

Safely navigating kidney transplantation during the COVID-19 pandemic: the Singapore General Hospital's experience

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Background: The coronavirus disease 2019 (COVID-19) pandemic curtailed transplant activities worldwide, driven by concerns about increased COVID-19-related mortality among kidney transplant recipients (KTRs), infections originating from donors, and decreased availability of surgical and intensive care resources as healthcare resources are reallocated for pandemic response. We examined the outcomes of KTRs at our center before and during the COVID-19 pandemic.

Methods: We conducted a retrospective single-center cohort study examining the characteristics and outcomes of patients undergoing kidney transplantation during two periods: January 1, 2017 to December 31, 2019 (pre-COVID-19 era) and January 1, 2020 to June 30, 2022 (COVID-19 era). We reviewed perioperative and COVID-19 infection-related outcomes in both groups.

Results: A total of 114 transplants were performed during the pre-COVID-19 era, while 74 transplants were conducted during the COVID-19 era. No differences in baseline demographics were observed. Additionally, there were no significant differences in perioperative outcomes, except for a longer cold ischemia time during the COVID-19 era. However, this did not result in an increased incidence of delayed graft function. Among the KTRs infected with COVID-19 during the pandemic era, no severe complications such as pneumonia, acute kidney injury, or death were reported.

Conclusions: With the global transition to an endemic phase of COVID-19, it is imperative to revitalize organ transplant activities. Effective containment workflow, good vaccination uptake, and prompt COVID-19 treatment are essential to ensure that transplants can proceed safely.

Keywords: COVID-19; Organ transplantation; Safety

INTRODUCTION

Since the first case of coronavirus disease 2019

(COVID-19) was reported in Singapore in January 2020, there have been 2.1 million documented cases of COVID-19 infections in our nation of 6 million people over

HIGHLIGHTS

- Perioperative kidney transplant outcomes during coronavirus disease 2019 (COVID-19) were comparable to the prepandemic era.
- With appropriate measures, kidney transplantation can safely continue despite the pandemic.
- Vaccination, recipient-donor screening, and prompt treatment enable optimal outcomes.

the past 3 years [1]. During the initial wave of the pandemic, the Ministry of Health issued an advisory to halt nonurgent kidney transplants (KTs). Both deceased donor KT (DDKT) and living donor KT (LDKT) were suspended due to the uncertainties surrounding the novel virus and the need to reallocate healthcare resources for pandemic response (Fig. 1).

Early data indicated that KT recipients (KTRs) experienced a substantial risk of adverse events from COVID-19 infection, including acute kidney injury and mortality rates as high as 23% [2-4]. Both the British and European Renal Associations reported higher mortality in KTRs infected with COVID-19 than in patients on the waiting list [5-7]. Consequently, the initial limitations on transplant activities in Singapore mirrored a global trend to delay transplantation due to concerns about COVID-19-related mortality.

However, this delay in KT conferred the risks of continued dialysis, including the cumulative impact of comorbidities, access-related complications, and posttransplant outcomes [8,9]. A local survey on attitudes toward transplantation revealed that an overwhelming 90.8% of waitlisted patients had a positive response to proceeding with transplantation if organs were made available, even during the pandemic [10]. This sentiment was consistent with that of waitlisted patients in international research [11,12]. Furthermore, the subsequent development of

effective monoclonal antibodies, antivirals, and vaccinations has significantly reduced COVID-19 mortality and morbidity [13,14], prompting a reevaluation of the restrictions on KT. As the COVID-19 pandemic progressed and new data became available, nonurgent KT activities in Singapore were cautiously resumed on a limited basis [15]. Nevertheless, this resumption was closely regulated and monitored by public health officials.

Herein, we describe the outcomes of KT performed at our center from January 1, 2017 to June 30, 2022. KT outcomes during the COVID-19 pandemic were comparable with those in the prepandemic era. This evaluation of KT safety will contribute to guiding the program's sustainability as we transition into the endemic phase of COVID-19.

