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Clinical characteristics, outcomes, and management of COVID-19 in kidney transplant recipients across Asia: an ASTREGO report

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Background: Asia is the global epicenter of the coronavirus disease 2019 (COVID-19) pandemic; however, COVID-19–related mortality in Asia remains lower than in other parts of the world. It is uncertain whether the mortality of COVID-19-infected kidney transplant recipients (KTXs) from Asia follows the lower mortality trends of the younger Asian population.
Methods: Specific transplant centers from countries in the Asian Society of Transplantation were invited to participate in a study to examine the epidemiology, clinical features, natural history, and outcomes of COVID-19 infections in KTXs. Data were analyzed and compared with those of large cohort studies from other countries.
Results: The study population was 87 KTXs from nine hospitals in seven Asian countries. Within the study population, 9% were aged 60 years and older, and 79% had at least one comorbidity. The majority of patients (69%) presented with mild-to-moderate COVID-19 severity. Disease progression was more frequently encountered among those with moderate or severe infection (23%) and non-survivors (55%). The mortality rate was 23% (n=20) and differed according to the level of care: 12% (n=1/8), 15% (n=10/67), and 100% (n=9/9) of patients managed as outpatients, in the general ward, and in the intensive care unit, respectively. Disease severity at the time of presentation was an independent predictor of mortality. Compared with the mortality rates in other studies worldwide, mortality rates in the current study were comparable.
Conclusions: Mortality in Asian KTXs who were infected with COVID-19 remains high and could be related to comorbidity burden and the constraints of the general healthcare system when the COVID-19 caseload is high.

Keywords: Kidney transplantation; COVID-19; Asia; Registry

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HIGHLIGHTS

- This is the first multi-national Asian study of coronavirus disease 2019 (COVID-19) infections.
- The study population comprised of younger kidney transplant recipients with a lower comorbidity burden.
- Asymptomatic patients were frequent, but progression to more severe disease was uncommon.
- Mortality from COVID-19 remained high despite a population likely to have a lower risk of progression.
- There may be other factors affecting mortality in Asia such as timely access to higher levels of care.

INTRODUCTION

Since the coronavirus disease 2019 (COVID-19) pandemic was declared on March 11, 2020, nations around the world have struggled to contain the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) while striving for socioeconomic stability. This has become increasingly difficult with recurrent waves of more contagious SARS-CoV-2 variants and sluggish vaccination programs. As of December 1, 2021, there are 82,141,978 cases of COVID-19 in Asia. This represents the highest case load among all continents, thus making Asia the new global epicenter of COVID-19.

Many transplant programs in Asia were either shut down or overwhelmed by the increasing incidence of COVID-19 cases; therefore, transplantation in Asia, which is a region with already low transplantation rates, was dealt another huge blow by the COVID-19 pandemic [1]. However, there is paucity of data on morbidity and mortality from COVID-19 involving transplant recipients in Asia. In a systematic review of studies of COVID-19 in kidney transplant recipients (KTXs), only 10 out of 38 studies (26%) were from Asia [2]. Given that the mortality and morbidity of COVID-19 in KTXs is appreciably high, more studies from Asia are urgently required [3].

The Asian Society of Transplantation (AST), which is supported by the Korean Organ Transplant Registry, established an Asian Organ Transplantation Registry (ASTREG) in 2017 [4]. Data were collected from over 800 patients in Asia [4]. In 2020, a sub-registry task force was formed by a group of researchers (referred to as ASTREGO for ASTREG Research Group) to collect data on COVID-19 infections in Asian KTXs.

This multi-center retrospective observational study is a by-product of ASTREGO and aimed to provide insights into the characteristics, clinical phenotype, and management of COVID-19 in KTXs from transplant programs in various countries in Asia.

METHODS

This was a retrospective study that used a COVID-19 database developed by Dr. Terence Kee and Dr. Jong Cheol Jeong; this database was also disseminated to specific transplant programs from member countries of the AST. Some transplant centers from Bangladesh, Hong Kong, Mongolia, Malaysia, the Philippines, South Korea, and Singapore agreed to participate and form ASTREGO. Each center obtained approval from their own local institutional review boards and/or patients to collect data on COVID-19-infected KTXs who were admitted in their hospitals.

