ORIGINAL ARTICLE

Clinical insights into the role of immunosuppression in solid organ transplant recipients with COVID-19

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KEY WORDS

acute kidney injury, calcineurin inhibitor, drug metabolism, graft function, tacrolimus

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ABSTRACT

INTRODUCTION The COVID-19 pandemic has disproportionately affected patients who have undergone solid organ transplantation (SOT).

OBJECTIVES We aimed to assess a cohort of transplant recipients who developed COVID-19, with a focus on immunosuppressive regimen, blood tacrolimus levels, clinical course, and patient and graft outcomes.

PATIENTS AND METHODS During the first 12 months of the pandemic, we identified ambulatory SOT recipients, including kidney, liver, and heart transplant recipients, diagnosed with SARS-CoV-2 infection. Baseline and follow-up data on graft function, immunosuppression, and patient and graft outcomes were assessed.

RESULTS Of the 2091 ambulatory patients, we identified 201 transplant recipients (9.6%) with SARS-CoV-2 infection (kidney transplant, n = 112; heart transplant, n = 56; liver transplant, n = 33). Patients after recent kidney (during 2015–2020) or heart (during 2020) transplant were significantly more often diagnosed with COVID-19 than patients with a longer time since transplant. Additionally, blood trough tacrolimus levels measured during or shortly after COVID-19 in 23 kidney graft recipients were significantly increased by a median of 76.1% (interquartile range, 47.4%–109.4%) relative to predose trough levels. However, liver function parameters were not elevated, necessitating a tacrolimus dose reduction in 73.9% of the patients.

CONCLUSIONS In our study, kidney transplant recipients showed significant disturbances of tacrolimus metabolism, which may account for kidney function worsening during COVID-19. Moreover, infection was more common in patients with recent kidney or heart transplant, which suggests that the level of immunosuppression may affect morbidity related to SARS-CoV-2 infection.

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INTRODUCTION The ongoing pandemic of COVID-19 has brought about serious health problems for numerous patients. It was reported that patients with comorbidities are at higher risk for infection with SARS-CoV-2 and death,[1,2] with chronic kidney and cardiovascular diseases recognized as the most important risk factors for a fatal outcome.[3,4] Solid organ transplant (SOT) recipients are at even greater risk because of the mandatory immunosuppressive therapy.[5,6] An early report from the first pandemic wave identified several risk factors associated with COVID-19 among kidney transplant recipients (KTRs), including non-white ethnicity, obesity, asthma or chronic pulmonary disease, and diabetes mellitus.[7] According to a large cohort meta-analysis, 81% of SOT recipients with COVID-19 required hospital admission.[8] Age, comorbidities (congestive heart failure, chronic lung disease, obesity, diabetes), and clinical findings such as lymphopenia and abnormal chest imaging were

WHAT'S NEW?

Based on our experience in a cohort of solid organ transplant recipients during the first year of the COVID-19 pandemic, we found that patients with shorter posttransplant follow-up were more frequently diagnosed with SARS-CoV-2 infection. Moreover, in a large subgroup of kidney recipients, blood tacrolimus levels were significantly increased despite normal liver function test results, which may partly explain the widely reported worsening of kidney graft function during infection. Finally, after SARS-CoV-2 infection, the function of all transplanted organs in survivors was unchanged relative to baseline. Despite global vaccination efforts, the transplant population remains at high risk of severe SARS-CoV-2 infection. Our clinical insights might be useful for optimizing the clinical care of transplant recipients with SARS-CoV-2 infection.

associated with a markedly higher mortality in these patients compared with the general population.[4,9,10]

In Poland, the first confirmed COVID-19 case was identified on March 4, 2020. During the next year, more than 1 800 000 cases were confirmed countrywide, and more than 46 000 deaths related to SARS-CoV-2 infection were reported. Obviously, the COVID-19 pandemic not only challenges the current transplant programs but also raises safety issues for stable SOT recipients.[11,12] Therefore, we started to monitor all KTRs, liver transplant recipients (LTRs), and orthotopic heart transplant (OHT) recipients in 2 outpatient transplant clinics in the Upper Silesia region of Poland to identify patients with COVID-19, confirmed by polymerase chain reaction of nasopharyngeal swab samples. After collecting data on SOT recipients with COVID-19 over the period of 12 months, we assessed the clinical signs and symptoms before the diagnosis of COVID-19 as well as the clinical course of the disease, including modifications of the immunosuppressive regimen and the effect of COVID-19 on graft function and patient outcome. Following our early clinical impressions, we also examined the potential effect of the time since transplant on COVID-19–related morbidity and generated insights regarding concomitant disturbances of tacrolimus metabolism in SOT recipients.