METHODS

This study was approved by the Ethics Review Committee from the SingHealth Centralised Institutional Review Board (No. 2021/2823). Informed consent was waived due to the retrospective nature of this study.

Study Design

We conducted a retrospective single-center cohort study to examine the characteristics and outcomes of patients undergoing KT during two periods: January 1, 2017 to December 31, 2019 (pre-COVID-19 era) and January 1, 2020 to June 30, 2022 (COVID-19 era). Information was collected on baseline characteristics, such as sex, age, waiting time for transplant, and immunological characteristics. Perioperative outcomes and COVID-19 infection-related outcomes in both groups were also reviewed.

Donor Workflow Changes During COVID-19

Our center's COVID-19 workflow for living and deceased donors is described in Fig. 2. Both DDKT and LDKT donors

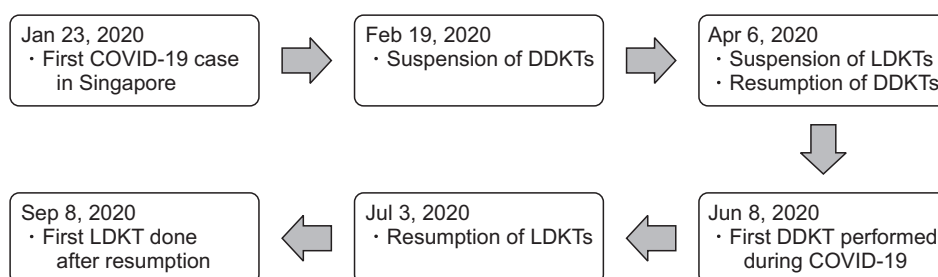


Fig. 1. Transplant timeline during the COVID-19 pandemic. COVID-19, coronavirus disease 2019; DDKT, deceased-donor kidney transplantation; LDKT, living-donor kidney transplantation.

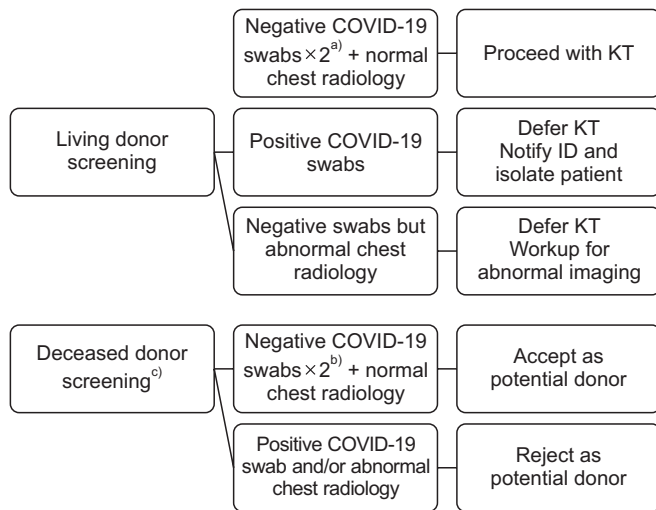


Fig. 2. Workflow for living and deceased donor assessment during the COVID-19 pandemic. COVID-19, coronavirus disease 2019; KT, kidney transplantation. ^{a)}COVID-19 swabs taken on D-7 and D-1 from KT; ^{b)}COVID-19 swabs taken at least 18–24 hours apart; ^{c)}Exclusion criteria: (1) any travel history in last 28 days, (2) COVID-19 suspects/cases at time of evaluation.

require negative COVID-19 polymerase chain reaction (PCR) tests and normal chest imaging prior to transplant.

Recipient Workflow Changes during COVID-19

Our center's COVID-19 workflow for recipients is described in Fig. 3. All potential transplant recipients require negative COVID-19 PCR tests and normal chest imaging prior to transplant. They should also not have any clinical suspicion for COVID-19 (e.g., respiratory symptoms or fever).