The inclusion criteria included adult KTXs (age >18 years) who were diagnosed with SARS-CoV-2 infection by reverse-transcription polymerase chain reaction (PCR) testing of nasopharyngeal and/or oropharyngeal samples from January 1, 2020, to June 30, 2021. Patients were followed up until June 30, 2021, or until they recovered or died. Data were extracted from medical records on demographic characteristics such as age, sex, type of kidney donor, transplant duration, comorbidities, and immunosuppressive regimen at the time of COVID-19 diagnosis. Information on COVID-19 epidemiology and phenotype, such as source of infection, symptomatology, complications, radiological features, and treatment, was also collected.

Each patient's presentation was stratified according to the severity categories defined by the National Institutes of Health (https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/): (1) asymptomatic or pre-symptomatic; (2) mild: having symptoms but without dyspnea or abnormal chest radiology; (3) Moderate: symptoms that included clinical evidence of lower respiratory tract disease or abnormal chest radiology but pulse oximetry >94% on room air; (4) severe: evidence of severe respiratory tract disease such as pulse oximetry <94% on room air, PaO_2/FiO_2 <300 mmHg, respiratory rate >30 breaths per minute, or lung infiltrates seen on >50% of imaging; (5) critical: presence of respiratory failure, septic shock, and/or multi-organ dysfunction. The collected data were also

compared between survivors and non-survivors to identify the risk factors associated with mortality.

Statistical Analysis

Continuous variables are presented as medians and ranges, and categorical variables are reported as frequencies and percentages. The chi-square test and Wilcoxon rank-sum test were used to compare the characteristics and outcomes between survivors and non-survivors. To determine the risk factors for mortality from COVID-19 infections, a multivariate analysis of baseline characteristics was performed using logistic regression analysis. The variables included in the logistic regression analysis model were age 60 years and older, female sex, presence of comorbidities, transplant duration less than 1 year, and disease severity at the time of presentation. Results from the multivariate analysis were presented as odds ratios with 95% confidence intervals. Differences were considered significant if the P-value was less than 0.05. Statistical analyses were performed using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). The clinical and research activities reported here are consistent with the principles of the Declaration of Istanbul.

RESULTS

Demographic Characteristics

Nine transplant centers from seven Asian countries participated in this study. The study population consisted of 87 patients who tested positive for SARS-CoV-2 from March 1, 2020, to May 19, 2021. The centers participating in the study included the Kidney Foundation Hospital and Research Institute (Bangladesh), National Transplant and Kidney Institute (Philippines), First Central Hospital (Mongolia), Hospital Kuala Lumpur (Malaysia), Queen Elizabeth Hospital (Malaysia), Seoul National Bundang Hospital (South Korea), Singapore General Hospital (Singapore), National University Hospital (Singapore), and Queen Mary Hospital (Hong Kong). Over 50% of the study population included patients from Bangladesh (32%, n=28), the Philippines (16%, n=14), South Korea (3%, n=3), Singapore (2%, n=2), and Hong Kong (1%, n=1). All patients received a kidney transplant alone, except one who received a simultaneous kidney–pancreas transplant.

Table 1 shows the baseline characteristics of the study population. The median age of infected KTXs was 43 years (range, 21–80 years), and only 9% of patients were 60 years of age or older. Most of the patients were male (72%) and were recipients of living donor kidney transplants (79%). The median time from transplant to presentation was 5 years (range, 5 days–27 years), and the median duration of follow-up for COVID-19 infection was 19 days (range, 3–162 days). Patients who were infected within 1 year of transplant surgery represented 12% of the study population, with one case of infection occurring within 5 days of transplant surgery because of nosocomial transmission.

The median estimated glomerular filtration rate (eGFR) at the time of presentation of COVID-19 was 40 mL/min/1.73 m^2 (range, 6–93) among 33 patients whose baseline eGFR value was available. Three patients (3.4%) presented with renal allograft failure (defined as eGFR <15 mL/min/1.73 m^2). When all these parameters were compared between survivors and non-survivors, the only significant difference observed was a lower median eGFR among the non-survivors than the survivors (28 vs. 45 mL/min/1.73 m^2, P=0.003). There was also a greater proportion of non-survivors who were older than 60 years (15% vs. 7%) and with a transplant duration of less than 1 year (15% vs. 10%). However, these differences were not statistically significant.

