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Global Effects of SARS-CoV-2 Era on Kidney Transplantation Activities: Analysis of WHO Data

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ABSTRACT

Background. Uncertainty raises questions in kidney transplant during the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic regarding the recipient, the donor, and health care professionals. The pandemic not only has disrupted kidney transplanted patients but also has influenced transplant systems, donation chains, and timely and safe transplant surgeries. In the present study, we aimed to explore the global effects of the SARS-CoV-2 pandemic on kidney transplant.

Methods. We collected transplantation statistics and SARS-CoV-2 pandemic data from the World Health Organization website on June 15, 2021. Spearman correlation analysis was applied to assess the strength of a monotonic relationship among quantitative variables. We also demonstrated the clinical characteristics of our kidney recipients with SARS-CoV-2 infection.

Results. Comparison of the mean of global kidney transplantation statistics between 2010 and 2019 with 2020 statistics showed a significant decrease in kidney transplant from living donors ($P < .001$). From the beginning of the pandemic to June 15, 2021, 1 of the 43 kidney transplant patients we treated in our clinic died of SARS-CoV-2 infection after discharge. Two of the patients we transplanted and saw in follow-up before the pandemic died of SARS-CoV-2 infection.

Conclusion. While the overall kidney transplant numbers have increased in the year to date, kidney transplants decreased drastically at the onset of the pandemic.

THE emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, which spread from Wuhan, China, to the rest of the world, has negatively influenced countries' health systems worldwide [1], causing over 173 million cases and 3.73 million deaths as of June 2021 [2]. The spectrum of SARS-CoV-2 infection differs from being asymptomatic to acute respiratory distress syndrome and multi-organ failure, which are associated with increased morbidity and mortality [1].

The potential result of SARS-CoV-2 on immunosuppressive therapy required in solid organ transplant patients is not entirely understood but is possibly crucial for host inflammatory responses and appear to constitute a significant cause of associated organ damage [3]. Most of the studies published so far do not cover immunosuppressed solid organ transplant cases or describe features of immunosuppressive therapy-related risks.

This uncertainty raises questions on solid organ transplant during the SARS-CoV-2 pandemic regarding the recipient, the donor, and health care professionals. Statistics revealed a significant drop in deceased organ transplant activities in France and the United States (90.6% and 51.1%, respectively) [4], and the total number of all solid organ transplants showed a drop of nearly 75% per month in the Netherlands in the first 3 months of 2020 [5]. Thus, the emerging pandemic has significantly limited transplantation activities globally due to increased infection threats in immunosuppressed solid organ recipients.

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In this study, our primary aim was to express the global impact of the pandemic on kidney transplantation by highlighting its adverse outcomes. We also discuss how the most active countries in kidney transplantation were affected by the SARS-CoV-2 pandemic.

MATERIALS AND METHODS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Data collection: transplantation statistics

We collected transplantation statistics of 113 countries from the Global Observatory on Donation and Transplantation (<http://www.transplant-observatory.org>), a World Health Organization (WHO) Collaborating Center on Donation and Transplantation.

Obtaining data on the SARS-CoV-2 pandemic

We received data on the SARS-CoV-2 pandemic from the WHO website (<https://covid19.who.int/table>) on June 15, 2021. The SARS-CoV-2 data of the top 10 countries in kidney transplantation statistics were obtained by entering country names one by one into the search engine of the WHO Coronavirus Dashboard webpage (<https://covid19.who.int/table>).

Management of kidney receipt and donor candidates at our institution

Following the completion of the preoperative tests [6], the receipt and donor candidates were hospitalized 1 week before surgery after 2 consecutive and negative SARS-CoV-2 polymerase chain reaction (PCR) test results. The patients stayed in the clinic for 1 week before the operation and did not go out of the clinic. During this period, patients' relatives were not admitted to the clinic, and patient-patient relative meetings were held via video calls. If the third PCR test result, administered 24 hours before the surgery, was negative, the patient underwent surgery. The same strict rules continued to be applied after the surgery. After discharge, the recipient patient was recommended not to accept visitors at home, not to use public transportation, to be very careful about hand hygiene, to use an N-95 mask if having to meet with someone else, to come to the control visits early in the morning when the hospital's patient density is less, and to comply with these rules for 6 months.

