Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Is Early COVID-19 in Kidney Transplant Recipients Concerning Enough to Halt Transplantation? A Multicenter Comparative Analysis from India

Hari Shankar Meshram[a], Vivek B. Kute[a*], Himanshu V. Patel[a], Umapati Hegde[b], Pratik Das[c], Keshab Sil[c], Manisha Sahay[d], Sree Bhushan Raju[e], Arpita Ray Chaudhury[f], Vishwanath Siddini[g], Vivek Pathak[h], M.M. Bahadur[i], Urmila Anand[j], Amresh Krishna[k], Abi Abraham[l], Ansy H. Patel[m], Vineet Mishra[n], and Sanshriti Chauhan[a]

[a]Department of Nephrology, Institute of Kidney Diseases and Research Centre, Dr. H. L. Trivedi Institute of Transplantation Sciences, Ahmedabad, Gujarat, India; [b]Department of Nephrology, Muljibhai Patel Urological Hospital, Nadiad, Gujarat, India; [c]Department of Nephrology, Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata, West Bengal; [d]Department of Nephrology, Osmania General Hospital, Hyderabad, India; [e]Department of Nephrology, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, India; [f]Department of Nephrology, Institute of Post-Graduate Medical Education & Research, Kolkata, India; [g]Department of Nephrology, Manipal Hospital, Bangalore, India; [h]Department of Nephrology, Kovai Medical Centre and Hospital, Coimbatore, Tamil Nadu, India; [i]Department of Nephrology, Jaslok Hospitals, Mumbai, India; [j]Departmentt of Nephrology, Centre Yashoda Hospitals, Secunderabad, India; [k]Department of Nephrology and Renal Transplantation, Indira Gandhi Institute of Medical Science, Patna, India; [l]Lakeshore Hospital, Kochi, Kerala, India; [m]B. J. Medical Hospital, Civil Hospital, Ahmedabad, Gujarat, India; and [n]Department of Gynecology, Institute of Kidney Diseases and Research Centre, Dr. H. L. Trivedi Institute of Transplantation Sciences, Ahmedabad, Gujarat, India

ABSTRACT

Background. Limited data exist on the incidence and outcome of early coronavirus disease 2019 (COVID-19) in kidney transplantation recipients (KTR).

Methods. A retrospective multicenter research study was conducted across 12 centers in India. We explored the symptomatology, demographic, laboratory findings, and outcome of COVID-19 within 30 days of transplantation. The outcome was compared with the overall KTR and waitlisted patients acquiring COVID-19.

Results. The incidence of early COVID-19 was 2.6% (n = 22) for the cumulative 838 renal transplants performed since nationwide lockdown in March 2020 until May 2021. Overall, 1049 KTR were diagnosed with COVID-19 and 2% of those had early COVID-19. The median age of the early COVID-19 cohort was 43 (31-46) years. COVID-19 severity ranged from asymptomatic (18.2%), mild (59.1%), moderate (9.1%), and severe (13.6%). Among clinical symptoms, dyspnea and anosmia were frequent, and in laboratory parameters, neutrophil lymphocyte ratio, high-sensitivity C-reactive protein, and D-dimer were higher in patients requiring oxygen. The mortality in early COVID-19 was not higher than overall KTR (4.5% vs 8.5%; $P = 1$). COVID-19 severity (23.9% vs 15.7%; $P = .0001$) and mortality (15.5% vs 8.5%; $P = .001$) among waitlisted patients (n = 1703) were higher compared with overall KTR.

Conclusions. We report higher burden of COVID-19 in waitlisted patients compared with KTR and a favorable outcome in early COVID-19 in KTR. Our report will help the transplant physicians in dealing with the ongoing dilemma of halting or resuming transplantation in the COVID-19 era.

CORO navirus disease 2019 (COVID-19) ceased transplantation activity in almost all parts of the world for a while, and resumption of transplantation became an altogether strenuous task, especially in densely populated nations like India with a high COVID-19 tally and unprecedented surges [1]. Many transplant centers resumed stepwise transplant activities

*Address correspondence to Vivek B. Kute, MD, DM, FCPS, FASN, FISOT, FISN, FRCP, Department of Nephrology and Clinical Transplantation, Institute of Kidney Diseases and Research Centre, Dr. H. L. Trivedi Institute of Transplantation Sciences (IKDRC-ITS), Ahmedabad, India. Tel.: +91 9099927543. E-mail: drvivekkute@rediffmail.com

0041-1345/20
https://doi.org/10.1016/j.transproceed.2021.08.034

following national and international advisory guidelines for transplantation during the COVID-19 era [2]. Because the safety of donors, recipients, and health care workers are jeopardized, the logistics and ethics involved for transplantation in the COVID-19 era are intricate. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in solid organ transplantation has been extensively reviewed in both developing and emerging nations with wide diversity in clinical profile and outcomes [3-11]. However, there is a scarcity of data from developing nations about COVID-19 as an early infection when transplantation was restarted after a halt by the pandemic. Early COVID-19 in a transplant patient can possibly have a lethal outcome. The three major research questions to contemplate in the context of resuming transplantation are:

1. Do kidney transplant recipients (KTR) acquiring early COVID-19 have a worse outcome compared with those who acquire COVID-19 later?
2. Is the outcome of early COVID-19 poor enough to the extent that it would hinder the transplant activity?
3. Is the severity of COVID-19 worse for transplant patients compared with waitlisted patients?

The aim of this report was to study the clinical profile and outcome of early COVID-19 in KTR and compare the outcomes of COVID-19 in KTR with waitlisted patients.