At the end of the study follow-up, 17% (n=15/87) of patients were reported to not have cleared their COVID-19 infection as defined by the clinical resolution of symptoms with or without a negative PCR result. In 29 patients who recovered from COVID-19 with available results from repeat PCR testing for SARS-CoV-2, the median time to a negative PCR result was 31 days (range, 4–31 days). With respect to comorbidity burden, 79% had at least one comorbidity (Table 1). The community transmission of COVID-19 is the most common route of transmission of infection.

Clinical Presentation and Progression of COVID-19

Within the ASTREGO population, data on clinical presentation were not available for 12 patients (14%), whereas another 13 patients (15%) were asymptomatic when tested positive for SARS-CoV-2 as part of the protocol screening. For the remaining 62 patients (71%), the most common presenting symptoms of COVID-19 infection were cough (66%), fever (63%), and loss of appetite (48%) (Table 2). Fever and headache were the most frequent symptoms among the non-survivors. Interestingly, arthralgia, palpitations, and orbital cellulitis were rare presentations in three patients.

Table 1. Baseline characteristics of the study population

Variable	All (n=87)	Survivor (n=67)	Non-survivor (n=20)	P-value
Age (yr)	43 (21–80)	43 (21–64)	45 (32–80)	0.470
Age ≥60 yr	8 (9)	5 (7)	3 (15)	0.306
Sex				0.768
Male	63 (72)	48 (72)	15 (75)	
Female	24 (28)	19 (28)	5 (25)	
Type of donor				0.584
Living	69 (79)	52 (78)	17 (85)	
Deceased	15 (17)	13 (19)	2 (10)	
Unknown	3 (3)	2 (3)	1 (5)	
Time after transplantation (yr)	5 (0.01–27)	5 (0.01–27)	5 (4–25)	0.790
Time after transplantation <1 yr	10 (12)	7 (10)	3 (15)	0.744
Lymphocyte depleting antibody exposure	8 (9)	5 (7)	3 (15)	0.306
Calcineurin Inhibitor				0.718
Tacrolimus	76 (87)	59 (88)	17 (85)	
Cyclosporine	11 (13)	8 (12)	3 (15)	
Corticosteroids	79 (91)	61 (91)	18 (90)	0.887
Anti-metabolite				0.915
Mycophenolic acid	58 (67)	44 (66)	14 (70)	
Azathioprine	4 (5)	3 (4)	1 (5)	
None	25 (29)	20 (30)	5 (25)	
mTOR inhibitor	3 (3)	3 (4)	0	0.336
Comorbidity burden				0.583
No comorbidity	18 (21)	13 (19)	5 (25)	
1–2 Comorbidity	60 (69)	48 (72)	12 (60)	
>2 Comorbidity	9 (10)	6 (9)	3 (15)	
Hypertension	46 (53)	35 (52)	11 (55)	0.828
Diabetes mellitus	19 (22)	13 (19)	6 (30)	0.314
Chronic lung disease/asthma	18 (21)	13 (19)	5 (25)	0.588
Obesity	13 (15)	10 (15)	3 (15)	0.993
Cardiovascular disease	11 (13)	6 (9)	5 (25)	0.058
Chronic liver disease	5 (6)	5 (7)	0	0.208
Cancer	3 (3)	3 (4)	0	0.336
eGFR at the time of presentation (mL/min/1.73 m^2)	40 (6–93)	45 (24–93)	28 (6–92)	0.003
Source of COVID-19 exposure				0.855
Community acquired	55 (63)	42 (63)	13 (65)	
Household cluster	17 (19)	12 (18)	5 (25)	
Workplace cluster	8 (9)	7 (10)	1 (5)	
Healthcare cluster	6 (7)	5 (7)	1 (5)	
Imported or overseas	1 (1)	1 (1)	0	

Values are presented as median (range) or number (%).

mTOR, mammalian target of rapamycin; eGFR, estimated glomerular filtration rate; COVID-19, coronavirus disease 2019.

