Supplementary Digital Content

Table of Contents

Methods

Patient population and study design

We conducted a retrospective cohort study of kidney transplant recipients followed by the Renal Transplant Program of St. Michael's Hospital (Unity Health Toronto), Toronto, Ontario. This initiative was formally reviewed by institutional authorities at Unity Health Toronto and deemed to require neither Research Ethics Board approval nor written informed consent from participants.

We surveyed adult patients (aged ≥ 18 years) who had received a kidney transplant and had a functioning allograft. All such patients were considered eligible for inclusion. Our survey encompassed all prevalent patients as of June 7, 2021, and incident patients who received transplants between June 7, 2021 and July 19, 2021.

Patients were contacted by telephone or email, and surveyed (Appendix S1) to determine the details of their Covid-19 vaccination and infection status, and outcomes of Covid-19 infection between the period of March 11, 2020 to July 19, 2021. The date of March 11, 2020 was chosen as this was the date that the World Health Organization declared worldwide Covid-19 infections as a global pandemic. The email and/or phone surveys were conducted between June 7, 2021 and July 19, 2021.

Data sources

Patient demographics, clinical characteristics and covariates, and any missing, conflicting or incomplete data related to Covid-19 vaccination or infection status were collected from the transplant patient clinical database and electronic health records.

Follow-up for each patient started from the patient's transplant date or Mar 11, 2020, whichever was later.

Transplant duration was calculated as the time from the date of transplant, to the earlier of 1) Date of Covid-19 infection, or 2) July 19th 2021.

A record of the weekly community rates of infection for each of Ontario's 34 public health units is publicly available from (https://www.publichealthontario.ca/en/data-andanalysis/infectious-disease/covid-19-data-surveillance/covid-19-data-tool?tab=trends). These data were used to compile quartiles of community infection risk.

Patients were assigned to their respective community (public-health unit) by the postalcode of their place of residence, using the online tool available at (https://www.phdapps.health.gov.on.ca/phulocator/).

The co-morbidities likely to influence Covid-19 infection and severity were obtained from the list of conditions identified by the Centers for Disease Control and Prevention (CDC) obtained from (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). This list includes 17 broad categories of diseases. All patients in our Renal Transplant Clinic automatically fulfilled criteria for three categories including Chronic Kidney Disease, Immunocompromised State, and Solid Organ or Blood Stem Cell Transplant. We calculated a score ('CDC-score') for the total number of coexisting conditions identified by the CDC as risk factors for severe Covid-19.

Outcomes

The primary outcome was Covid-19 infection in our study population. Severe Covid-19 infection (as defined by COVID-19 infection complicated by hospitalization and death) was analysed as a secondary outcome.

Statistical Analysis

Population demographics and clinical covariates were summarized using descriptive statistics.

A time-varying Cox Proportional Hazards (Cox-PH) model examined the relationship between vaccine status and the primary outcome of contracting Covid-19. Vaccine status was categorized in 3 levels: no dose (zero doses or <14 days following first dose), one dose (>14 days after their first dose, and/or <14 days after their second dose), and two doses (>14 days after their second dose), and was treated as a time-dependent variable. The model was parametrized to interpret the additional effect of a second dose as compared to a single dose. A contrast was used to estimate the effect of two doses as compared to zero doses of vaccine. Transplant vintage, coded as less than three months, three to twelve months and greater than 12 months; as well as the weekly incidence of Covid-19 were treated as time-dependent variables. The model also adjusted for age, sex, most recent eGFR value and CDC score. Schoenfeld residuals were used to test the proportional hazards assumption in the time invariant variables, and the proportional hazards assumption was met. A similar analysis was conducted examining the association of vaccine status and severe Covid-19 infection, defined as infection with hospitalization or death. A sensitivity analysis was performed treating vaccine status as a binary variable comparing at least one dose versus no doses.

Complete case analysis was used. Three participants died before contracting Covid-19. They were censored at their death time and included in the Cox Proportional hazards model, as the model is valid in the context of competing risk.[1] Survival curves were created for Covid-19 community infection burden and transplant vintage, and were computed by exponentiating the hazard function.

Analyses were done in the R statistical environment (Version 4.0.2).[2]

Supplementary Table S1. Demographic characteristics and clinical features of the study population

Characteristic	Total study population N=1793	Covid-19 Infected N=114	Non-infected N=1679
Male sex, n (%)	1141 (63.5%)	71 (59.7%)	1070 (63.7%)
Group/residential living	9 (0.5%)	5 (4.4%)	4 (0.2%)
Transplant Type			
Living donor, n (%)	764 (42.7%)	34 (29.8%)	730 (43.5%)
Deceased donor, n (%)	1029 (57.3%)	80 (70.2%)	949 (56.5%)
Latest eGFR (ml/min/1.73m^2)	54.1 (39.7, 70.1)	51.7 (36.8,69.1)	54.4 (40.0, 70.4)
Number of CDC-identified medical conditions, median (IQR)	5 (5, 6)	5 (5, 6)	5 (5, 6)
Age (years), median (IQR)	60.4 (51.0, 69.2)	60.0 (47.7, 69.3)[§]	60.4 (51.0, 69.2)
Transplant duration (years), median (IQR)	8.1 (3.9, 13.6)	7.3 (2.5, 12.7)[§]	8.1 (3.9, 13.7)
Covid-19 Vaccination Status			
1st Dose Vaccinated	1543 (85.8%)	26 (22.8%)[§]	1459 (86.9%)
2nd Dose Vaccinated	1404 (78.1%)	5 (4.4%)[§]	1336 (79.6%)

§- These values are at the time of Covid-19 infection. The remaining values are calculated at study close.