PATIENTS AND METHODS We examined all consecutive SOT recipients, including patients after kidney, liver, and heart transplants, who regularly attended the outpatient clinics in 2 regional transplant centers and who had an established diagnosis of SARS-CoV-2 infection based on a positive result of the nasopharyngeal swab test. Patients diagnosed with COVID-19 between March 4, 2020 and March 3, 2021 were included in the analysis. Most data were collected by phone calls, during scheduled or additional ambulatory visits, or from regional hospitals designated for the care of patients with SARS-CoV-2 infection. In addition, we investigated outpatient medical records of all SOT recipients during March and April 2021 to identify other individuals with a confirmed COVID-19 episode.

Demographic and clinical data were collected, including baseline laboratory parameters at the last ambulatory visit before the diagnosis of COVID-19 (ie, serum creatinine levels, white blood cell count, and blood trough levels of tacrolimus). Data on comorbidities and immunosuppression, including the previous use of thymoglobulin and / or acute rejection episodes, were collected from the center-operated prospective database and original medical records. The study was performed in accordance with the Declaration of Helsinki. The bioethics committee of the Medical University of Silesia granted permission to maintain the prospective transplant database and to perform this analysis based on anonymized data. Informed consent was not necessary because data analysis did not meet the criteria of a medical experiment.

The details of clinical symptoms and the need for hospitalization or admission to the intensive care unit (ICU) were examined. Changes in immunosuppressive regimen during SARS-CoV-2 infection were also assessed, along with patient and graft outcomes. Additionally, based on the laboratory data, we identified a subgroup of patients who, during SARS-CoV-2 infection, showed significant abnormalities in previously stable tacrolimus levels.

Kidney graft function was assessed using an estimated glomerular filtration rate (eGFR) calculated according to the Modification of Diet in Renal Disease formula. Liver graft function was assessed by measuring γ-glutamyltranspeptidase activity and the serum levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin. Finally, heart graft function was assessed using left ventricular ejection fraction measured by echocardiography.

Statistical analysis Values were presented as means with SD, medians with interquartile ranges (IQRs), or frequencies. Comparisons between groups were performed using the *t* test for quantitative variables or the χ^2 test for qualitative variables. Variables with a skewed distribution were compared using the Mann–Whitney test with Bonferroni correction. Changes in serum creatinine levels and liver function before and after the diagnosis of COVID-19 were assessed with the Wilcoxon test. The percentage of patients diagnosed with COVID-19 in different calendar years was compared using the χ^2 test. For all analyses, a *P* value of less than 0.05 was considered significant. The analysis was performed using STATISTICA 13.3 PL for Windows (Tibco Inc, Palo Alto, California, United States) and MedCalc v19.2.1 (MedCalc Software, Mariakerke, Belgium).

RESULTS **Study population** This study was performed in an ambulatory cohort of 2091 stable SOT recipients, including 1372 KTRs, 246 LTRs, and 473 OHT recipients, all followed at 2 regional transplant centers in Katowice and Zabrze, Poland. During the 12-month follow-up, COVID-19