Chest X-ray data were available for 71 patients. A normal chest radiograph was the most common finding observed in 49% of the cases and was more frequent among survivors than among non-survivors (58% vs. 19%, P=0.004) (Table 2). Pulmonary consolidation was the second most common abnormality (32%), but it was more fre-

Table 2. Symptoms and radiological features of COVID-19 infections

Variable	All (n=62)	Survivor (n=48)	Non-survivor (n=14)	P-value
Cough	41 (66)	31 (65)	10 (71)	0.634
Fever	39 (63)	26 (54)	13 (93)	0.008
Loss of appetite	30 (48)	21 (44)	9 (64)	0.176
Fatigue	26 (42)	19 (40)	7 (50)	0.487
Myalgia	19 (31)	14 (29)	5 (35)	0.640
Headache	16 (26)	8 (17)	8 (57)	0.002
Anosmia	15 (24)	10 (21)	5 (36)	0.253
Loss of taste	15 (24)	12 (25)	3 (21)	0.784
Dyspnea	13 (21)	9 (19)	4 (29)	0.427
Sputum production	13 (21)	10 (21)	3 (21)	0.962
Sore throat	13 (21)	10 (21)	3 (21)	0.962
Nausea	12 (19)	7 (15)	5 (36)	0.078
Altered mental status	11 (18)	7 (15)	4 (29)	0.228
Diarrhea	9 (14)	7 (15)	2 (14)	0.978
Vomiting	7 (11)	3 (6)	4 (29)	0.061
Rhinorrhea	4 (6)	4 (8)	0	0.264
Abdominal pain	3 (5)	2 (4)	1 (7)	0.648
Other symptom				0.346
Arthralgia	1 (2)	1 (2)	0	
Palpitations	1 (2)	0	1 (7)	
Orbital Cellulitis	1 (2)	0	1 (7)	
Chest X-ray finding[a]				
No abnormality	35 (49)	32 (58)	3 (19)	0.004
Consolidation	23 (32)	14 (25)	9 (56)	0.037
Pleural effusion	9 (13)	5 (9)	4 (25)	0.169
Ground glass opacity	4 (6)	4 (7)	0	0.286
Computed tomography chest finding[b]				
No abnormality	23 (55)	19 (59	4 (40)	0.283
Ground glass opacities	8 (19)	6 (19)	2 (20)	0.365
Pleural effusion	5 (12)	3 (9)	2 (20)	0.240
Reticular or lobular thickening	4 (9)	4 (12)	0	0.930
Pulmonary nodule	2 (5)	0	2 (20)	0.010

Values are presented as number (%).
[a]All (n=71), survivor (n=55), non-survivor (n=16); [b]All (n=42), survivor (n=32), non-survivor (n=10).

quently found in non-survivors than in survivors (56% vs. 25%, P=0.037).

In terms of disease severity (Table 3), the majority of patients (69%) presented with mild and moderate COVID-19 infections, whereas another 15% had either asymptomatic or pre-symptomatic infection at the time of presentation. Not surprisingly, a greater proportion of non-survivors had COVID-19 infections of moderate severity (65% vs. 39%, P=0.039) or critical COVID-19 infections (15% vs. 1%, P=0.011) than survivors. Progression to

more severe COVID-19 infection was also more frequent among non-survivors than among survivors (55% vs. 10%, P<0.005). Progression to a more severe disease was associated with the initial disease severity at the time of presentation; 85% and 90% of asymptomatic and mildly infected patients did not progress in disease severity, respectively. By contrast, 23% of patients presenting with COVID-19 infections of moderate severity progressed to a more severe disease, whereas 60% and 100% of patients with severe and critical COVID-19 infection remained in the

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Table 3. Severity, complications, and management of COVID-19 infections