MATERIALS AND METHODS

Ethical Statement

The study was designed as a retrospective study and was approved by the institutional ethical committee (ECR/143/Inst/GJ/2013/RR-19). All transplant activities performed in the centers were in accordance with the regulations of the Declaration of Helsinki, Declaration of Istanbul, and Transplantation of Human Organs Act. The research strictly adheres to the Strengthening The Reporting of Observational Studies in Epidemiology checklist for reporting the data.

Settings

Data were explored from the following 12 transplant centers in India: Institute of Kidney Diseases and Research Centre, Dr. H. L. Trivedi Institute of Transplantation Sciences, Ahmedabad, Gujarat; Rabindranath Tagore International Institute of Cardiac Sciences, Kolkata; Muljibhai Patel Urological Hospital, Nadiad, Gujarat; Osmania General Hospital, Hyderabad; Nizam's Institute of Medical Sciences. Panjagutta, Hyderabad; Institute of Post-Graduate Medical Education & Research, Kolkata; Manipal Hospital, Bangalore; Kovai Medical Centre and Hospital, Coimbatore, Tamil Nadu; Jaslok Hospitals, Mumbai; Centre Yashoda Hospitals, Secunderabad; Indira Gandhi Institute of Medical Science, Patna; and Lakeshore Hospital, Kochi, Kerala.

Study Population

All KTR with confirmed COVID-19 diagnosed through SARS-CoV-2 real-time polymerase test from nasopharyngeal sample were included in the study period of May 2020 to January 2021(n = 10). For two centers (Institute of Kidney Diseases and Research Centre and Rabindranath Tagore International Institute of Cardiac Sciences), the data were adjudicated until May 2021. The waitlisted patients detected with COVID-19 were also included in the study. KTR with early COVID-19 were described for symptoms, laboratory findings, and treatment alternatives. The COVID-19 severity was divided as per the World Health Organization (WHO) grading into asymptomatic, mild, moderate, and severe [12].

Transplantation Protocol Followed in the Centers in the COVID-19 Era

All the donor recipient pairs (DRP) were advised to practice COVID-19 etiquette such as social distancing, face masks, and hand hygiene for 14 days before surgery. All the DRP underwent routine pretransplant evaluation as per the Kidney Disease: Improving Global Outcomes guidelines [13,14]. Additionally, two consecutive negative SARS-CoV-2 real-time polymerase test results with normal radiology and no symptoms were mandatory for proceeding for transplant in DRP. Dedicated separate health care worker staffs were assigned to minimize the chances of hospital-acquired transmission. All the doctors and health care workers involved underwent routine preliminary clinical and epidemiologic daily checkups for COVID-19. In summary, all transplantation activity carried out in the COVID-19 era was conducted as per the national guidelines [15] for transplantation. The authors also have previously documented the protocol for donor-recipient management in COVID-19-recovered donors [16] and recipients [17] in the context of living-related transplantation. There was no modification in practice of induction or immunosuppressive drug regimen, and the decision was based on the patient's immunologic profile. The duration of admission before transplant for DRP was restricted to 1 to 2 days. Additionally, the discharge from the hospital after surgery was done as early as possible to prevent hospital-acquired infection.

Management of Early COVID-19 in KTR

The ideal regimen for the management of early COVID-19 is unknown. As a mark of caution, antimetabolites were stopped in even asymptomatic and mild cases of early COVID-19, whereas in moderate to severe COVID-19, both calcineurin inhibitors and antimetabolites were reduced. Because of the uncertainty in the course of early COVID-19, most patients patients were hospitalized regardless of their clinical condition and were strictly followed through telemedicine for any unfavorable outcome once discharged. Even in mild cases, some centers have used antiviral drugs like remdesivir. Systemic steroids were used in all of the moderate and severe cases.

Data Collection and Statistical Analysis

A national call was raised to the 21 transplant centers, of which data from 12 centers were collected. The detailed pro forma for the study was created by two authors (V.B.K. and H.S.M.) in a Microsoft Excel (Microsoft Corporation, Redmond, Wash, United States) spreadsheet and distributed to all the centers through email. The final data were assembled in a master Excel spreadsheet and analyzed in SPSS v 21 (IBM Corp., Armonk, NY) software. No specified sample size was planned in the study. Continuous data were expressed as median and interquartile range and categorical data as numbers and percentage. The characteristics of recent transplants were compared between modified WHO ordinal scale ≤ 3 and ≥ 4. The modified WHO ordinal scale [18] used was as follows: 1 = At home with no limitations of activities; 2 = At home with slight limitations; 3 = Hospitalized and on ambient air; 4 = Low-flow oxygen therapy; 5 = High-flow oxygen or non-rebreather mask; 6 = Bilevel positive pressure ventilation; 7 = Mechanical ventilation; and 8 = Death. The comparison between the 2 groups was made through χ^2 test with Yates

correction, Fisher exact test, and *t* test as appropriate. The data comparing the severity of COVID-19 and associated mortality in waitlisted, recent transplants and overall KTR were also analyzed. The limitation of the design was that the finer details comparing the differences in risk factors for mortality in the 3 groups were not investigated from all of the centers. A 2-tailed *P* value of $< .05$ was considered statistically significant.

RESULTS

Since the imposition of a national lockdown in India in late March 2020, 838 renal transplants were performed across 12 centers until May 2021. Deceased donor transplantation contributed to only 9.6% (n = 81) of the total transplants. Further, 47 recovered recipients and 20 recovered donors were transplanted across these centers. Thus, the incidence of early COVID-19 calculated overall was 2.6%. The incidence was higher in deceased transplants (6.1% vs 2.37%; *P* = .06) compared with living-related transplants, although not statistically significant. In total, 1049 KTR were diagnosed with COVID-19 and 2% (n = 22) of those had early COVID-19. A total of 1703 waitlisted patients were reported in the study.