Immunological Risk

During the initial response to the COVID-19 pandemic, DDKT and LDKT programs were halted (Fig. 1). Subsequently, the DDKT program was first resumed on April 6, 2020 for potential recipients who were considered to have standard immunological risk (i.e., negative flow panel reactive antibodies and negative B and T cell CDC cross-matching with the deceased donor). Similarly, when the LDKT program resumed on July 3, 2020, ABO or human leucocyte antigen-incompatible transplants were not permitted by the Health Ministry. These pandemic measures were implemented to reduce the potential consumption of healthcare resources (such as plasmapheresis in the event of rejection) and to avoid augmented immunosuppression in recipients. This approach was subsequently liberalized with the resumption of our high

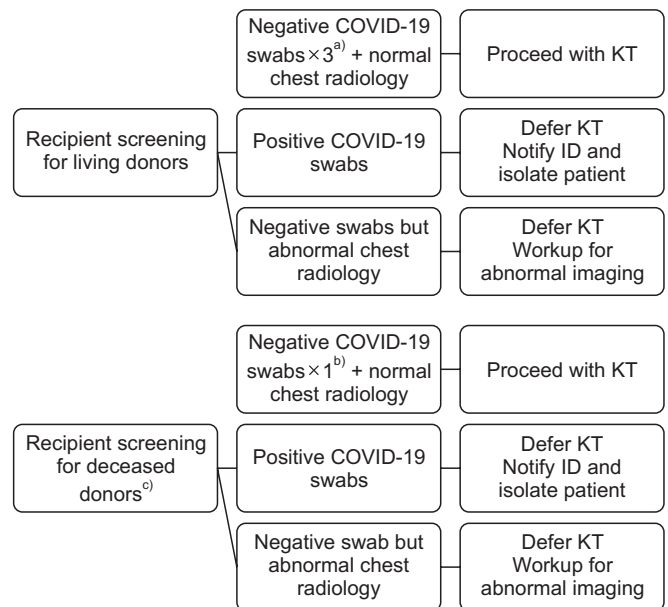


Fig. 3. Workflow for recipient assessment during COVID-19. COVID-19, coronavirus disease 2019; KT, kidney transplantation. ^{a)}COVID swabs taken on D-7, D-2 and D-1 from KT; ^{b)}COVID-19 swab taken before KT; ^{c)}Exclusion criteria: (1) any travel history in last 14 days, (2) COVID-19 suspects/cases at time of evaluation.

immunological risk transplants in March 2021.

COVID-19 Preventive Measures

Pretransplant, donors and recipients were advised to self-isolate as much as possible for 2 weeks prior to their admission for LDKT. During this period, we experienced no cancellations or postponements amongst our LDKT pairs due to COVID-19 infection. Posttransplant, they were also advised to minimize congregating in large groups, practice safe distancing, and wear masks. Posttransplant visits were restricted to two named caregivers throughout the admission.

Transplant physicians and allied healthcare staff adhered to hospital infection-control policies. Mandatory twice-daily temperature checks with electronic logs were implemented from February 8, 2020 to March 11, 2021 before these measures were discontinued for vaccinated healthcare workers. Mandatory twice-weekly COVID-19 PCR testing was also implemented from May 8, 2021 to March 21, 2022. Strict safe distancing and mandatory mask wearing have been observed in the transplant unit since the beginning of the pandemic and continue to be enforced. Any staff member diagnosed with COVID-19 was required to take medical leave and provide a negative

COVID-19 PCR test result before returning to work.

Vaccination Uptake

With the rollout of mass vaccinations, donors and recipients were advised to be fully vaccinated and boosted against COVID-19 pretransplant. The vaccination schedule adhered to national directives, which consisted of an enhanced primary series with three doses and one booster for KTRs [16]. For KTRs who had not yet started or completed their vaccination, this was done 6 months post-transplant. We achieved a vaccination rate of more than 90% amongst our transplant recipients despite vaccine hesitancy [17]. Nationally, 93% of the Singaporean population has completed the full vaccination regimen and 80% have received a booster [1].