Variable	All (n=87)	Survivor (n=67)	Non-survivor (n=20)	P-value
Disease severity at time of presentation				
Asymptomatic	13 (15)	12 (18)	1 (5)	0.155
Mild	21 (24)	21 (31)	0	0.004
Moderate	39 (45)	26 (39)	13 (65)	0.039
Severe	10 (11)	7 (10)	3 (15)	0.575
Critical	4 (5)	1 (1)	3 (15)	0.011
Progression to more severe COVID-19 infection	18 (21)	7 (10)	11 (55)	0.005
Admission to hospital	79 (91)	60 (89)	19 (95)	0.459
Admission to the ICU	9 (10)	0	9 (45)	<0.001
Oxygen supplementation[a]	21/62 (34)	12/48 (25)	9/14 (64)	0.025
AKI	25 (29)	11 (16)	14 (70)	<0.001
Multi-organ failure	13 (15)	0	13 (65)	0.005
Respiratory failure requiring ventilation[a]	9/62 (14)	1/48 (2)	8/14 (57)	<0.001
Renal replacement therapy[a]	9/62 (14)	0/48 (0)	9/14 (64)	<0.001
Renal allograft rejection	10 (11)	1 (1)	9 (45)	<0.001
Cardiac injury	7 (8)	3 (4)	4 (20)	0.025
Shock	7 (8)	0	7 (35)	0.005
Arrhythmias	5 (6)	2 (3)	3 (15)	0.043
Cytopenias	3 (3)	0	3 (15)	0.001
Liver injury	3 (3)	2 (3)	1 (5)	0.665
Thrombosis	1 (1)	0	1 (5)	0.066
Coagulopathy	1 (1)	0	1 (5)	0.066
Secondary infections	4 (5)	2 (3)	2 (10)	0.189
Increased doses of corticosteroids[a]	41/62 (66)	30/47 (64)	11/15 (73)	0.534
Anticoagulation[a]	38/62 (61)	24/47 (51)	14/15 (93)	0.003
Antivirals[a]	31/62 (50)	18/47 (38)	13/15 (87)	0.001
Antibiotics[a]	28/62 (45)	18/47 (38)	10/15 (67)	0.025
Reduction in immunosuppression[a]	27/62 (43)	21/47 (45)	6/15 (40)	0.750
Reduction or discontinuation of calcineurin inhibitors	16/62 (26)	11/47 (23)	5/15 (33)	0.243
Reduction or discontinuation of anti-metabolite	29/62 (47)	23/47 (49)	6/15 (40)	0.444
Hydroxychloroquine[a]	12/62 (19)	8/47 (17)	4/15 (27)	0.410
Azithromycin[a]	10/62 (16)	6/47 (13)	4/15 (27)	0.150

Values are presented as number (%).
COVID-19, coronavirus disease 2019; ICU, intensive care unit; AKI, acute kidney injury.
[a]Data for 25 patients not available.

Table 4. Multivariate analysis of risk factors associated with mortality from COVID-19

Variable	Multivariate analysis		
	OR	95% CI	P-value
≥60 yr	10.93	0.97−122.67	0.053
Female sex	1.06	0.28−3.93	0.933
Transplant duration less than 1 year	2.01	0.40−10.03	0.396
Presence of comorbidities	0.43	0.10−1.76	0.240
Moderate, severe, and critical disease at time of presentation	41.00	3.43−489.56	0.003

COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval.

Table 5. Comparison of clinical characteristics, outcomes, and management with other large cohort studies of COVID-19 in KTXs