Demographic Characteristics

The median age of the early cohort was 40.5 (31-46) years with oxygen requirement more in the older age group, although statistically insignificant (38 [25-45] vs 46 [31-54.5]; *P* = .19). A high proportion of cases occurred in living-related transplantation (n = 17, 77.3%) compared with deceased donor (n = 5, 22.7%). The induction used varied according to the immunologic profile and included thymoglobulin (n = 17, 77.3%) no induction (n = 3, 13.6%), and interleukin 2 (IL-2) blocker (n = 2, 9.1%). There was no difference in severity of COVID-19 as per the native kidney disease as detailed in Table 1.

Table 1. Demographic of the Cohort Compared as per the WHO Ordinal scale of COVID-19 Severity

Characteristic	Total Cases (n = 22)	WHO Ordinal scale ≤3 (n = 17)	WHO Ordinal Scale ≥4 (n = 5)	*P* Value
Age (y)	40.5 (31-46)	38 (25-45)	46 (31-54.5)	.19
Female sex	5 (22.7)	4 (23.5)	1 (20)	> .99
Blood group distribution				
A	1 (4.5)	1 (5.9)	0 (0)	> .99
B	7 (31.8)	5 (29.5)	2 (40)	> .99
AB	4 (18.1)	4 (23.5)	0 (0)	.53
O	10 (45.6)	7 (41.1)	3 (60)	.62
Transplant type				
Deceased donor	5 (22.7)	4 (23.5)	1 (20)	> .99
Living-related compatible	17 (77.3)	13 (76.5)	4 (80)	> .99
Native kidney disease				> .99
Diabetes	8 (36.5)	6 (35.2)	2 (40)	> .99
Hypertension	5 (22.7)	3 (17.6)	2 (40)	.54
Unknown etiology	3 (13.6)	2 (11.7)	1 (20)	> .99
Chronic glomerulonephritis	3 (13.6)	3 (17.6)	0 (0)	> .99
Obstructive uropathy	2 (9.1)	2 (12.1)	0 (0)	> .99
Others	1 (4.5)	1 (5.8)	0 (0)	> .99
Induction regimen				
Thymoglobulin	17 (77.3)	14 (82.4)	3 (60)	.54
Interleukin-2 blocker	2 (9.1)	1 (5.9)	1 (20)	.41
Grafalon	0 (0)	0 (0)	0 (0)	> .99
No induction	3 (13.6)	0 (0)	1 (20)	.22
Comorbidities, n (%)				
Hypertension	16 (72.7)	12 (70.5)	4 (80)	> .99
Diabetes	6 (27.2)	4 (23.5)	2 (40)	.58
Heart disease	1 (4.5)	1 (5.9)	0 (0)	> .99
Obesity	5 (22.7)	3 (17.6)	2 (20)	.54
None	3 (13.6)	2 (11.7)	1 (20)	> .99
≥2 comorbidities	4 (18.1)	2 (11.7)	2 (40)	.2
Days from transplantation to COVID-19	14 (10-25)	13 (9-22)	14 (11-26)	.61
Other characteristics				
ACEi/ARB use	15 (68.1)	12 (70.5)	3 (60)	> .99
History of pneumococcal vaccine	2 (9.1)	1 (5.9)	1 (20)	.41
History of desensitization therapy	1 (4.5)	1 (5.9)	0 (0)	> .99
History of antirejection therapy given	3 (13.6)	2 (11.7)	1 (20)	> .99
History of COVID-19 in pretransplant period	1 (4.5)	1 (16.7)	0 (0)	> .99
Hospital-acquired COVID-19	4 (18.1)	3 (17.6)	1 (20)	> .99

Data expressed as numbers (percentage) or median (interquartile range) as appropriate.

Fisher exact test or χ^2 test with Yates correction used for calculating *P* value. WHO ordinal scale ≤3 = All patients at home or hospitalized on air. WHO ordinal scale ≥4 = Any form of oxygen requirement.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COVID-19, coronavirus disease 2019; WHO, World Health Organization.

Presence of more than 2 comorbidities was associated with WHO ordinal scale ≥4, although statistical difference was not achieved (13 [9-22] vs 14 [11-26]; P = .1). Hospital-acquired COVID-19 (n = 4, 18.1%) accounted for a smaller number of cases.

Inflammatory Markers and Laboratory Profile

The laboratory parameters that were higher and statistically significant in cases with WHO ordinal scale ≥4 were as follows: Neutrophil lymphocyte ratio: (5 [1.8-6.5] vs 11.2 [16.3-6.1]; P = .005), high-sensitivity C-reactive protein: (15 [7-37.2] vs 56 [12-76]; P = .002), and D-dimer (960 [2760-560] vs 2500 [473-5240]; P = .04). In contrast, there was no difference in baseline, peak, and discharge serum creatinine (1.16 [0.82-1.38] vs 1.4 [1.18-1.89] vs 1.15 [0.93-1.45]) among the ordinal scales. Similarly, interleukin-6 (14 [2-45] vs 28 [53-10]), serum ferritin (378 [859-145] vs 600 [334-1381]), and lactate dehydrogenase (324 [231-351] vs 200 [158-721]) were not higher with WHO ordinal scale ≥4.