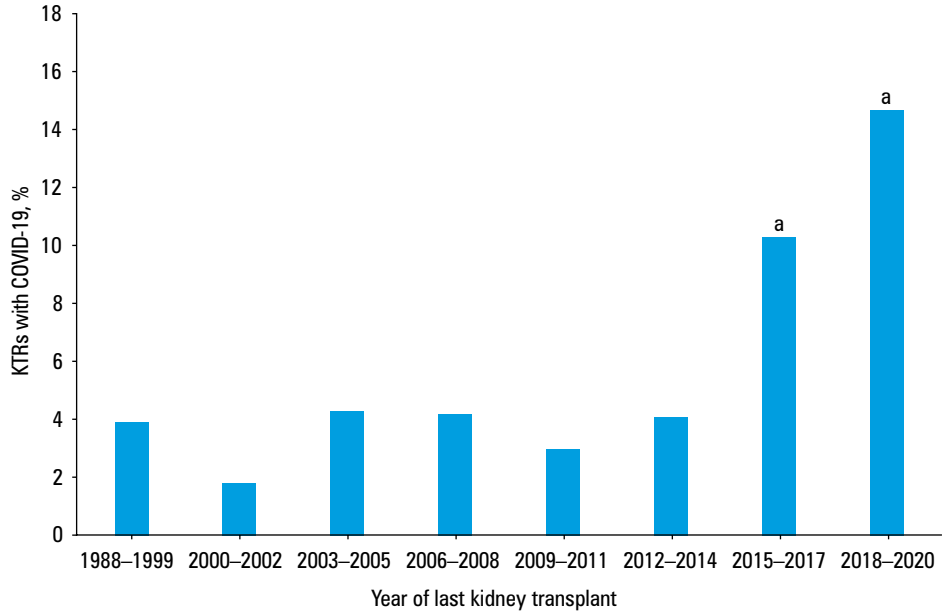

FIGURE 1 Percentage of kidney transplant recipients (KTRs) diagnosed with COVID-19 in relation to all patients who received kidney transplants in the consecutive periods of 3 calendar years
a P <0.001 vs the period before 2015

was confirmed in 201 patients (9.6%). Overall, hospitalization was reported in 57 patients (28.4%), while ICU admission was required in 17 of the 57 hospitalized patients (29.8%). Death due to COVID-19 occurred in 16 of the 17 patients (94.1%) treated in the ICU. All deceased patients had important comorbidities including hypertension, diabetes, obesity, cancer, tuberculosis, ischemic heart disease, chronic kidney disease requiring dialysis, or advanced chronic kidney disease with an eGFR of approximately 16 ml/min/1.73 m^2. Three patients had 1 comorbidity, 8 patients had 2 comorbidities, 3 patients had 3 comorbidities, and 2 patients had 4 comorbidities. The number of comorbidities in deceased patients was similar in KTRs, LTRs, and OHT recipients. The median time from COVID-19 diagnosis to death was shorter in the KTR (n = 9) than in the OHT (n = 6) subgroup (9 days [IQR, 6–21] and 33 days [IQR, 27–43], respectively, P = 0.02). Patients with a posttransplant follow-up of 6 months or less did not differ from those with a follow-up of more than 6 months in the rates of COVID-19 hospitalization (33.3% and 27.6%, respectively; P = 0.54) or death (14.8% and 6.9%, respectively; P = 0.16).

The most common primary clinical signs and symptoms of SARS-CoV-2 infection were fever (59.7%) and cough (48.8%), followed by weakness (29.9%), dyspnea (21.9%), diarrhea (20.4%), anosmia and/or taste disorder (18.9%), and muscle and bone pain or headaches (18.9%). Of note, 9.9% of patients reported no symptoms, and nasopharyngeal swabs were performed because of a suspected contact with another infected person or as a routine procedure before a planned hospital admission. However, some significant differences in the clinical manifestation of COVID-19 were observed between transplant recipient subgroups (TABLE 1). Compared with other SOT recipients, LTRs more often reported weakness and muscle and bone pain or headaches, while OHT recipients reported cough less frequently than the remaining patients and fever less frequently than KTRs did.

Kidney transplant recipients Of the 1372 KTRs at our outpatient center, we identified 112 (8.2%) with confirmed COVID-19. The baseline clinical characteristics of the group are summarized in TABLE 2. The causes of end-stage renal disease were as follows: glomerulonephritis (50.9%), diabetes mellitus (4.5%), pyelonephritis (8.9%), autosomal dominant polycystic kidney disease (9.8%), hypertensive nephropathy (10.7%), and other or unknown (15.2%). In the KTR group, 97.3% of patients received the organ from a deceased donor, and 9.8% of patients underwent retransplantation. The maintenance immunosuppressive regimen consisted of cyclosporine A (n = 19) or tacrolimus (n = 92), mycophenolate mofetil or sodium (n = 103) or everolimus (n = 3), and steroids (n = 92). The median time from dialysis therapy prior to transplant was 29 months (IQR, 18–42).