Variable	ASTREGO (n=87)	South Asia (n=250)	West Asia (n=130)	Europe (n=279)	North America (n=54)	South America (n=491)
Representative nation	East and Southeast Asia	India [5]	Saudi Arabia [6]	France [7]	New York [8]	Brazil [9]
Age (yr)	43 (21–80)	43 (35–51)	48.7±14.4	Outpatient, 55.6 (48–61.1); inpatient, 61.6 (50.8–69.0)	57 (29–83)	53 (43–60)
Living donor kidney transplant	79	90	80	NA	69	33
COVID-19 within the first year of transplantation	12	20	16	14.4	Outpatient, 18; inpatient, 13	13.8
Hypertension	53	84	79	80.6	93	68
Diabetes	22	32	45	37.2	30	32
Cardiac disease	13	12	17	31.2	35	12
Most common immunosuppression[a]						
Calcineurin inhibitor	100	94.4	96	83.1	100	Tacrolimus
Prednisolone	91	100	98	72.8	31.5	Prednisolone
Anti-metabolite	71	100	93	79.8	96.3	Mycophenolate
mTOR inhibitor and others	3	5.6	5	11.9	3.7	46
Asymptomatic case	15	6	1	0	0	3
Most common symptom	Cough, 66; fever, 63; anorexia, 30	Fever, 88; cough, 72; sputum, 52	Fatigue, 62; fever, 60; cough, 58	Fever, 80; cough, 63.6; diarrhea, 43.5	Fever, 74; cough, 59; dyspnea, 52	Cough, 62; fever, 60; dyspnea, 51
Radiological abnormality	50.7	51	33.1	87	NA	97.3
Hospital admission	90.8	80	55	87	72	69
ICU admission	10.3	21	21	36	33	61
Ventilation	14.5	12	42	30	28	32
AKI	28.7	48.4	27	43.6	51	47
Shock	8	NA	11	11	NA	29
Secondary infection	5	20	29	23.5	48	36
Mortality	23	12	11	23	13	28
Reduction or discontinuation of immunosuppression						
Calcineurin inhibitor	26	34	35	29	33	1
Antimetabolite (azathioprine/ mycophenolic acid)	47	98	88	71	72	12
Adjustment in corticosteroids	68	40	77	NA	9	2
Azithromycin	16	80	31	25	22	45
Hydroxychloroquine	19	64	11	25	62	12
Antivirals	50	36	20	8	4	0
Antibiotics	45	NA	31	63	39	14
Immunotherapy	0	14	5	5	4	0
Convalescent plasma	0	6	5	0	2	0

Values are presented as median (interquartile range), mean±standard deviation, or percentages.

COVID-19, coronavirus disease 2019; KTX, kidney transplant recipients; ASTREGO, ASTREG research group; NA, data not available; mTOR, mammalian target of rapamycin; ICU, intensive care unit; AKI, acute kidney injury.

[a]Data presented from the French study include only those who are hospitalized.

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same disease severity at the end of follow-up, respectively.

Among the asymptomatic patients, one patient was diagnosed with COVID-19 five days after transplant surgery. This patient was tested for SARS-CoV-2 because of contact with a positive COVID-19 case. As a result, the dose of mycophenolate was reduced, and the dose of prednisolone was increased. No allograft rejection occurred, and the patient recovered from the infection with no disease progression.

Complications of COVID-19 Infection

The majority of patients (91%) required hospital admission and complications, including acute kidney injury (AKI), respiratory failure, cardiac injury, shock, arrhythmias, multi-organ failure, cytopenia, and renal allograft rejection, which were more frequently encountered in non-survivors than in survivors (Table 3). The need for oxygen supplementation, ventilator support, and renal replacement therapy was also more common in non-survivors than in survivors. The rate of admission to the intensive care unit (ICU) was 10%. The overall mortality rate was 23% (n=20) and was spread out according to different levels of care: 12% (n=1/8), 15% (n=10/67), and 100% (n=9/9) of patients managed as outpatients, in the general ward, and in the ICU, respectively. Three patients were admitted to high-dependency units, but none of them died. All graft losses were attributed to the patient's death.

Baseline characteristics were analyzed for predictors of mortality from COVID-19 infection via multivariate analysis (Table 4). Only moderate or more severe disease at the time of presentation was found to be an independent predictor of mortality from COVID-19 infection.

Management of COVID-19

Data on treatment were available for 62 patients (Table 3). The most common COVID-19 specific treatments were corticosteroids (66%), antivirals (50%), and reduction of immunosuppression (43%). Antibiotics were used in 45% of patients, and there was a high usage of anticoagulants because of local COVID-19 management protocols. Antibiotics, antivirals, and anticoagulation treatments were administered to a greater proportion of non-survivors than survivors.

DISCUSSION

To the best of our knowledge, this is the first study to examine the clinical characteristics and outcomes of KTXs infected with COVID-19 from three regions of Asia (East, South, and Southeast Asia). The key findings of this study were that those infected were mostly below the age of 60 years; however, the mortality rate remained appreciably high. Notably, 55% of the mortality occurred in general ward and outpatient settings. Multivariate analysis showed that disease severity at the time of presentation was an independent predictor of mortality.