Clinical Spectrum and Outcome

The cohort was classified as asymptomatic (n =4, 18.1%), mild (13, 59.1%), moderate (n = 2, 9.1%), and severe cases (n = 3, 13.6%) (Table 2). WHO ordinal scale of COVID-19 for the cohort included scales of 1 (n = 1, 4.5%), 2 (n =1, 4.5%), 3 (n = 15, 68.3%), 4 (n = 2, 9.2%), 5 (n = 1, 4.5%), 6 (n = 1, 4.5%), 7 (n = 1, 4.5%), and 8 (n = 1, 4.5%). The most common symptoms reported were depression (n = 14, 63.6%), sleep disturbances (n =13, 59%), cough (n =13, 59%), fever (n =13, 59%), fatigue (n = 9, 40.9%), and anxiety (n = 9, 40.9%). Radiologic involvement was reported in most of the cases (n = 13, 59%) but was higher with increasing ordinal scale (n = 8, 47% vs n = 5, 100%; P = .05)

Mycophenolate mofetil was stopped (n = 18, 81.8%) or tapered (n = 4, 18.1%) in most of the cases, and there was no difference between the 2 groups. Likewise, calcineurin inhibitors were stopped (n = 1, 4.5%) or tapered (n = 7, 31.8%) in a few cases. The common therapeutics used were remdesivir (n = 13, 59%), steroids (n = 9, 40.9%), and anticoagulation (n = 8, 36.4%). Acute kidney injury (n = 10, 45.4%) was reported in almost half of the cases.

Comparative Analysis

Table 3 shows the comparison of three groups of early COVID-19 (n = 22), overall COVID-19 (n = 1049), and waitlisted patients (n = 1703).

In the analysis, early COVID-19 cases had relatively lesser mortality (n = 1, 4.5% vs n = 87, 8.5%; P = 1) compared with COVID-19 in KTR beyond 1 month. The proportion of mild cases (n = 13, 59.1% vs 398, 38.7%; P = .07) was higher in early COVID-19 and lower in moderate (n = 2, 9.1% vs n = 279, 27.1%; P = .08) cases compared with COVID-19 in KTR beyond 1 month. There was a trend toward lesser severity and mortality in early COVID-19, but the difference was not statistically significant.

On comparison, the COVID-19 severity between overall KTR and waitlisted patients showed higher severity in the waitlisted groups. The proportion of asymptomatic cases (n = 193, 18.4% vs 380, 22.3%; P = .01) was higher in waitlisted patients compared with KTR. Mild (n = 411, 39% vs 517, 30.4%; P = .0001) and moderate (281, 26.8% vs 399, 23.4%; P = .05) cases were higher in KTR. Severe cases (n = 164, 15.7% vs 407, 23.9%; P = .0001) were disproportionately higher in waitlisted patients. The 28-day case fatality (n =88, 8.4% vs n = 262, 15.4%; P = .001) reported in the waitlisted group was quite high compared with the overall KTR.

DISCUSSION

Early COVID-19 in organ transplantation has been reported scarcely with mixed results. Our study sheds light on this critical aspect of kidney transplantation in India where COVID-19 has exploded with global peaks in recent times. This retrospective cohort conducted amid the SARS-CoV-2 pandemic explored nationwide repositories of renal transplantation and waitlisted data. We explore a comprehensive analysis of the clinical profile and outcome of early COVID-19. The first case of COVID-19 in India was reported on January 27, 2020. The nation had complete lockdown in March 2020, with graded unlock periods to combat the spread of infection. During the months of lockdown, transplantation was at a complete halt. It was restored gradually, up until March 2021, when the second wave struck. Currently, in the second wave, all transplantation activities are ceased in many centers for the last 2 months. Overall, 838 renal transplantations (live = 757 and deceased = 81) were performed during the study period. The reported incidence of 2% early COVID-19 in our study was quite low. The exact source of infection is difficult to elucidate, but hospital-acquired infection occurred in only four cases. Moreover, all donors were tested thrice negative for COVID-19 before transplant and none of the donors had a history of recovery from COVID-19 before the nephrectomy, so the chance of donor-derived transmission was minimized.

Ideal Immunosuppression Protocol in the COVID-19 Era

The decision to tailor the immunosuppression protocol routinely during COVID-19 is tricky and controversial. There have been many reports of transplant centers reducing the immunosuppression protocol during the COVID-19 era [19,20]. The authors have previously reported no change in immunosuppression in their study of COVID-19-recovered donors or transplant candidates and found no COVID-19−related or unrelated complications in the follow-up. Recent US data showed a reduction in lymphocyte-depleting agent in the COVID-19 era and an increasing trend in IL-2 blockers [21]. Another study reported a 30% increase in IL-2 blocker use in the COVID-19 era [22]. In our report, there was no change in the induction or immunosuppression regimen routinely in the centers in the 838 transplants performed. In our report, we have precautionarily tailored the

Table 2. Detailed Comparison of the Clinical Symptoms, Laboratory Analysis, and Outcomes of the Cohort