The prevalence of SARS-CoV-2 infection in the KTR group was assessed. The diagnosis of COVID-19 was more common among patients who received a transplant within the previous 6 years vs those transplanted at least 6 years earlier. The proportion of confirmed COVID-19 cases was higher among patients who received a transplant in the years from 2015 to 2020 than among those undergoing a transplant before 2015 (P <0.001) (the whole pre-2015 period was considered as a reference). The percentage of KTRs diagnosed with COVID-19 relative to all patients who received kidney transplant in the 3-year periods is presented in FIGURE 1. Of note, patients who underwent kidney transplant before 2015 differed from those who underwent a transplant after 2015 in the rates of current steroid use (57% vs 95% of patients, respectively; P <0.001) and previous thymoglobulin use (0% vs 21% of patients, respectively; P = 0.004). On the other hand, the rate

TABLE 1 Comparison of baseline clinical signs and symptoms of SARS-CoV-2 infection between kidney, liver, and heart transplant recipients

Clinical sign or symptom	Solid organ transplant recipients			*P* value
	Kidney (n = 112)	Liver (n = 33)	Heart (n = 56)	
Fever	77 (68.8)	18 (54.5)	25 (44.6)	0.009
Cough	66 (58.9)	18 (54.5)	14 (25.0)	<0.001
Dyspnea	27 (24.1)	9 (27.3)	8 (14.3)	0.25
Anosmia and/or taste disorder	18 (16.1)	8 (24.2)	12 (21.4)	0.49
Muscle/bone pain or headache	8 (7.1)	17 (51.5)	13 (23.2)	<0.001
Weakness	29 (25.9)	23 (69.7)	8 (14.3)	<0.001
Diarrhea	28 (25.0)	5 (15.2)	8 (14.3)	0.19
No symptoms	10 (8.9)	4 (12.1)	6 (10.7)	0.84

Data are presented as number (percentage) of patients.

Significant differences at a *P* value of less than 0.05.

of previous acute rejection episodes was similar in both groups (17% vs 14%, respectively). Patients with previous thymoglobulin use had lower median absolute lymphocyte count that those without such therapy (1.2×10^3/µl [IQR, 0.9–1.7] vs 1.8×10^3/µl [IQR, 1.4–2.3], respectively; *P* = 0.002). They also had lower median lymphocyte percentage (21.6% [IQR, 18.4%–27.5%] vs 27.6% [IQR, 21.9%–30.9%], respectively; *P* = 0.02). Finally, patients who underwent a transplant after 2015 had a higher median eGFR value than those who received a transplant before 2015 (49.6 [IQR, 40.7–64.8] vs 44.4 [IQR, 28.9–56.4] ml/min/1.73 m^2, respectively; *P* = 0.02).

The median serum creatinine level at the last ambulatory visit before SARS-CoV-2 infection was 1.5 mg/dl (IQR, 1.2–1.9) and ranged from 0.7 to 4.2 mg/dl. Of note, 14.3% of the patients had an eGFR value lower than 30 ml/min/1.73 m^2. The median doses and blood levels of calcineurin inhibitors are presented in TABLE 2. In 16 patients (14.3%), lymphocyte-depleting antibodies were previously used as an induction or antirejection therapy. The use of this regimen was not associated with mortality. After the diagnosis of COVID-19, immunosuppressive drug doses were reduced in 61 patients (54.5%), including temporary reduction (30.4%) or subsequent cessation (24.1%) of mycophenolate mofetil, usually for no longer than 10 to 14 days. The dose of a calcineurin inhibitor was reduced only in 6.3% of the patients. In most patients, a steroid dose was increased (usually up to 10 mg/d) or steroid therapy was reinstituted in patients on steroid-free maintenance treatment.

Overall, 37 patients (33%) were admitted to the hospital because of SARS-CoV-2 infection. Three more patients were diagnosed during their first posttransplant hospital stay. Among the hospitalized patients, 8 (21.6%) required ICU care. There were 9 deaths (8.0%), which occurred at a median of 9 days (IQR, 6–21) after the COVID-19 diagnosis. Patients who died were older than the survivors (median age, 59.5 years [IQR, 57.0–67.0] vs 52.9 years [IQR, 41.7–62.5]; *P* = 0.04). However, no differences were noted with regard to baseline body mass index, kidney graft function, calcineurin inhibitor levels, and lymphocyte count or percentage (data not shown). Two of the deceased patients underwent dialysis during COVID-19. Three other patients required dialysis therapy during the COVID-19 episode (median eGFR at baseline, 35 ml/min/1.73 m^2). Finally, 3 other patients (median eGFR at baseline, 29.1 ml/min/1.73 m^2) developed severe acute kidney injury (AKI), with a serum creatinine level of up to 6 mg/dl. One of these patients required 4 hemodialysis sessions. Complete graft function recovery was reported in all 3 patients.