As of December 1, 2021, Asia has the highest incidence rate (cumulative incidence of 18,009 per million population) of COVID-19 infections worldwide. Despite this high case load, knowledge of COVID-19 infections among Asian KTXs is limited to a few single-center case reports, except for a large multi-center study from India [5]. Expanding COVID-19–related knowledge in Asia is important because most information on COVID−19 in transplant recipients thus far is derived from published studies in other geographical areas that may not necessarily be similar or applicable to the Asian transplant population [10]. One example is information on COVID-19–related mortality, which was observed to be significantly lower in Asia than in Europe (2.7 vs. 197 deaths per million population, P<0.001) [11]. This observation was attributed to a younger population, better national pandemic responses, greater community adherence to social distancing, and wearing of face masks in Asia.

In view of these considerations, the findings of the ASTREGO study were compared with those of other similar studies from India, Saudi Arabia, France, and the Americas (Table 5) [5-9]. The comparisons revealed that the ASTREGO study population and those from India and Saudi Arabia were younger than the European or American study population. Furthermore, the proportion of KTXs aged 60 years and older was significantly lower in the ASTREGO (9%) and Indian (3.6%) cohorts than in the United States, Italy, and Spain (56.2%) [12]. This younger age profile may partly explain the lower frequency of diabetes and heart disease in the ASTREGO and Indian populations. Calcineurin inhibitors were the mainstay of immunosuppression regimens for all cohorts, but steroid-sparing and mammalian target of rapamycin (mTOR) inhibitor-based regimens were more frequently employed in North American and European centers, respectively. However, it remains uncertain whether different immunosuppressive regimens have any

effect on the natural history and outcomes of COVID-19 infections.

Fever and respiratory symptoms were the most common presenting symptoms in the ASTREGO cohort. These findings were similar to those of other studies on COVID-19-infected KTXs. However, normal chest radiology was frequently observed in the ASTREGO (49.3%), Indian (49%), and Saudi Arabian (67.9%) cohorts despite the dominance of respiratory symptoms. This could be partly attributed to the higher proportion of patients who were asymptomatic or mildly infected in these populations. As a result, radiological findings alone may be insufficient and highlight the need to rely on other assessment tools to stratify patients suspected of having COVID-19. Unfortunately, other assessment methods may not be sufficiently specific and sensitive, particularly in regions where the community prevalence of COVID-19 infections may be high. As a result, the universal swabbing of inpatients for COVID-19 is advocated because COVID-19 can be diagnosed in 1.6% to 15.4% of unsuspected patients who were admitted and swabbed [13-16]. Filtering out unsuspected COVID-19 infections by universal swabbing could reduce hospital-acquired COVID-19 infections, which occurred in 6.9% of the ASTREGO cohort.

Little is known about the natural history of asymptomatic COVID-19 infections in KTXs, as reflected by the small number of asymptomatic cases reported in various studies. In this study, there were 13 asymptomatic patients, which represent 15% of the study population, but only two patients (15%) experienced progression of their infections during follow-up. By contrast, the frequency of non-transplant patients who tested for SARS-CoV2 but were asymptomatic can be as high as 56.5%, with progression to symptomatic infections in 31.4% [17]. Although more studies are required in this area, the low frequency of disease progression in KTXs may suggest that outpatient management is possible in a highly selected group of asymptomatic patients. This would enable hospitals to conserve beds at a higher risk of severe infections. The outpatient management of stable COVID-19-infected KTXs appears to be effective and safe when implemented in the United States, Italy, and France but may otherwise be challenging to implement in some Asian countries because of the lack of telephone and internet access [7,18,19]. Another potential problem is prompt access to hospital facilities, which may be difficult in rural parts of Asia, because COVID-19-infected patients who are managed in outpatient settings may eventually require hospitalization at a rate as high as 20% [6].

