among healthy LDs is likely negligible.

Conclusion

Pursuing transplantation, whether LD or DD, has been shown to offer superior survival to remaining waitlisted outside of the pandemic. Similar observations were made during the COVID-19 pandemic prior to the rollout of SARS-CoV-2 vaccines. Our analyses suggest that short delays allowing pretransplant receipt of 2-dose SARS-CoV-2 vaccine offered comparable to greater effectiveness than pursuing transplantation without delay (followed by vaccination), suggesting transplant candidates should be prioritized to receive 2-dose SARS-CoV-2 vaccine pretransplant whenever possible. Our scenario and sensitivity analyses also suggest that caution must be exercised when declining DD donor offers in patients who are offered low risk DD and are likely to incur significant delays in future access to transplantation. While population-level herd immunity may decrease infection risk in transplant patients, more data are required on the actual efficacy of vaccines against SARS-CoV-2 and VOC in transplant candidates and recipients, as well as on how this efficacy may be modified by a third vaccine dose, maintenance immunosuppression, and timing of induction and rejection therapies.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

All authors consented to publication.

Availability of Data and Materials

Analyses were conducted using publicly published data. For other materials, please contact corresponding author.

Author Contributions

Study conception and design: I.Y., S.P., A.D., R.S.P.; acquisition of data: I.Y., M.G., R.S.P.; analysis and interpretation of data: I.Y., M.G., A.D., R.S.P.; drafting of manuscript: I.Y., M.G., R.S.P.; critical revision: I.Y., M.G., M.P.C., S.P., D.K., A.D., R.S.P.

Declaration of Conflicting Interests

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from GEn1E Lifesciences (as a member of the scientific advisory board), personal fees from nplex biosciences (as a member of the scientific advisory board), outside the submitted work. He is the co-founder of Kanvas Biosciences and owns equity in the company. In addition, Dr. Cheng has a patent Methods for detecting tissue damage, graft versus host disease, and infections using cell-free DNA profiling pending, and a patent Methods for assessing the severity and progression of SARS-CoV-2 infections using cell-free DNA pending. Dr. Kumar reports a competing interest by her work as a consultant to Trillium Gift of Life Network. Other authors report no relevant conflicts of interest.

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Supplemental Material

Supplemental material for this article is available online.

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