COVID-19 Treatment

KTRs who contracted COVID-19 infection were triaged virtually via video consultation with transplant physicians. Depending on their clinical status, they were either enrolled in a remotely monitored home recovery program or admitted for inpatient care at our transplant center [18]. However, patients who were critically ill were taken to their nearest hospitals, which may not have had transplant services. In those cases, nephrologists usually consulted the primary transplant physician for guidance if needed.

For patients on triple immunosuppression, the anti-metabolite (azathioprine, mycophenolate mofetil [MMF]) was reduced or suspended for KTRs who had moderate severity of COVID-19 infection, such as radiological evidence of pneumonia, or had lymphopenia. Additional antivirals (remdesivir) or monoclonal antibodies (tixagevimab/cilgavimab, casirivimab/imdevimab, sotrovimab) were administered for KTRs based on the severity of their COVID-19 infection, symptom duration, vaccination status, and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) receptor binding domain levels.

Statistical Analyses

Continuous variables are presented as means and standard deviations if normally distributed, while non-normally distributed data are presented as median and interquartile range. Categorical variables are reported as frequencies and percentages. The chi-square test and the independent-sample t-test were used to compare characteristics between KTRs in the pre-COVID-19 era and those in the COVID-19 era. A two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were performed using

IBM SPSS ver. 25.0 (IBM Corp.).

RESULTS

Baseline Demographics

In total, 114 transplants were done during the pre-COVID-19 era, while 74 transplants were performed during the COVID-19 era. Patients' baseline demographics are shown in Table 1. No statistically significant differences were observed, except that deceased donor recipients during the COVID-19 era had a shorter waiting time (3.2 years) than before COVID-19 (5.3 years).

Transplant Characteristics

During the COVID-19 era, LDKTs were more prevalent than during the pre-COVID-19 era (66% vs. 45%, $P < 0.05$). The majority of transplants performed in both periods were in patients at standard immunological risk (82% in the COVID-19 era vs. 84% in the pre-COVID-19 era, $P = 0.38$), and KTRs primarily received basiliximab for induction therapy (69% in the COVID-19 era vs. 90% in the pre-COVID-19 era, $P < 0.05$). However, there was a higher overall percentage of KTRs receiving thymoglobulin (antithymocyte globulin [ATG]) for induction in the COVID-19 era than in the pre-COVID-19 era (31% vs. 10%, $P < 0.05$). This increase was due to a change in our induction protocol for intermediate-risk transplants (positive donor-specific antibodies with negative cross-matching), which shifted from basiliximab to ATG. In the pre-COVID-19 era, 97% of our KTRs were placed on a tacrolimus-based regimen, while only 77% were on this regimen during the COVID-19 era. This change was also due to a shift in our center's immunosuppression protocol, which transitioned to a cyclosporine-based regimen for KTRs at standard immunological risk. This decision was based on in-center data that showed increased infective complications (e.g., BK virus) among KTRs on tacrolimus-based regimens.

Perioperative Outcomes

There were no significant differences between the two groups in terms of surgical complications, postoperative infectious complications, length of hospital stay, or 6-month graft and patient survival (Table 2). We observed a longer cold ischemia time in the COVID-19 era than in the pre-COVID-19 era (6.7 vs. 4.0 hours, $P < 0.05$). However, this increase in cold ischemia time did not result in a

higher incidence of delayed graft function (34% vs. 23%, $P=0.10$) or biopsy-proven rejection (20% vs. 5%, $P=0.01$).