Management of health care personnel

Unvaccinated health care personnel never contacted patients who had undergone transplant surgery or were candidates for transplant (receipt and donor). In addition, all health care personnel caring for transplant patients used N-95 masks and paid maximum attention to hand hygiene rules. Symptomatic health care personnel were allowed to return to practice if the results of 2 back-to-back SARS-CoV-2 PCR tests were negative.

Immunosuppressant therapy protocol applied in our institution

The immunosuppressant therapy was applied according to protocols at our institution [7].

Statistical analysis

We used the STATA version 17 statistical software (StataCorp, College Station, TX) to assess the data. To evaluate data, we applied descriptive statistical techniques (mean, standard deviation, median, first and third quadrants, frequency, percentage, minimum, and maximum). Spearman correlation analysis was applied to assess the strength of a monotonic relationship among quantitative variables [8]. Statistical significance was set at $p < .05$.

RESULTS

Global results

A total of 37,000 kidney transplants from living donors and 60,065 kidney transplants from deceased donors were performed in 2019, before the SARS-CoV-2 era. Compared with 2019, during 2020, there was a decrease of 18.5% in transplants from deceased donors and a decrease of 52.5% in transplants from living donors. The kidney transplant statistics for the years 2010-2020 are shown in Fig 1.

From 2019 to 2020, 10 of 133 countries (United States, Thailand, Denmark, Malaysia, Latvia, Slovenia, Estonia, Republic of Moldova, Iceland, Trinidad and Tobago) increased kidney transplants from a deceased donor. The increase in the number of countries in terms of kidney transplants from a deceased donor from 2018 to 2019 was 39.

Furthermore, from 2019 to 2020, 12 of 133 countries (People's Republic of China, Thailand, Israel, Finland, Ireland, Greece, Ecuador, Malaysia, Bolivia, Estonia, Mongolia, Trinidad, and Tobago) increased the number of kidney transplants from a living donor. The increase in the number of countries in terms of kidney transplants from living donors from 2018 to 2019 was 40.

In the comparison of the mean of global kidney transplantation statistics between 2010 and 2019 with 2020 statistics, there was a significant decrease in kidney transplants from living donors (46.8%) ($P < .001$), and a slight increase in deceased donor numbers was observed (2.3%) ($P > .05$).

If we analyze the data of the top 10 countries that have performed the most kidney transplant surgeries in the last 10 years, there was a low correlation between the percentage change in transplants from deceased kidney donors and the number of SARS-CoV-2 cases and the number of deaths ($r = 0.28$ and $P > .05$; $r = 0.26$ and $P > .05$, respectively). Also, there was no correlation between the percentage change in transplants from living kidney donors and the number of SARS-CoV-2 cases. There was a moderate correlation between the percentage change in transplants from living kidney donors and the number of deaths ($r = 0.04$ and $P > .05$; $r = 0.52$ and $P > .05$, respectively) (Table 1).

Our institutional results

Between March 2020 and July 2021, 43 kidney transplants were performed at our institution. During this period, the Turkish Ministry of Health held all kidney transplant surgeries between April and May 2020 (Fig 2). In November 2020, 3 of our kidney transplant patients died (1 patient had transplant surgery