In our cohort, only a minority of patients were hospitalized for COVID-19, mostly at another hospital designated for COVID-19. The hospitalization away from the transplant center hindered the assessment of calcineurin inhibitors levels. Nevertheless, even after the exclusion of the 3 patients who were infected with SARS-CoV-2 during their first posttransplant hospitalization, we identified 23 individuals in whom blood tacrolimus levels were measured during or early after the disease. Six of these patients underwent their last transplant within the previous 6 months, while 17 patients had a median time since transplant of 41 months (IQR, 29–70). All these 23 patients showed a significant increase in median tacrolimus levels up to 12.8 ng/ml (IQR, 11.5–16.0) during the first weeks after the diagnosis of COVID-19 compared with the median value calculated from the last 4 measurements before the diagnosis (7.5 ng/ml [IQR, 6.9–9.0]; *P* <0.001). Importantly, the results of liver function tests were within the reference range (median alanine aminotransferase levels, 24 U/l [IQR, 19–29]), and no patients received antiviral drugs with potential pharmacokinetic interactions. The tacrolimus dose had to be tapered in 17 patients (73.9%), and the last follow-up dose (after a median of 4 months [IQR, 2–5]) was still lower (by a median of

TABLE 2 Baseline clinical characteristics of solid organ transplant recipients diagnosed with SARS-CoV-2 infection (n = 201)

Parameter		Solid organ transplant recipients		
		Kidney (n = 112)	Liver (n = 33)	Heart (n = 56)
Demographic and transplant data				
Age, y, median (IQR)		53.2 (43.4–62.5)	55.3 (48.4–62.5)	54.9 (48.0–64.2)
Sex, n	Male	67	17	12
	Female	45	15	44
BMI, kg/m^2		26.8 (4.8)	26.8 (3.6)	26.7 (3.9)
Overweight, %		45.5	30.3	48.2
Obesity, %		17.9	21.2	17.9
Time since transplant, mo, median (IQR)		51.5 (16.1–91.5)	77.0 (48.0–97.0)	65.0 (15.3–160.5)
Hypertension		107 (95.5)	18 (54.5)	47 (83.9)
Diabetes		31 (27.7)	10 (30.3)	26 (46.4)
Overall comorbidity, median (IQR)		2.0 (2.0–3.0)	2.0 (2.0–2.0)	2.0 (2.0–2.0)
Laboratory parameters				
eGFR, ml/min/1.73 m^2, median (IQR)		48.0 (35.0–63.4)	65.0 (56.4–65.0);	47.1 (31.5–56.8)
eGFR <30 ml/min/1.73 m^2		17 (15.2)	1(3.0)	8 (14.3)
Lymphocyte count, × 10^3/μl		1.83 (0.82)	1.57 (0.78)	1.61 (0.95)
Lymphocyte percentage, %		26.2 (8.5)	25.6 (8.9)	24.4 (13.1)
Alanine aminotransferase, U/l, median (IQR)		–	23.9 (16.1–31.4)	–
Aspartate aminotransferase, U/l, median (IQR)		–	22.9 (20.2–25.4)	–
γ-Glutamyltranspeptidase, U/l, median (IQR)		–	51.9 (21.1–97.4)	–
Bilirubin, μmol/l, median (IQR)		–	12.1 (9.6–14.0)	–
LVEF, %		–	–	56 (8)
Immunosuppressive treatment				
Cyclosporine dose, mg/d, median (IQR)		150 (150–175)	–	134 (100–175)
Cyclosporine blood trough level, ng/ml, median (IQR)		120 (93–132)	–	98 (82–107)
Tacrolimus dose, mg/d, median (IQR)		3.5 (2.5–5.0)	3.0 (2.0–4.5)	5.3 (3.0–6.0)
Blood tacrolimus level, ng/ml, median (IQR)		7.5 (6.4–8.8)	6.0 (5.3–7.3)	9.6 (7.7–11.2)
Mycophenolate mofetil dose, mg/d, median (IQR)		1000 (1000–1500)	750 (500–1000)	1309 (1000–1500)
Steroid dose, mg/d, median (IQR)		5.0 (5.0–7.5)	5.0 (5.0–5.0)	6.5 (5.0–7.5)

Data presented as mean (SD) unless indicated otherwise.