Table 1. Demographics and transplant characteristics

Variable	Pre-COVID-19 (n=114)	COVID-19 (n=74)	P-value
Age (yr)	47.7±10.5	47.5±10.9	0.9
Male sex	58 (51)	45 (61)	<0.05
Ethnicity			0.29
Chinese	79 (69)	55 (74)	
Malay	19 (17)	9 (12)	
Indian	6 (5)	6 (8)	
Other	10 (9)	4 (5)	
Cause of renal failure			0.38
Glomerulonephritis	74 (65)	46 (62)	
Diabetic kidney disease	19 (17)	11 (15)	
Polycystic kidney disease	11 (10)	4 (5)	
Other	10 (9)	13 (18)	
Diabetes mellitus	18 (16)	18 (24)	0.15
Coronary artery disease	22 (19)	22 (30)	0.09
Renal replacement therapy			0.12
None (preemptive)	5 (4)	9 (12)	
Hemodialysis	86 (75)	49 (66)	
Peritoneal dialysis	23 (20)	16 (22)	
Waiting time for transplant (yr)	5.3±4.9	3.2±3.8	<0.05
Type of donor			<0.05
Living donor	51 (45)	49 (66)	
Standard-criteria deceased donor	42 (37)	17 (23)	
Expanded-criteria deceased donor	17 (15)	3 (4)	
Donation after cardiac death	4 (4)	5 (7)	
Preemptive transplant	14 (12)	12 (16)	0.4
High immunological risk transplant			0.38
ABO-incompatible	7 (6)	8 (11)	
Positive cross-match	12 (10)	5 (7)	
Preformed DSA	32 (28)	25 (34)	0.4
Antibody induction			<0.05
Basiliximab	103 (90)	51 (69)	
Thymoglobulin	11 (10)	23 (31)	
Immunosuppression regimen			<0.05
CsA + PRED + MPA	3 (3)	16 (22)	
TAC + PRED + MPA	111 (97)	57 (77)	
CsA + PRED + MPA + EVL	0	1 (1)	

Values are presented as mean±standard deviation or number (%). COVID-19, coronavirus disease 2019; DSA, donor-specific antibodies; CsA, cyclosporin A; PRED, prednisone; MPA, mycophenolic acid; TAC, tacrolimus; EVL, everolimus.

COVID-19-Related Outcomes

The vaccination rates in both our pre-COVID-19 and COVID-19 era groups were high with 89% and 95% of the recipients, respectively, having received at least three doses (Table 3) and there were no cases of donor-transmitted COVID-19 infection.

Among the KTRs who contracted COVID-19, no significant differences in outcomes were observed compared to patients in the pre-COVID-19 era (Table 4). KTRs in the COVID-19 era who did contract the virus did not experience severe complications, such as pneumonia, acute kidney injury, intensive care unit admissions, or death,

Table 2. Perioperative outcomes

Variable	Pre-COVID-19 (n=114)	COVID-19 (n=74)	P-value
Cold ischemia time (hr)	4.0±4.7	6.7±5.8	<0.05
Delayed graft function	39 (34)	17 (23)	0.10
Postoperative admission to intensive care unit	2 (2)	2 (3)	0.66
Return to operating theater	2 (2)	2 (3)	0.66
Biopsy proven rejection	23 (20)	4 (5)	0.01
Surgical complication	9 (8)	9 (12)	0.33
Postoperative infective complication	24 (21)	13 (18)	0.56
Postoperative cardiovascular complication	5 (4)	5 (7)	0.48
Discharge estimated glomerular filtration rate (mL/min)	57±28	58±25	0.76
Length of hospital stay (day)	17±10	18±8	0.36
Readmission within 30 days of surgery	38 (33)	29 (39)	0.53
6-Month graft survival	113 (99)	74 (100)	0.42
6-Month patient survival	113 (99)	74 (100)	0.42

Values are presented as mean±standard deviation or number (%). COVID-19, coronavirus disease 2019.

Table 3. COVID-19-related demographics

Demographics	Pre-COVID-19 (n=114)	COVID-19 (n=74)	P-value
At least three COVID-19 vaccine doses	101 (89)	70 (95)	0.19
Pretransplant COVID-19	NA	4 (5)	NA
Posttransplant COVID-19	48 (42)	26 (35)	0.34
Donor-transmitted COVID-19	NA	0	NA

Values are presented as number (%). COVID-19, coronavirus disease 2019; NA, not applicable.