Variable	Total Cases (n = 22)	WHO Ordinal Scale ≤3 (n =17)	WHO Ordinal Scale ≥4 (n = 5)	*P* Value
Cumulative COVID-19 symptoms				
Asymptomatic	4 (18.1)	4 (23.5)	0 (0)	.53
Subjective fever	13 (59)	9 (52.9)	4 (80)	.36
Cough	13 (59)	10 (58.8)	3 (60)	> .99
Expectoration	4 (18.1)	3 (17.6)	1 (20)	> .99
Dyspnea	7 (31.8)	2 (11.7)	5 (100)	.0008*
Diarrhea	1 (4.5)	1 (5.9)	0 (0)	> .99
Myalgia	7 (31.8)	5 (29.4)	2 (40)	> .99
Fatigue	9 (40.9)	6 (35.2)	3 (60)	.6
Headache	2 (9.1)	2 (11.7)	0 (0)	> .99
Anosmia	3 (13.6)	3 (17.6)	0 (0)	> .99
Ageusia	6 (27.2)	3 (17.6)	3 (60)	.1
Sleep disturbances	13 (59)	8 (47)	5 (100)	.053
Anxiety	9 (40.9)	6 (35.2)	3 (60)	.64
Depression	14 (63.6)	10 (58.8)	4 (80)	.61
Alopecia	2 (9.1)	2 (11.7)	0 (0)	> .99
Others	3 (13.6)	3 (17.6)	0 (0)	> .99
Radiologic abnormalities detected	13 (59)	8 (47)	5 (100)	.05*
Laboratory analysis of the cohort				
Hemoglobin, g/dL	9.5 (9-11.5)	9.8 (9-11.9)	9.2 (9.1-9.8)	.45
White blood cell count, per mm^3	6600 (5400-8800)	6600 (6200-8800)	6250 (3700-9470)	.82
Neutrophil lymphocyte ratio	6 (2-9)	5 (1.8-6.5)	11.2 (16.3-6.1)	.005*
Platelet count, $\times 10^3/mm^3$	197 (155-268)	230 (183-281)	90 (84-187)	.09
IL-6, pg/mL	16.1 (5.8-45.7)	14 (2-45)	28 (53-10)	.64
hsCRP, mg/dL	15 (6-49.7)	15 (7-37.2)	56 (12-76)	.002*
D-dimer, ng/mL	535 (1030-2765)	960 (2760-560)	2500 (473-5240)	.04*
Ferritin, ng/mL	400 (145-920)	378 (859-145)	600 (334-1381)	.28
LDH, IU/L	324 (215-376)	324 (231-351)	200 (158-721)	.2
Serum creatinine, mg/dL				
Prior to COVID-19	1.16 (0.82-1.38)	1.18 (0.8-1.55)	1.14 (0.9-1.28)	.93
Peak	1.4 (1.18-1.89)	1.23 (1.04-1.87)	1.8 (1.32-3)	.29
Discharge	1.15 (0.93-1.45)	1.2 (0.87-1.49)	1.1 (0.9-1.5)	.78
Immunosuppression modulation in COVID-19				
MMF tapered	4 (18.1)	3 (17.6)	1 (20)	> .99
MMF stopped	18 (81.8)	14 (82.3)	4 (80)	> .99
CNI tapered	7 (31.8)	4 (23.5)	3 (60)	.27
CNI stopped	1 (4.5)	0 (0)	1 (20)	.22
Therapeutic regimen				
Remdesivir	13 (59)	8 (47)	5 (100)	.053
Steroids	9 (40.9)	4 (23.5)	5 (100)	.004*
Anticoagulation	8 (36.4)	3 (17.6)	5 (100)	.002*
Others	7 (31.8)	5 (29.4)	2 (40)	> .99
Graft outcome				
AKI	10 (45.4)	6 (35.2)	4 (80)	.13
AKI requiring HD	1 (4.5)	0 (0)	1 (20)	.22
WHO ordinal scale of oxygen requirement for COVID-19				
≤3	17 (77.3)	17 (100)	0 (0)	
4	2 (9.2)	–	2 (40)	
5	1 (4.5)	–	1 (20)	
6	1 (4.5)	–	1 (20)	
7	1 (4.5)	–	1 (20)	
28-day mortality in COVID-19	1 (4.5)	–	1 (20)	

Data expressed as numbers (percentage) or median (interquartile range) as appropriate. Fisher exact test or χ^2 test with Yates correction used for calculating *P* value. WHO ordinal scale for COVID-19 severity: 1 =At home with no limitations of activities; 2 = At home with slight limitations; 3 = hospitalized and on ambient air; 4 = low-flow oxygen therapy; 5 = high-flow oxygen or non-rebreather mask; 6 = Bilevel positive pressure ventilation; 7 = mechanical ventilation; 8 = Death.

AKI, acute kidney injury defined by Kidney Disease: Improving Global Outcomes guidelines; CNI, calcineurin inhibitors; COVID-19, coronavirus disease 2019; HD, hemodialysis; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; MMF, mycophenolate; WHO, World Health Organization.

* indicate a *P*-value value which is statistically significant.

Table 3. Gross Comparison of COVID-19 Outcome in Renal Transplant Recipients vs Waitlisted Patients

	Group 1		
WHO COVID-19 Severity	Early COVID-19 (n = 22)	Waitlisted Patients (n = 1703)	*P* Value
Asymptomatic	4 (18.2)	380 (22.3)	.79
Mild	13 (59.1)	517 (30.4)	1186
Moderate	2 (9.1)	399 (23.4)	.13
Severe	3 (13.6)	407 (23.9)	.32
Mortality	1 (4.5)	262 (15.4)	.23

	Group 2		
WHO COVID-19 Severity	Early COVID-19 (n = 22)	COVID-19 Beyond 1 Month (n = 1027)	*P* Value
Asymptomatic	4 (18.2)	189 (18.4)	> .99
Mild	13 (59.1)	398 (38.7)	.07
Moderate	2 (9.1)	279 (27.1)	.08
Severe	3 (13.6)	161(15.8)	> .99
Mortality	1 (4.5)	87 (8.5)	> .99

	Group 3		
WHO COVID-19 Severity	COVID-19 (n = 1049) Overall KTR	Waitlisted Patients (n = 1703)	*P* Value
Asymptomatic	193 (18.4)	380 (22.3)	.01*
Mild	411 (39.1)	517 (30.4)	.0001*
Moderate	281 (26.8)	399 (23.4)	.05
Severe	164 (15.7)	407 (23.9)	.0001*
Mortality	88 (8.4)	262 (15.4)	.001*

Data expressed as numbers and percentage. Statistical analysis for comparison between groups was done by χ^2 test and Fisher exact test. WHO severity was defined as follows: Asymptomatic = No symptoms; Mild = Upper respiratory symptoms or symptoms not requiring hospitalization; Moderate = Signs of pneumonia with oxygen saturation of <94% on ambient air; Severe = Severe pneumonia with oxygen saturation <90% on room air.