Overall comorbidity includes hypertension, diabetes, obesity, cancer, tuberculosis, ischemic heart disease, chronic kidney disease requiring dialysis treatment or advanced chronic kidney graft disease with an eGFR of approximately 16 ml/min/1.73 m^2.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LVEF, left ventricular ejection fraction

16.7% [IQR, 0%–40.9%]) compared with the dose before the diagnosis, while the blood trough levels of tacrolimus from the period before the infection were safely restored.

The analysis of serum creatinine levels in 96 survivors with preserved kidney graft function (including those with AKI) revealed lower median creatinine levels measured at a median of 6 weeks (IQR, 5–10) after the diagnosis compared with the levels before the diagnosis (1.4 mg/dl [IQR, 1.1–1.7] compared with 1.5 mg/dl [IQR, 1.2–1.8]; P <0.001]. After the exclusion of patients with the time since transplant of less than 6 months, serum creatinine levels were unchanged (Δ <5%) in 25 patients, while they were higher in 45 and lower in 11 patients as compared with the last measurement before the diagnosis. Nevertheless, subsequent measurements (median time since infection of 5.3 months [IQR, 4.1–6.8]) showed no differences in median serum creatinine levels after the diagnosis compared with baseline (1.5 mg/dl [IQR, 1.2–1.9] compared with 1.5 mg/dl [IQR, 1.2–1.9]; P = 0.56).

Liver transplant recipients Of the 246 LTRs, we identified 33 (13.5%) with confirmed COVID-19. The baseline clinical characteristics of these patients are presented in TABLE 2. The indications for liver transplant included autoimmune liver diseases (39.4%; primary sclerosing cholangitis in 6 patients; autoimmune hepatitis, in 4; primary biliary cholangitis, in 3), viral hepatitis (21.2%), alcoholic liver disease (12.1%), cryptogenic cirrhosis (9.1%), hepatocellular carcinoma (6.1%),

and other causes (9.1%). The percentage of patients with autoimmune liver diseases was higher among individuals with confirmed COVID-19 than in the whole LTR group (39.4% and 18.1%, respectively; $P = 0.002$). Maintenance immunosuppression consisted of tacrolimus (n = 32) or cyclosporine A (n = 1), mycophenolate mofetil or sodium (n = 11) or azathioprine (n = 2) or everolimus (n = 4), and steroids (n = 22). In 7 patients (21.2%), a triple immunosuppressive regimen was used, and 4 patients (12.1%) were treated with tacrolimus monotherapy. The results of liver function tests at the last ambulatory visit before SARS-CoV-2 infection as well as median doses and blood levels of calcineurin inhibitors are presented in TABLE 2.

After the diagnosis of COVID-19 in 8 patients (24.2%), the immunosuppressive drug doses were modified. Three patients were weaned from mycophenolate mofetil. In another 5 patients, the doses of mycophenolate mofetil or calcineurin inhibitors or everolimus were reduced. Steroid doses remained unchanged.

Five patients (15.2%) were admitted to the hospital because of SARS-CoV-2 infection. In 4 patients, hospitalization was necessitated by viral pneumonia, while 1 patient was transferred to the ICU, where he died. One patient was diagnosed with COVID-19 in a transplant unit on day 8 after liver transplant, but the clinical course of the disease was asymptomatic.

At a median follow-up of 4 months (IQR, 2–6) after the diagnosis of COVID-19, there were no significant changes in liver function parameters or serum creatinine levels measured during ambulatory visits (data not shown).

Heart transplant recipients Of the 473 OHT recipients, 56 (11.8%) were diagnosed with COVID-19. The baseline clinical characteristics of these patients are presented in TABLE 2. The causes of end-stage heart failure were as follows: ischemic cardiomyopathy (n = 19; 33.9%), dilated cardiomyopathy (n = 27; 48.2%), valvular disease (n = 2; 3.6%), hypertrophic cardiomyopathy (n = 1; 1.8%), and other causes (n = 6; 10.7%). One patient required another transplant because of graft insufficiency. The maintenance immunosuppressive regimen consisted of tacrolimus (n = 45) or cyclosporine A (n = 8), mycophenolate mofetil (n = 42) or sirolimus (n = 1) or everolimus (n = 2), and steroids (n = 13). The median doses and blood levels of calcineurin inhibitors are presented in TABLE 2.