In a systematic review of 20 studies, the proportion of patients requiring ICU admission varied from 9% to 42% [20]. Therefore, the ICU admission rate in the 10% ASTREGO cohort was considerably lower. When the ICU admission and secondary infection rates were compared with those of the other cohorts (Table 5), the ASTREGO cohort had the lowest rates. These observations could be explained by a large proportion (87%) of patients not having severe or critical COVID-19 infections during the course of their illness; however, mortality remained high at 23%, which was not lower than the 18%−43% mortality rates observed in other studies [20]. This may be explained by the high rates of death occurring outside the ICU (75%), which may have been a surrogate marker of a lack of timely access to the ICU. In studies from India and Saudi Arabia, the mortality rate was lower at 11%−12%. This could have been due to the greater proportion of younger patients in their series than that in the ASTREGO cohort [5,6].

This study observed that disease severity at the time of presentation was an independent predictor of mortality, and this finding is consistent with those of other studies where other risk factors include older age, lymphopenia, comorbidities, treatments for rejections/infections, radiological abnormalities, acute respiratory distress syndrome, AKI, admission to ICU, ventilator support, and various biomarkers (e.g., increased levels of inflammatory markers) [5,6,10,21].

It remains uncertain whether immunosuppression may protect against or facilitate the replication of SARS-CoV-2. *In vitro* studies suggest that calcineurin inhibitors, mammalian target of rapamycin inhibitors, and mycophenolate may inhibit the replication of SARS-CoV-2 [22]. However, systematic reviews suggest that solid organ transplant status is associated with a greater risk of mortality (hazard ratio, 1.54; 95% confidence interval, 1.03−2.32; P=0.037) compared with non-solid organ transplant status [23]. This uncertainty may be reflected in diverse approaches to modify immunosuppression during COVID-19 infections. The discontinuation or reduction of calcineurin inhibitors and antimetabolites varied between 1% to 35% and 12% to 98% of the cohorts examined, respectively (Table 5). A higher proportion of patients from the ASTREGO and Saudi Arabia cohorts had their corticosteroids adjusted (68%−77% vs. 2%−9%) than patients from other regions. Antiviral drug therapies were most often used in the ASTREGO group (50% vs. 0% to 36%), whereas hydroxychloroquine was more frequently used for patients in India and North

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America (62%–64%). No patient from the ASTREGO cohort received immunotherapies or convalescent plasma, but this was administered to 2%–6% of patients in other regions. These observations show that there is no consistent approach to the management of COVID-19 in solid organ transplant recipients, but some countries have developed national COVID-19 management protocols to standardize treatments [24]. As a result, this diversity in therapeutic approaches hampers the interpretation of treatment and outcome data.

The major limitation of this study is that not all centers from each country participated, and even within centers, data were incomplete for specific data domains due to the retrospective study design. This was caused by some patients being managed remotely at home, while other investigators had difficulty completing data submissions due to competing demands imposed by increasing COVID-19 workload in their hospitals. In addition, there may have been selection bias in the study population, as not all KTXs infected with COVID-19 would have been screened for SARS-CoV-2. As a result, ASTREGO is still recruiting new collaborators to collect more data on COVID-19-infected transplant recipients so that more accurate interpretations and conclusions can be obtained. Furthermore, the effect of vaccination and monoclonal antibody therapies will also need to be examined in the future as these treatments become more readily available in Asia. Nevertheless, the current study remains valuable because of its focus on COVID-19 infections in KTXs from various regions of Asia and on the regional differences in the phenotype of the infection.

Contrary to the impression that COVID-19 mortality is lower in Asia, this study demonstrated that COVID-19 infection was just as lethal among Asian KTXs as it is in other regions of the world despite the Asian region having a younger population, lower comorbidity burden, and a greater proportion of asymptomatic cases in the AS-TREGO cohort. There may be other factors in Asia that influence mortality from COVID-19 infection, such as timely access to higher levels of care, which can be overwhelmed in countries with a high daily caseload of COVID-19 infections. This study also revealed that asymptomatic cases and normal chest radiology may pose challenges in identifying patients for SARS-CoV-2 and proposed a proposition for hospitals to perform surveillance swabs of all patients being admitted to inpatient units. Finally, little is known about asymptomatic COVID-19 infections in KTXs; however, this study reported a low rate of disease progression

and suggested that outpatient protocols should be implemented to carefully monitor asymptomatic or mildly infected KTXs at home. Unfortunately, this may be difficult to implement in regions in Asia where telephony and internet penetration are low.

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KTXs during the COVID-19 pandemic while assisting in the data recording process.

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