Table 4. COVID-19 infection outcomes

COVID-19 infected patients	Pre-COVID-19 (n=48)	COVID-19 (n=26)	P-value
SARS-CoV-2 IgG >1,000 AU/mL	15 (31)	8 (31)	0.97
ISARIC 4-C score	4.8±2.6	4.2±2.3	0.36
Pneumonia	8 (17)	0	0.08
Oxygen therapy	3 (6)	1 (4)	0.83
Admission to intensive care unit	1 (2)	0	0.48
Acute kidney injury	3 (6)	0	0.39
Death	1 (2)	0	0.69

Values are presented as number (%) or mean±standard deviation. COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; IgG, immunoglobulin G.

even though their transplants were more recent at the time of COVID-19 infection.

DISCUSSION

Data on the outcomes of KT performed in Asia during the COVID-19 era are limited to single-center case studies and one multi-center study from India [19,20]. Therefore, it was crucial for us to examine our own center's data to determine whether the outcomes of KTs conducted during this period were consistent with those reported in the literature. During the COVID-19 era, KT outcomes were found to be comparable to those performed before the pandemic. Although fewer transplants were conducted, our data indicate that the perioperative outcomes of KTs in the COVID-19 era were not inferior to those in the pre-COVID era.

Despite the longer cold ischemia time resulting from the extended assessment period for DDKT recipients due to the need for COVID-19 PCR processing, there was no increase in rates of delayed graft function. Several factors may contribute to this observation. First, there was a decreased incidence of biopsy-proven rejection, which was not unexpected since only standard immunological risk transplants were allowed during the initial pandemic response. Second, more LDKTs than DDKTs were performed during the COVID-19 period, and LDKTs generally have lower rates of delayed graft function. Finally, fewer extended-criteria donor kidneys were transplanted during this time.

The reduction in the proportion of DDKTs can be attributed to strict infection control measures, which likely

excluded a significant number of potential deceased donors considered at risk for transmission. Additionally, our DDKT recipients during the COVID-19 era experienced shorter waiting times for transplantation, likely due to the exclusion of sensitized patients on the waitlist, who were deemed to be at a higher immunological risk.

During the COVID-19 era, over 30% of our KTRs developed COVID-19 infections; however, none experienced severe complications or mortality. This outcome was likely due to high vaccination rates and prompt COVID-19 treatment, with the majority of our patients receiving either antiviral medications or monoclonal antibodies. Furthermore, we observed the emergence of SARS-CoV-2 variants that were more infectious but had lower mortality rates. In Singapore, the Delta B16172 strain became dominant in April 2021, followed by the Omicron BA.1 strain in January 2022. This led to a resurgence of cases. In July 2022, the Omicron BA.4/5 variant drove a surge in COVID-19 cases, and from September 2022 onwards, the Omicron XBB variant became dominant. Similar observations were reported in the United States and Europe, where they also experienced a higher number of COVID-19 cases amongst transplant recipients during the Omicron surge. However, there was no increase in mortality or hospitalization rates [13,14].

Our study findings provide reassurance that, with appropriate precautions, safe renal transplantation can be carried out for patients during the ongoing pandemic. It is also essential to encourage recipients to receive COVID-19 vaccinations and stay current with booster shots against emerging variants, as vaccines have been demonstrated to lessen complications and decrease mortality risk in the event of a COVID-19 infection [17,21,22].

Our study had some limitations. First, this was a single-center study; however, our research was conducted at the largest quaternary-level KT center in Singapore, which provides care to the majority of the nation's KTRs (approximately 867 recipients). Second, there may be limitations to the generalizability of our findings. Singapore has a high vaccination rate among the general population, with vaccination universally encouraged. COVID-19-related care in government institutions, including monoclonal and antiviral therapy as well as hospitalization, is heavily subsidized by the government, resulting in limited out-of-pocket costs for patients. Furthermore, the robust communications and healthcare infrastructure enable remotely monitored home recovery programs. However, these resources may not be available to all healthcare institutions.

As COVID-19 transitions from a pandemic to an endemic disease, it is crucial for countries to recommence transplant activities. We are confident that through a meticulous workflow involving careful screening, high vaccination uptake, and swift treatment for COVID-19, we can safely continue performing transplants for our patients.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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