COVID-19, coronavirus disease 2019; KTR, kidney transplant recipients; WHO, World Health Organization.

* indicate a *P*-value value which is statistically significant.

immunosuppression even in mild and asymptomatic cases of early COVID-19. However, there is evidence to support that reduction in immunosuppression may not necessarily contribute to a decrease in the mortality or severity [23,24].

Diverse Outcome of Early COVID-19 in Organ Transplant Recipients

Data have been published, mostly from the developed world, but there is huge discrepancy in the management protocol, severity, and mortality. Hence, a definitive conclusion from previous studies is difficult. There are some reports of poor outcomes associated with early COVID-19 in transplants. Kędzierska-Kapuza et al [25] reported one kidney transplant recipient with higher severity in early COVID-19. Abuzeineh et al [26] reported a poor outcome in a deceased donor kidney transplant patient with early COVID-19. Akalin et al showed 2 cases, both of whom succumbed [27]. Banerjee et al [28] showed 2 early COVID-19 cases with severe disease. Lima et al [29] showed negative impact of COVID-19 in 5 heart transplants. Tchana-Sato et al [30] reported 2 fatalities in perioperative COVID-19 heart transplant patients with COVID-19. Keller et al [31] detailed a deceased donor lung transplant patient who acquired early COVID-19 and required mechanical ventilation. Dale et al [32] described two cases of early liver transplant patients who contracted severe COVID-19 and recovered. Liver transplants had poor outcomes, mostly related to comorbidities and not because of immunosuppression [33]. In a contrasting observation, there are also reports of mild illness. Kolonko et al [34] described 3 kidney transplant patients and 1 liver transplant patient with early COVID-19 having a good outcome. Decker et al [35] reported mild COVID-19 in a heart transplant patient with prolonged infectivity. Massoumi et al [36] reported liver transplant recipients with early COVID-19 having a favorable course. Koczulla et al [37] reported 2 lung transplant recipients with mild illness in early COVID-19. Shingare et al [38] showed a favorable course regarding two cases of deceased-donor kidney transplantation in early COVID-19. Pereira et al described 3 kidney transplant patients with 2 mild cases and one severe case of COVID-19 within 1 month of transplant [39].

Waitlisted vs Transplant Patient Comparison

In international surveys of the waitlisted patients, most patients were willing to resume transplant [40,41]. The data comparing the burden of COVID-19 in the 2 groups are conflicting. Recently published preliminary UK data showed KTR experiencing higher mortality compared with waitlisted patients [42]. A national UK registry showed higher mortality in KTR compared with waitlisted patients, with increasing age as the most important predictor for mortality [43]. The Registry of the European Renal Association − European Dialysis and Transplant Association showed 1.28 times higher mortality in KTR compared with matched waitlisted patients.

Contrarily, there are also data suggesting worse outcomes in waitlisted patients compared with KTR. The European Renal Association COVID-19 Database study reportedly found patients within higher mortality in waitlisted compared to transplant patients [44]. A US study reported higher mortality in waitlisted patients [45]. A French registry showed higher mortality in waitlisted patients, concluding safety of resuming transplantation in low viral load areas. In our report, the severity of COVID-19 along with the mortality in waitlisted patients is significantly higher than the transplant group. Moreover, there was no differential mortality observed in the early COVID-19 group.

Importance of Vaccination

Vaccination will play a prime role in combating COVID-19. And immunizing pretransplant patients before transplantation will be the new dictum in the COVID-19 era. Indian authorities have approved 3 vaccines (ChAdOx1 nCoV-19, BBV152. and Sputnik V) as of April 2021. As a staged approach for vaccination, individuals aged 45 years and older were included in April 2021, and people aged 18 years and over were included for inoculation in May 2021. Although vaccination is being effectively implemented in many nations, India is battling its way

out to inoculate such a bulk population. Currently, a vast majority of waitlisted patients and transplant candidates are unvaccinated in India. In our study where 831 transplant candidates underwent transplant, none received vaccination before surgery. The reports of adequate antibody response to COVID-19 vaccine in dialysis patients are encouraging [46]. Conversely, recent reports of low immunogenicity of the COVID-19 vaccine in organ transplants have raised the alarm bell for further research in the field of vaccine and transplantation [47-49].

Strength of the Study

The study describes the COVID-19 presentation and outcome in early transplant patients and is the largest cohort from the developing world reported to date. The large sample-sized data of KTR and waitlisted patients further adds to the study. The study involved a large number of patients, so applicability or universalization of the study is ensured. We found the incidence of early COVID-19 as low and with favorable outcomes. The telemedicine used for managing patients discharged after transplant proved to be an effective tool for preventing the spread of infection. Observations from the study can pioneer transplant centers to further boost their transplant activity while undertaking all preventive measures. More data are needed to better streamline the treatment protocol in the peritransplant period. Inflammatory phenotype was associated with high mortality in large meta-analysis both in general and in transplant patients [50].

