INTRODUCTION

The ongoing pandemic of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) affected the global population heavily. Special concerns arose concerning chronic kidney disease (CKD) patients, as the meta-analysis of early data suggested that CKD was associated with severe clinical course of coronavirus disease 2019 (COVID-19). Still more close attention should be paid to kidney transplant recipients (KTRs), as their immunity is further compromised by the immunosuppression regimen. To date, several papers reported diverse symptomatology and clinical course in KTR subjects. Acute kidney graft impairment and overall mortality were high. The modification of immunosuppressive treatment varied and was related to clinical course, including discontinued administration of antimetabolite drugs and reduction of calcineurin inhibitor dose, or even immunosuppression withdrawal. Until now, there has been only limited experience concerning clinical characteristics and treatment of stable KTRs with co-occurring COVID-19 and virtually no publication concerning transplant recipients infected during the early period after transplantation.

In March and April 2020, the COVID-19 infection during the first post-transplant hospital stay was confirmed in our transplant center in 3 KTRs and in one liver transplant recipient (LTR). Following the first diagnosed case, epidemiological investigation revealed an in-hospital cluster of infection, which comprised the transplant surgical ward and operating room personnel. Patients were immediately referred to the regional hospital dedicated specifically for COVID-19 infected patients. Hereby, we report the characteristics, management, clinical course, and outcomes of these patients.

CASE SERIES

The clinical characteristics of 4 patients with COVID-19 are provided in Table 1. All patients signed their informed consent for performing the transplantation in the time of increased epidemiological risk and have had nasopharyngeal swabs performed, whose results were negative immediately before the transplant procedure. Both of the deceased donors were negatively screened for COVID-19, using nasopharyngeal swab specimens and high-resolution computed tomography (HRCT), prior to taking the final decision concerning the organ procurement in other hospitals. All patients received basiliximab as induction therapy and standard maintenance immunosuppressive regimen, including tacrolimus (TAC), mycophenolate mofetil (MMF), and steroids. The first and third referred KTRs had the organs transplanted from the same donor (from whom the liver for patient 4 was also procured). The second referred patient had undergone the transplantation 3 days earlier. All patients were operated on at the same operating block and shared the same nursing personnel thereafter. Informed consent for publication of their clinical data was obtained from the patients or their relatives.
Table 1: Clinical characteristics of transplant patients infected with SARS-CoV-2 coronavirus in the early period after transplantation

| Organ transplanted | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
|---------------------|-----------|-----------|-----------|-----------|
| Age [y]             | 61        | 24        | 42        | 52        |
| Sex                 | M         | M         | M         | M         |
| BMI [kg/m²]         | 28.4      | 22.1      | 22.6      | 20.4      |
| Dialysis vintage [mo]| 18        | 18        | 57        | -         |
| MELD score          | -         | -         | -         | 26        |
| Hypertension        | Yes       | Yes       | Yes       | No        |
| Diabetes            | Yes       | No        | No        | No        |
| Transplant No       | 1         | 1         | 1         | 1         |
| Donor age [y]       | 23        | 40        | 23        | 23        |
| HLA mismatch        | 3         | 4         | 4         | -         |
| CIT [h]             | 11.6      | 18.7      | 22.8      | 5.8       |
| SARS-Cov-2 infection diagnosis, POD | 7 | 10 | 8 | 8 |

Abbreviations: BMI, body mass index; CIT, cold ischemia time; MELD, model for end-stage liver disease; POD, post-operative day; SARS, severe acute respiratory syndrome.