Abbreviations: CDC, Centers for Disease Control; Covid-19, SARS-CoV-2; eGFR, Estimated Glomerular Filtration Rate; IQR, Inter-quartile range.

Supplementary Table S2. Outcomes: Hospitalizations, Intensive Care Unit (ICU) Admissions, Intubation Status, and Deaths by Vaccination Status in 114 Covid-19-infected Patients

Vaccination Status	Infected	Hospitalized	ICU	Intubation	Death
No doses	88	50	23	14	16

<= 14 days post 1st dose	12	8	2	2	2
>14 days post 1st dose, no 2nd dose	9	8	1	1	0
<= 14 days post-2nd dose	2	2	1	1	1
15-21 days post 2nd dose	1	1	1	1	1
>21 days post-2nd dose	2	1	0	0	0
Total	114	70	28	19	20

Abbreviations: ICU, Intensive Care Unit

Supplementary Table S3: Vaccine type received in 2-dose vaccinated cohort

Patients Vaccinated with 2 Doses: n (%)			1402 (100)
Single vaccine agent used for both doses: n (%)			1349 (96.2)
	Both Pfizer-BioNTech	1048	
	Both Moderna	253	
	Both AstraZeneca	48	
Mixed-dose vaccine: n (%)			53 (3.8)
	First dose: Pfizer-BioNTech **Second dose:** Moderna	29	
	First dose: Pfizer-BioNTech **Second dose:** AstraZeneca	1	
	First dose: Moderna **Second dose:** Pfizer-BioNTech	5	
	First dose: AstraZeneca **Second dose:** Pfizer-BioNTech	7	
	First dose: AstraZeneca **Second dose:** Moderna	7	
	First dose: Other **Second dose:** AstraZeneca	4	

Pfizer-BioNTech Covid-19 mRNA vaccine: Tozinameran or BNT162b2
Moderna Covid-19 vaccine: mRNA-1273
AstraZeneca Covid-19 vaccine: ChAdOx1-S

Appendices

Supplementary Appendix S1: Email Survey sent to all kidney transplant recipients

Subject: UPDATE **PLEASE RESPOND ASAP** St. Michael's Kidney Transplant Clinic: Patient Survey - COVID-19

If you have any concerns or require assistance with completing the survey below, please only direct your calls to the following number: 416-XXX-XXXX Thank you, St. Michael's Hospital Kidney Transplant Program

PATIENT SURVEY – COVID-19

Dear Patient,

Recent research has shown that COVID-19 infection can be more severe in kidney transplant patients. The St. Michael's Hospital Kidney Transplant Clinic is therefore advising all of our patients to get vaccinated unless you have a known allergy to a component of the available COVID-19 vaccines.

There is some evidence that suggests that the COVID-19 vaccines may not be as effective in transplant patients as compared to the general population. To help us understand how effective the vaccines are at protecting against COVID-19, our clinic is attempting to track COVID-19 vaccinations and infections in our patients.

To help with this effort, we have several questions below. This information will be entered into your clinical file, and will be accessible only to clinic staff. Please feel free to respond via email (preferred) with your answers. By responding via email, you are aware and understand the limits of email confidentiality and security.

Note - Please DO NOT call the Transplant Clinic with the COVID update information requested below. If we do not receive an email response by next week, the clinic will be contacting you by phone to complete the survey.

Have you received a COVID-19 vaccine?: Yes / No: _____

If YES, please provide responses to the following:

Manufacturer (Moderna / Pfizer / AstraZeneca / Janssen): _____

Date First Dose received/scheduled: _____

Date Second Dose received/scheduled: _____

Side effect(s)? _____

If NO, please provide responses to the following:
is it by choice or are there barriers? _____

If there are barriers to getting the vaccine, please give us a call and we will help (416XXX-XXXX).

Do you have any concerns about receiving the vaccine and if Yes, what are your concerns:
_____

Have you had a COVID-19 infection?: Yes / No: _____

If YES:
Date of positive test: _____
Were you hospitalized? _____
Did you need to be put on a ventilator? _____
Did you require transfer to an intensive care unit (ICU)? _____

Finally, our program does a lot of research.

Would it be okay for someone from our research team to contact you some day if there is a study that might be of interest to you? If you say yes, you will not be contacted very often.
Yes / No: _____

Thank you for filling out this information. We are always here to support you.

References

1. Austin, P.C., Lee, D.S. & Fine, J.P. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* **133**, 601-609 (2016).
2. Team, R.C. R: A language and environment for statistical computing. (R Foundation for Statistical Computing, Vienna, Austria. 2020).