Limitations

This retrospective analysis had a few inherent limitations. First, the results cannot be completely applied for other solid organ transplantation. However, the fact that the cohort had a high immunologic risk of receiving superadded immunosuppression negates this limitation. Secondly, COVID-19 has shown wide diversity in mortality and treatment modalities worldwide, so results should be interpolated accordingly. Third, a larger sample size of early COVID-19 cases could have enhanced the comparison performed.

CONCLUSIONS

We suggest the reason for cessation of transplantation should not be the fear of contracting COVID-19 in the early postrenal transplant period. The decision to halt should be primarily based on the resources available and the regional COVID-19 surge. The important message conveyed from our study is that with the available safety measures, it is clear that transplant centers should proceed with transplantation, checking the COVID-19 surge in their localities.

ACKNOWLEDGMENTS

We acknowledge Professor Stephen Tullius, Harvard Medical School, for his valuable opinion and edits in the manuscript. We also express our sincere gratitude to all the resident doctors and health care staff who are tirelessly doing a mammoth job of managing the COVID-19 cases in India, despite facing a resource crisis.

REFERENCES

[1] World Health Organization. WHO Coronavirus (COVID-19) Dashboard. < https://covid19.who.int/table >; 2021. [accessed 21.07.21].

[2] Lembach H, Hann A, McKay SC, Hartog H, Vasanth S, El-Dalil P, et al. Resuming liver transplantation amid the COVID-19 pandemic. Lancet Gastroenterol Hepatol 2020;5:725–6.

[3] Raja MA, Mendoza MA, Villavicencio A, Anjan S, Reynolds JM, Veraprapas K, et al. COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. Transplant Rev (Orlando) 2021;35:100588.

[4] Kute VB, Bhalla AK, Guleria S, Ray DS, Bahadur MM, Shingare A, et al. Clinical profile and outcome of COVID-19 in 250 kidney transplant recipients: a multicenter cohort study from India. Transplantation 2021;105:851–60.

[5] Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant 2021;21:925–37.

[6] Coll E, Fernández-Ruiz M, Sánchez-Álvarez JE, Martínez-Fernández JR, Crespo M, Gayoso J, et al. COVID-19 in transplant recipients: the Spanish experience. Am J Transplant 2021;21:1825–37.

[7] Domínguez-Gil B, Fernández-Ruiz M, Hernández D, Crespo M, Colmenero J, Coll E, et al. Organ donation and transplantation during the COVID-19 pandemic: a summary of the Spanish experience. Transplantation 2021;105:29–36.

[8] Hadi YB, Naqvi SF, Kupec JT, Sofka S, Sarwari A. Outcomes of coronavirus infectious disease -19 (COVID-19) in solid organ transplant recipients: a propensity matched analysis of a large research network. Transplantation 2021;105:1365–71.

[9] Marcondes-Braga FG, Murad CM, Belfort DSP, Dantas RCT, Lira MTSS, Aragão CAS, et al. Characteristics and outcomes of heart transplant recipients with coronavirus-19 disease in a high-volume transplant center [e-pub ahead of print]. Transplantation. doi:10.1097/TP.0000000000003770, accessed August 11, 2021.

[10] Cristelli MP, Viana LA, Dantas MTC, Martins SBS, Fernandes R, Nakamura MR, et al. The full spectrum of COVID-19 development and recovery among kidney transplant recipients. Transplantation 2021;105:1433–4.

[11] Avery RK, Chiang TP, Marr KA, Brennan DC, Sait AS, Garibaldi BT, et al. Inpatient COVID-19 outcomes in solid organ transplant recipients compared to non-solid organ transplant patients: a retrospective cohort. Am J Transplant 2021;21:2498–508.

[12] Ministry of Health and Family Welfare. < https://www.mohfw.gov.in/ >; 2021 [accessed 21.05.21].

[13] Chadban SJ, Ahn C, Axelrod DA, Foster BJ, Kasiske BL, Kher V, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation 2020;104(4S1):S11–103.

[14] Lentine KL, Kasiske BL, Levey AS, Adams PL, Alberú J, Bakr MA, et al. KDIGO clinical practice guideline on the evaluation and care of living kidney donors. Transplantation 2017;101(8 suppl 1):S7.

[15] Kute V, Guleria S, Prakash J, Shroff S, Prasad N, Agarwal SK, et al. NOTTO transplant specific guidelines with reference to COVID-19. Indian J Nephrol 2020;30:215–20.

[16] Kute VB, Godara S, Guleria S, Ray DS, Aziz F, Hegde U, et al. Is it safe to be transplanted from living donors who recovered from COVID-19? Experience of 31 kidney transplants in a multicenter cohort study from India. Transplantation 2021;105:842–50.

[17] Kute VB, Ray DS, Yadav DK, Pathak V, Bhalla AK, Godara S, et al. A multicenter cohort study from India of 75 kidney transplants in recipients recovered after COVID-19. Transplantation 2021;105:1423–32.

[18] World Health Organization. WHO R&D Blueprint. COVID-19 Therapeutic Trial Synopsis. February 18, 2020. < https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf >; 2020 [accessed 23.05.21].

[19] Boyarsky BJ, Po-Yu Chiang T, Werbel WA, Durand CM, Avery RK, Getsin SM, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. Am J Transplant 2020;20:1809–18.

[20] Loupy A, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. Lancet 2020;395:e95–6.

[21] Bae S, McAdams-DeMarco MA, Massie AB, Ahn JB, Werbel WA, Brennan DC, et al. Early changes in kidney transplant immunosuppression regimens during the COVID-19 pandemic. Transplantation 2021;105:170–6.