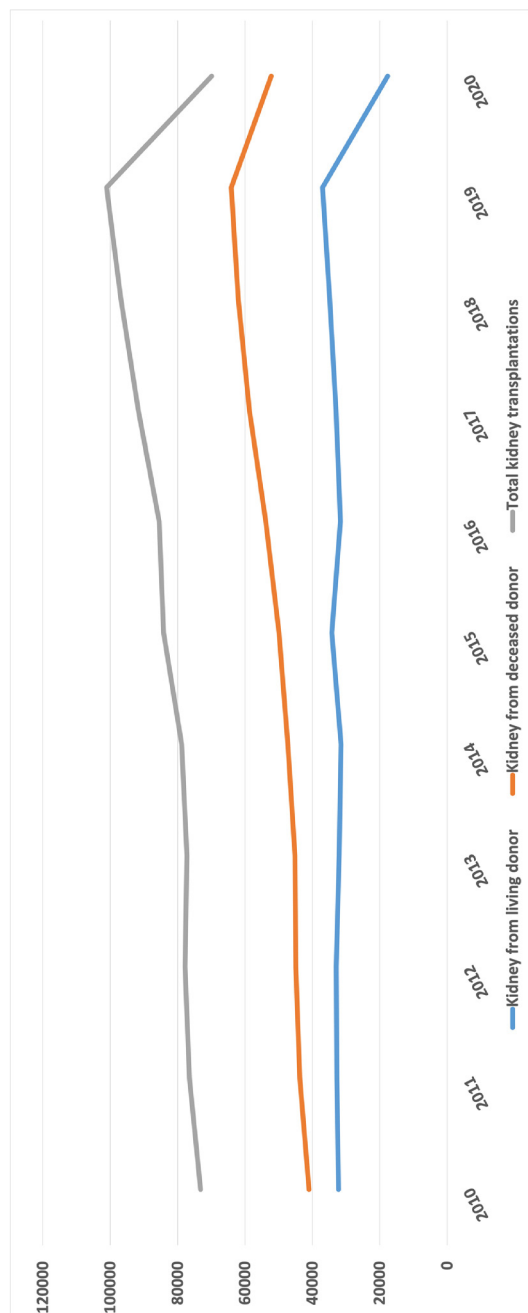


Fig 1. Global kidney transplant statistics for the years 2010-2020.

during the SARS-CoV-2 pandemic, and the other 2 patients were operated on before the pandemic) consecutively due to SARS-CoV-2 infection, so we suspended transplant surgeries from December 2020 to February 2021 (Table 2). After the pandemic began, one nurse on the transplantation team became infected with SARS-CoV-2, and none of the medical doctors on the transplantation team became infected. Symptomatic health care personnel were checked with PCR testing and did not return to duty until 2 subsequent negative PCR test results.

DISCUSSION

Herein, we report global trends in kidney transplantation during the SARS-CoV-2 pandemic. The pandemic has been negatively influencing kidney transplantation activities worldwide.

The pandemic has not only disrupted kidney transplant patients but has also influenced transplantation systems, donation chains, and timely and secure transplant surgeries [9]. As the SARS-CoV-2 virus outbreak progresses, transplantation centers meet various difficulties that have pressured a steep decline in kidney transplants, including living or deceased donor transplants [10]. In addition to these obstacles, because kidney transplant recipients are immunologically vulnerable and have a higher mortality risk from SARS-CoV-2 infection than the general population [11], medical professionals have become hesitant about the solid organ transplant process during the pandemic, and this hesitation has increased the decline in global transplantation activities.

Compared with 2019, there was a decrease of 18.5% in transplants from deceased donors and a decrease of 52.5% in transplants from living donors during the pandemic. The drop in kidney transplantation numbers has many causes, including limited intensive care unit and hospital beds, reduced new transplant referrals and listing, limited operating room availability, and commercial flight cancellations (Fig 3). In our clinic, although the monthly number of transplants was 5.4 before the pandemic, in line with global pandemic trends, our number of transplants decreased to 0 in some months after the pandemic. The first reason for this decline was the temporary restriction of kidney transplantation activities by the Turkish Ministry of Health. The second reason was the death of 3 of our patients due to SARS-CoV-2 infection and our team's temporary interruption of transplant surgery decision. The purpose of this brief pause was to review whether there is a deficiency in our SARS-CoV-2 precautions algorithm that we apply in our clinic. However, 2 of 3 patients who experienced SARS-CoV-2 infection died 718 days and 632 days after the operation, respectively. The third patient was diagnosed with SARS-CoV-2 twenty-five days after transplant; however, his story showed that he did not comply with the restriction rules we recommend to transplant patients. As a result, we concluded that there was no deficiency in the clinical algorithm we determined.