### 2.1 Patient 1

A 61-year old man with the history of type 2 diabetes treated with insulin, arterial hypertension, and atrial fibrillation, underwent transplant after 18 months of hemodialysis. Before transplantation, he received TAC 5.5 mg BID, MMF 750 mg BID, and steroids in standard protocol (iv methylprednisolone during operation procedure and post-transplant day (POD) 1, then 20 mg of oral prednisone). The early graft function was excellent, and serum creatinine concentration (S_{Cr}) reached 1.1 mg/dL on POD 7. The TAC through blood level (C0) on POD 2 was 24.7 ng/mL, then on POD 5 and 7 C0 values were 9.4 and 7.1 ng/mL, respectively. On POD 6, high fever was noted up to 40°C and C-reactive protein (CRP) levels increased to 107 mg/L (normal range, 0-5 mg/L), whereas procalcitonin level was normal. No other clinical abnormalities were observed. Meropenem administration was started. The following day, he was positively tested for COVID-19. Oxygen saturation was normal. HRCT revealed mild patchy ground-glass shadows located in the upper pulmonary lobes. Thus, MMF was ceased. During the following weeks, his general condition was still good, despite high CRP levels (160 mg/L on POD 12), so levofloxacin was started. He did not receive antiviral medications. Blood and urine cultures were negative, and the body temperature was normal. S_{Cr} was stable (0.8 mg/dL). On POD 15, the body temperature increased to 38.2°C. On the following day, his clinical condition deteriorated rapidly, S_{Cr} rose to 1.8 mg/dL and systolic blood pressure lowered to 100 mm Hg with tachycardia. CRP level increased to 280 mg/L and procalcitonin level to 0.26 ng/mL. In the abdominal CT scan, the signs of perigraft fluid collection and ileus were revealed. During the preparation for surgery, the patient died suddenly after cardiac arrest.

### 2.2 Patient 2

A 24-year old man with a history of vesico-ureteral reflux, right-side nephrectomy, and arterial hypertension, diagnosed 5 years before hemodialysis treatment, received TAC 6 mg BID, MMF 750 mg BID with steroids at transplantation. Immediately, S_{Cr} started to decrease and reached 2.7 mg/dL on POD 11. TAC C0 on POD 2 was 5.8 mg/mL, then on POD 4 and 7 was 8.5 and 9.9 mg/mL, respectively. The maximum CRP level was noted on POD 4 (62.5 mg/L) and then decreased to 8.9 mg/L on POD 11, and patient was to be discharged. However, as COVID-19 infection was diagnosed in patient 1, the referred patient has also been tested and the result was positive. As the clinical condition was excellent, the decision concerning HRCT has been delayed. Because of non-optimal kidney graft function at that moment and the lack of information about MMF blood level, due to the temporary reference laboratory shutdown caused by COVID-19 epidemic, MMF was maintained at a reduced dose (250 mg BID). During the 35-day stay at reference infectious hospital, no clinical or biochemical signs of infection were observed. The consecutive TAC C0 results were between 8 and 10 ng/mL. Prednisone dose was reduced to 7.5 mg/d. The patient did not receive antiviral medications. His swab test was positive on POD 24, 31, and 38 and negative on POD 45 and 47, and then, he was discharged home, with S_{Cr} of 1.5 mg/dL.

### 2.3 Patient 3

A 42-year old man had been diagnosed with arterial hypertension and CKD at advanced stage, its detailed cause was not clarified. During hemodialysis, autoimmunehepatic hepatitis was diagnosed with clinical manifestations of pleural fluid and ascites. It was successfully treated with methylprednisolone, and the patient was put on the waiting list. During transplantation, he received TAC 7 mg BID, MMF 750 mg BID, and steroids. After the surgery, S_{Cr} decreased, reaching 2.0 mg/dL on POD 9. The TAC C0 on POD 1 was >30 mg/mL, the dose was then adjusted, and the consecutive C0 were 17.6 and 8.0 mg/mL, respectively. The maximum CRP level was noted on POD 9 (23.7 mg/L), when COVID-19 infection was confirmed. MMF was maintained at a reduced dose (250 mg BID). HRCT was not performed. During the 23-day stay at reference hospital, no clinical or biochemical signs of infection were observed, despite subsequent TAC levels of 17.5 and 23.7 mg/mL, which required further dose reduction to 1 mg BID. Prednisone dose was reduced to 7.5 mg/d. The patient did not receive antiviral medication. His swab test was positive on POD 21 and negative on POD 28 and 29, and then, he was discharged home with S_{Cr} of 1.4 mg/dL.
2.4 | Patient 4