[22] Von Stein L, Witkowsky O, Samidurai L, Doraiswamy M, Flores K, Pesavento TE, et al. Modification in induction immunosuppression regimens to safely perform kidney transplants amid the COVID-19 pandemic: a single center retrospective study [e-pub ahead of print]. Clin Transplant. doi:10.1111/ctr.14365, accessed August 11, 2021.

[23] Kates OS, Haydel BM, Florman SS, Rana MM, Chaudhry ZS, Ramesh MS, et al. COVID-19 in solid organ transplant: a multi-center cohort study [e-pub ahead of print]. Clin Infect Dis. doi:10.1093/cid/ciaa1097, accessed August 11, 2021.

[24] Hartzell S, Bin S, Benedetti C, Haverly M, Gallon L, Zaza G, et al. Evidence of potent humoral immune activity in COVID-19-infected kidney transplant recipients. Am J Transplant 2020;20:3149–61.

[25] Kędzierska-Kapuza K, Zielińska D, Matejak-Górska M, Durlik M. The course of SARS-CoV-2 in a patient after a recent kidney transplant: a literature review on COVID-19 therapy. Transplant Proc 2021;53:1194–201.

[26] Abuzeineh M, Desai N, Brennan DC, Alasfar S. COVID-19 early after a deceased donor kidney transplant surgery. Transplantation 2020;104:e354–5.

[27] Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and kidney transplantation. N Engl J Med 2020;382:2475–7.

[28] Banerjee D, Popoola J, Shah S, Ster IC, Quan V, Phanish M. COVID-19 infection in kidney transplant recipients. Kidney Int 2020;97:1076–82.

[29] Lima B, Gibson GT, Vullaganti S, Malhame K, Maybaum S, Hussain ST, et al. COVID-19 in recent heart transplant recipients: clinicopathologic features and early outcomes. Transpl Infect Dis 2020;22:e13382.

[30] Tchana-Sato V, Ancion A, Tridetti J, Sakalihasan N, Hayette MP, Detry O, et al. Clinical course and challenging management of early COVID-19 infection after heart transplantation: Case report of two patients. BMC Infect Dis 2021;21:89.

[31] Keller BC, Le A, Sobhanie M, Colburn N, Burcham P, Rosenheck J, et al. Early COVID-19 infection after lung transplantation. Am J Transplant 2020;20:2923–7.

[32] Dale M, Sogawa H, Seyedsaadat SM, Wolf DC, Bodin R, Partiula B, et al. Successful management of COVID-19 infection in 2 early post-liver transplant recipients. Transplant Proc 2021;53:1175–9.

[33] Waisberg DR, Abdala E, Nacif LS, et al. Coronavirus Disease 2019 in the early postoperative period of liver transplantation: is the outcome really so positive? Liver Transpl 2021;27:1357–9.

[34] Kolonko A, Dudzicz S, Wiecek A, Król R. COVID-19 infection in solid organ transplant recipients: a single-center experience with patients immediately after transplantation. Transpl Infect Dis 2021;23:e13381.

[35] Decker A, Welzel M, Laubner K, Grundmann S, Kochs G, Panning M, et al. Prolonged SARS-CoV-2 shedding and mild course of COVID-19 in a patient after recent heart transplantation. Am J Transplant 2020;20:3239–45.

[36] Massoumi H, Rocca J, Frager S, Kinkhabwala M. Changes in liver transplant center practice in response to coronavirus disease 2019: unmasking dramatic center-level variability. Liver Transpl 2020;26:1198–9.

[37] Koczulla RA, Szczepanski B, Koteczki A, Kuhnert S, Hecker M, Askevold I, et al. SARS-CoV-2 infection in two patients following recent lung transplantation. Am J Transplant 2020;20:2928–32.

[38] Shingare A, Bahadur MM, Raina S. COVID-19 in recent kidney transplant recipients. Am J Transplant 2020;20:3206–9.

[39] Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. Am J Transplant 2020;20:1800–8.

[40] Couzi L, Manook M, Caillard S, Épailly E, Barrou B, Anglicheau D, et al. Impact of Covid-19 on kidney transplant and waiting list patients: lessons from the first wave of the pandemic. Nephrol Ther 2021;17:245–51.

[41] Thind AK, Beckwith H, Dattani R, Dhutia A, Gleeson S, Martin P, et al. Resuming deceased donor kidney transplantation in the COVID-19 era: what do patients want? Transplant Direct 2021;7:e678.

[42] Mohamed IH, Chowdary PB, Shetty S, Sammartino C, Sivaprakasam R, Lindsey B, et al. Outcomes of renal transplant recipients with SARS-CoV-2 infection in the eye of the storm: a comparative study with waitlisted patients. Transplantation 2021;105:115–20.

[43] Ravanan R, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ transplant recipients in England: a national cohort study. Am J Transplant 2020;20:3008–18.

[44] Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant 2020;35:1973–83.

[45] Craig-Schapiro R, Salinas T, Lubetzky M, Abel BT, Sultan S, Lee JR, et al. COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. Am J Transplant 2021;21:1576–85.

[46] Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis [e-pub ahead of print]. Clin J Am Soc Nephrol. doi:10.2215/CJN.03500321, accessed August 11, 2021.

[47] Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021;75:435–8.

[48] Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, et al. Reduced humoral response to mRNA SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. Am J Transplant 2021;21:2719–26.

[49] Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, et al. Antibody response to 2-dose SARS-CoV-2 mRNA vaccine series in solid organ transplant recipients. JAMA 2021;325:2204–6.

[50] Ji P, Zhu J, Zhong Z, Li H, Pang J, Li B, et al. Association of elevated inflammatory markers and severe COVID-19: a meta-analysis. Medicine (Baltimore) 2020;99:e23315.