Of the 61 patients who received a transplant in 2020, 13 (21.3%) were diagnosed with COVID-19. The prevalence of COVID-19 was lower among the remaining OHT recipients (10.4%; $P = 0.02$). Of note, all patients with shorter time since transplant were maintained on triple immunosuppressive therapy, including prednisone, which was withdrawn in all other patients. The median serum creatinine level before the diagnosis of COVID-19 was 1.4 mg/dl (IQR, 1.1–1.9). However, 6 patients required chronic dialysis therapy prior to infection, while 2 other patients required hemodialysis during the COVID-19 episode.

Immunosuppressive drug doses were tapered after the diagnosis of COVID-19 in 19 patients (33.9%), including mycophenolate mofetil reduction or cessation in 13 patients. The dose of calcineurin inhibitors was not reduced during the infection. No changes were made to maintenance steroid doses.

Overall, 15 patients (26.8%) were admitted to the hospital because of SARS-CoV-2 infection, of whom 8 patients required ICU care. During the episode of COVID-19, respiratory failure occurred in 6 patients (10.7%) and acute coronary syndrome was noted in 1 patient. Additionally, 2 patients were diagnosed with COVID-19 during their first posttransplant hospitalization. There were 6 deaths (10.7%), which occurred after a median of 32 days (IQR, 9–43) from the diagnosis of COVID-19. Three patients died during their first year after transplant. In survivors, left ventricular ejection fraction remained unchanged at a median follow-up of 2.2 months (IQR, 1.1–3.5).

DISCUSSION

In the present study, we assessed the clinical characteristics and outcomes of ambulatory patients who tested positive for SARS-CoV-2 after kidney, liver, or heart transplant. In the KTR group, COVID-19 cases were significantly more common among patients who underwent transplant during the years 2015 to 2020 than among those with longer time since transplant. Additionally, considerable disturbances in tacrolimus metabolism were reported in KTRs for whom a tacrolimus measurement was available during or shortly after the COVID-19 episode. Finally, there were considerable differences in clinical manifestations between KTRs, LTRs, and OHT recipients. To our knowledge, our study is the first to assess the specific types of transplant recipients, unlike previous reports that focused on the clinical picture or outcomes of SOT recipients in general.[8,9,13]

While previous studies covering the period of up to the first 9 months of the COVID-19 pandemic reported high hospitalization rates (63%–91%),[7,8,14,15] our study with a 12-month follow-up showed a significantly lower rate of hospital admissions due to COVID-19 (28.4%). This discrepancy did not result from limited hospital bed capacity but rather from the lower severity of clinical signs and symptoms, allowing home-based treatment of these patients. The overall mortality in our study cohort (8%) is in line with previous reports for SOT recipients[15] and local general population.[16] On the other hand, a recent meta-analysis of a large cohort of SOT recipients reported the overall mortality rate of 18.6%. Of note, we observed high mortality rates among our ICU patients, which is consistent with recent findings for comparable transplant[17] and dialysis cohorts.[18] Similarly, previous studies reported markedly different COVID-19 mortality rates for KTRs[7,14] and other transplant recipients.[8,15]

These discrepancies can be due to the relatively low number of patients included in most studies.

In our study, the incidence of SARS-CoV-2 infection was higher in patients who underwent a kidney transplant within the previous 6 years, including 2020, compared with patients with a longer time since kidney transplant. These subgroups differed significantly in terms of current and past immunosuppressive regimen, with higher rates of current steroid use and previous thymoglobulin use as induction or antirejection treatment observed for patients with shorter time since transplant. Of note, patients with a history of polyclonal antibody therapy had a significantly lower lymphocyte count and percentage that those without such therapy. A lymphocyte count of $0.3 \times 10^3/\mu l$ and the use of maintenance steroids were previously reported in patients readmitted to the hospital for COVID-19 early after kidney transplant.[19] It cannot be excluded that the intensity and net effect of immunosuppressive therapy play a role as potential risk factors for COVID-19, despite negative findings from a previous study.[7] There is no reliable tool that could help compare the cumulative effect of the numerous different immunosuppressive regimens currently used in SOT recipients. Nevertheless, an increased incidence of COVID-19 in OHT recipients with a short time since transplant who received triple immunosuppressive therapy may indirectly support the possible role of more potent immunosuppression as a risk factor for COVID-19 in SOT recipients. However, the higher COVID-19 morbidity rates among LTRs with the primary diagnosis of autoimmune liver disease in our study may suggest the involvement of an underlying immune deficiency or the complex immunosuppressive regimen that is typically used in these patients.