The wait-list time for people with end-stage kidney disease ranges between 3 and 5 years, and numerous determinants influence this waiting time. Additionally, patients with an elevated panel reactive antibody panel also have a more limited chance of finding a matching kidney due to more powerful

Table 1. Most Active First 10 Countries in Terms of Kidney Transplants and SARS-CoV-2 Statistics

	No. of Transplants From Deceased Donors in 2019	No. of Transplants From Deceased Donors in 2020	% Change in Transplants From Deceased Donors From 2019 to 2020	No. of Transplants From Living Donors in 2019	No. of Transplants From Living Donors in 2020	% Change in Transplants From Living Donors From 2019 to 2020	Total Cases	Total Deaths
USA	17,406	18,410	+5.7	6,867	5,234	-23.8	35,487,490	628,098
People's Republic of China	10,389	9,399	-9.5	1,375	1,638	+19.1	92,811	4,636
India	5,227	No data available	-	8,613	No data available	-	31,528,114	422,695
Brazil	5,227	4,385	-16.1	1,071	445	-59	19,797,516	553,272
France	3,133	2,205	-29.6	510	390	-23.5	6,054,049	111,735
UK	2,627	2,009	-23.5	1,022	558	-45.4	5,770,928	129,430
Turkey	1,808	249	-86.2	3,055	2,249	-26.3	5,660,469	51,124
Spain	3,088	2,443	-20.9	335	259	-22.6	4,395,602	81,396
Mexico	926	283	-69.4	2,050	630	-69.3	2,790,874	239,616

*Mean of kidney transplant numbers between 2010 and 2020.

immunoreactivity and thus have increased risk of rejection. A small number of transplant centers have reported patients with high panel reactive antibody panels who have missed the chance to receive a kidney because they had a positive SARS-CoV-2 test result on the day of the surgery. Unfortunately, those who continue on the waiting list need kidney replacement treatment. For these patients, 3 times per week, hemodialysis is the mainstay of end-stage kidney disease therapy [9]. These patients remain indoors for 4 hours in frequent contact with other patients and health care staff, increasing their risk of acquiring SARS-CoV-2. Morbidity and mortality rates in patients who require hemodialysis are notably higher. In April 2020, the mortality of the patients on the kidney transplant waiting list multiplied by 43.0% based on the United Network for Organ Sharing data [12].

The common belief among health professionals was to reduce kidney transplant procedures, selectively suspend transplants, and treat patients with end-stage kidney disease in SARS-CoV-2-free units [13]. However, opinions have considerably varied between health care professionals, considering the absence of consensus on solid organ transplant since the pandemic's beginning. Additionally, transplantation professionals have a higher chance of contamination, as they might travel to high-incidence areas when retrieving organs for transplant. Also, some countries do not have a centralized organ retrieval procedure, and transplantation teams travel outside their regions to procure organs. A "traveling organs" system, such as the National Organ Retrieval System in the United Kingdom or Eurotransplant in Central Europe, assists in avoiding transplant teams traveling from low-to high-incidence areas and restrain the spread within medical professionals [14]. Despite all these hesitations, we believe that kidney transplant can be performed safely by minimizing the risk of contamination. The kidney transplant team should reevaluate receipt candidate patients on the waiting list, and urgent or pre-emptive patients with end-stage kidney disease should be prioritized. A multidisciplinary medical team should consider the risks and advantages for both donor and receipt candidates in the context of SARS-CoV-2 [15].

Transplant centers should create SARS-CoV-2-secure areas for pretransplant evaluation and post-transplant follow-up for both donors and receipts. Moreover, these centers must have the opportunity of rapid turnaround testing for SARS-CoV-2. Also, lessening face-to-face contact with the patients is crucial. Before hospital admission, a medical interview should be completed using online communication to guarantee that patients have no SARS-CoV-2 signs [16].

For receipts with overall good general health and stable kidney functions, follow-up visits should be limited, and, if possible, an online, face-to-face meeting is suggested [15,17,18]. Online prescription and pharmacy deliveries to home are preferable. Medical professionals should support stable receipts to give follow-up blood tests at home [19]. If recipients or donors are obliged to do face-to-face interviews, the contamination risks of SARS-CoV-2 should be minimized by reducing the number of accompanying people. Public transportation use should be avoided as well [15]. Also, reducing medical appointment waiting time is critical. Medical professionals must refer