A 53-year old man with the diagnosis of primary sclerosing cholangitis and ulcerative colitis was referred for liver transplantation 12 months earlier. During wait-listing, his MELD score increased steadily from 8 to 26 before transplantation. He had no history of variceal hemorrhage, encephalopathy, or ascites. His kidney function was normal. The patient received TAC 1.5 mg BID, MMF 250 mg BID, and steroids, with 200 mg of fluconazole as standard antifungal prophylaxis. After the surgery, the patient was admitted to intensive care unit for 4 days. TAC C0 on POD 2 and 7 was 6.7 and 6.0 ng/mL, respectively. The clinical course was not complicated. After positive screening for COVID-19, despite the primary cause of liver disease, MMF treatment was discontinued. During the 14-day stay at reference infectious hospital, no clinical or biochemical signs of infection were observed. Procalcitonin and CRP levels were low. Liver function tests improved and on the day of discharge were as follows: bilirubin—2.8 mg/dL, AST—18 IU/L, ALT—55 IU/L, GGT—101 IU/L, and INR—1.0. The consecutive TAC C0 results were 5.1 and 7.4 ng/mL. Prednisone dosage was reduced to 10 mg. His swab tests were negative on POD 22 and 23, ultimately he was discharged home.

3 | DISCUSSION

In this report, we present our experience with COVID-19 infection, diagnosed in 4 solid organ recipients during early post-transplant period. Importantly, SARS-CoV-2 pandemic rapidly changed the everyday medical care of CKD patients, including transplant programs. The limited accuracy of PCR tests was raised as a potential hazard, as COVID-19 could be not detected both in donors and waitlisted recipients who are asymptomatic. Another diagnostic procedure, HRCT, appeared to be not applicable to potential organ transplant recipients during the final pre-transplant decision making period. Additionally, the time required to swab test the patient would increase the cold ischemia time and can therefore negatively affect the outcomes. Moreover, the issue of virus transmission by asymptomatic or pre-symptomatic hospital staff members has recently become evident. Finally, the intensive post-transplant immunosuppression regimens, including induction therapy, could be harmful and hazardous in virus-infected patients.

On the other hand, as the pandemic appears to continue and extend in time, the long-term suspension of kidney transplant programs will also have inevitable negative effect on CKD patient outcome. Hence, according to the specific guidelines of the Polish Transplantation Coordinating Center, within a month we performed one liver and 8 kidney transplantations, avoiding patients who need polyclonal antibody induction. Unexpectedly, a transplant surgeon who had operated on patient 1 earlier presented with typical symptoms and was positively tested for COVID-19. The subsequent systematic screening revealed further cases of COVID-19 infection, involving 4 solid organ recipients and 12 staff members. However, the exact way of infection transmission to the referred patients (nosocomial or intraoperative) was not definitely confirmed and might not be uniform in those patients.

As regards the patient with fatal outcome, his clinical course after diagnosing COVID-19 was generally stable, despite high CRP levels, and it deteriorated rapidly a day before his death, which was preceded by apparent symptoms of sepsis. The probable source of septic infection was a perigraft structure (fluid?) with subsequent ileus detected in CT scan, and hence, the same day reoperation was planned. It is worth to noting that the patient, except for the obvious risk factor, that is, contact with the asymptomatic virus-infected doctor, had several potential co-existing risk factors, that is, advanced age, diabetes, and overweight, which may negatively influence his prognosis in case of any post-transplant infectious complications. Indeed, they presented a serious hazard, despite optimal kidney graft functioning, mild initial symptoms, and reduction of immunosuppressive regimen. In our opinion, the patient has died due to other post-transplant complications leading to septic shock, which were not directly related to COVID-19 infection. In all of our virus-positive KTRs, we aimed to maintain the tacrolimus troughs around 7-8 ng/mL (in LTR even 5-7 ng/mL) and minimized prednisone doses to 7.5-10 mg/d before the end of the third post-transplant week. It is worth noting that none of those patients was highly immunized and all received basiliximab induction, and thus, we were able to realize such a scenario. Steroids were not escalated, as was suggested by some authors, mainly due to good clinical condition of our patients. Interestingly, the prolonged viral shedding time observed in patient 2 may be attributed to immunosuppressive regimen. As recent studies describing the inpatient care of COVID-19 in KTRs differ widely in disease severity, time from transplantation, and the immunosuppression modifications, it is important to collect more data about the treatment and outcome of this specific population of patients. We would like to conclude that, in spite of the fact that patients immediately after solid organ transplantation are among the group of high risk of complications and mortality related to the COVID-19 infection, our results may suggest a relatively low symptomatic clinical course and positive outcome of this disease.

CONFLICT OF INTEREST

All authors have no conflict of interest to disclose.

AUTHORS CONTRIBUTION

AK participated in study concept, data curation, and writing of the original manuscript. RK participated in study concept and writing the paper. SD participated in data curation. AW critically revised the manuscript.

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