The most interesting novel finding of our study is the significant increase in blood trough levels of tacrolimus during confirmed SARS-CoV-2 infection. These increased levels were still detectable in some patients even several weeks after the diagnosis. Because tacrolimus levels in this subgroup increased abruptly by a median of 74.3% (IQR, 47.4%–109.4%) and exceeded 11 ng/ml in almost all patients, it may represent one of the major mechanisms of AKI reported during COVID-19 in SOT recipients. To date, numerous pathomechanisms of AKI during SARS-CoV-2 infection have been proposed, including direct viral tissue injury, collapsing glomerulopathy, systemic inflammation, and altered hemodynamics leading to renal ischemia.[20-22] Metabolic changes during viral infection may partly explain tissue injury leading to altered cell phenotype and function.[23] In SOT recipients, the increased calcineurin inhibitor levels also can cause AKI because of the interactions with pharmacologic treatments for SARS-CoV-2 infection.[24,25] However, none of the 23 KTRs in our study received antiviral drugs with known interaction potential. Additionally, the elevation of tacrolimus levels was similar in hospitalized and ambulatory patients with COVID-19, and only 8.7% of the patients reported diarrhea that might have increased tacrolimus exposure. Thus, one of the possible explanations is reduced tacrolimus metabolism in the liver, although there were no abnormalities in the levels of liver enzymes. This finding is in line with the most recent observations in 9 KTRs with COVID-19. In the majority of these otherwise stable KTRs, both specific ultrastructural changes in the liver caused by SARS--CoV-2[26] and elevated tacrolimus or sirolimus levels were noted.[27] Based on these results, we postulate that in order to prevent or reduce the severity of kidney injury during COVID-19, current blood levels of calcineurin inhibitors should be carefully monitored in addition to the already routine mycophenolate dose reduction or cessation according to the guidelines of the DESCARTES working group.[6]

In most COVID-19 survivors in our cohort, the graft function was maintained, including even KTRs with AKI. In the KTR group, 2.9% of patients returned to chronic dialysis therapy. Among LTRs and OHT recipients, biochemical and imaging parameters of graft function were normal during a median follow-up of 4.4 months (IQR, 2.6–6.0). In the KTR group, kidney graft function among survivors remained unchanged, which is in line with the results of other studies.[14,15]

The study has several limitations. First, data concerning the pharmacologic antiviral treatment of hospitalized patients were incomplete, so we were unable to perform a comprehensive analysis. Second, as most patients were managed on an outpatient basis, data on serum creatinine levels during the infection were limited. Therefore, we did not assess the frequency and risk factors of AKI. Third, the blood levels of mycophenolate mofetil / sodium were not routinely measured, so we could not determine whether increased mycophenolic acid levels caused diarrhea, frequently reported before and after the diagnosis of COVID-19. Finally, the 2 major study findings refer only to the KTR group, so they may not be generalized to the whole transplant population.

In conclusion, based on our experience from the first year of the COVID-19 pandemic in a cohort of SOT recipients, we suggest that the intensity of immunosuppressive therapy is associated with COVID-19–related morbidity. Our study revealed considerable disturbances in the metabolism of tacrolimus in KTRs, which could account for the worsening of kidney graft function during SARS-CoV-2 infection. Other studies showed a markedly reduced humoral response to mRNA--based COVID-19 vaccines in kidney and liver transplant recipients[28-30] as well as episodes of COVID-19 in vaccinated SOT patients.[31] Additionally, recent transplant recipients cannot be vaccinated for several months after transplant.[32] Thus, it is possible that despite global vaccination efforts, SOT recipients will remain at high risk for severe COVID-19. Our results might be useful for optimizing the clinical care of this patient population.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT AK and AW conceived the concept of the study. AK, AAK, and JM contributed to the design of the research. AK, AAK, JM, and NS-B were involved in data collection. AK, AAK, and JM analyzed the data. AK, AAK, and JM were involved in writing the manuscript draft. All authors edited and approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

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