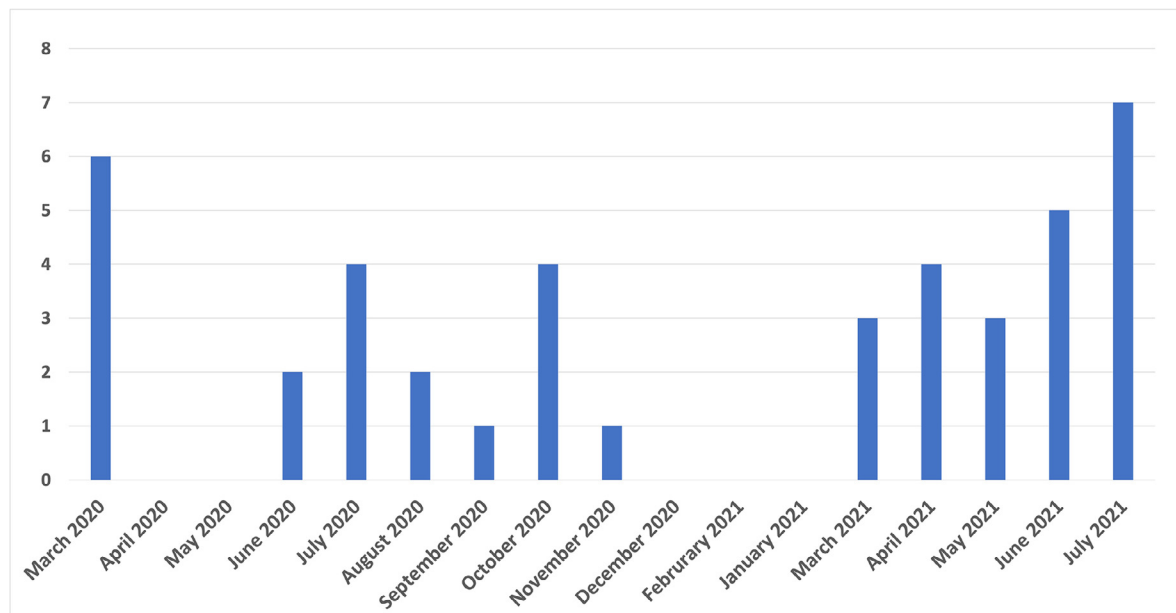


Fig 2. Monthly kidney transplant numbers at our institution during the pandemic.

Table 2. Clinical Characteristics of Our Patients Who Died Due to SARS-CoV-2 infection

	Case 1	Case 2	Case 3
Age, y	57	43	64
Sex, M/F	Male	Male	Male
Height, cm	172	168	162
Weight, kg	94	101	58
BMI, kg/m ²	31.7	35.8	22.2
Family history of chronic kidney disease	No	No	No
Smoker	No	No	No
Ex-smoker	No	No	Yes
SARS-CoV-2 infection during hospitalization, yes/no	No	No	No
SARS-CoV-2 infection after discharge, yes/no	Yes	Yes	Yes
SARS-CoV-2 positive day after transplant, d	718	25	632
Hospitalization time, d	19	21	24
Intensive care unit time, d	17	15	19
Mechanical ventilation time, d	17	15	19
Comorbid conditions			
Diabetes mellitus			
Diabetes mellitus + hypertension	Yes	Yes	Yes
Diabetes mellitus + hypertension + coronary artery disease			
Hypertension			
Hypertension + coronary artery disease			
Preoperative creatinine, mg/dL	6.53	8.7	4.9
Postoperative day 1 creatinine, mg/dL	2.21	4.8	1.7
Postoperative day 7 creatinine, mg/dL	1.18	1.9	1.1
Postoperative day 30 creatinine, mg/dL	1.06	2.4	0.7
Postoperative day 180 creatinine, mg/dL	1.19		0.7
Previous hemodialysis, mo	120	3	84
Previous CAPD, mo			
Previous blood transfusion, units	2	0	0
Last immunosuppressive therapy before SARS-CoV-2 infection	5 mg steroid TAC* 1.5 + 1.5 mg MPA* 720 + 360 mg	5 mg steroid TAC* 2.5 + 2 mg MPA* 720 + 720 mg	5 mg steroid TAC* 2.0 + 2 mg MPA* 720 + 720 mg

*MPA, mycophenolate mofetil; TAC, tacrolimus.

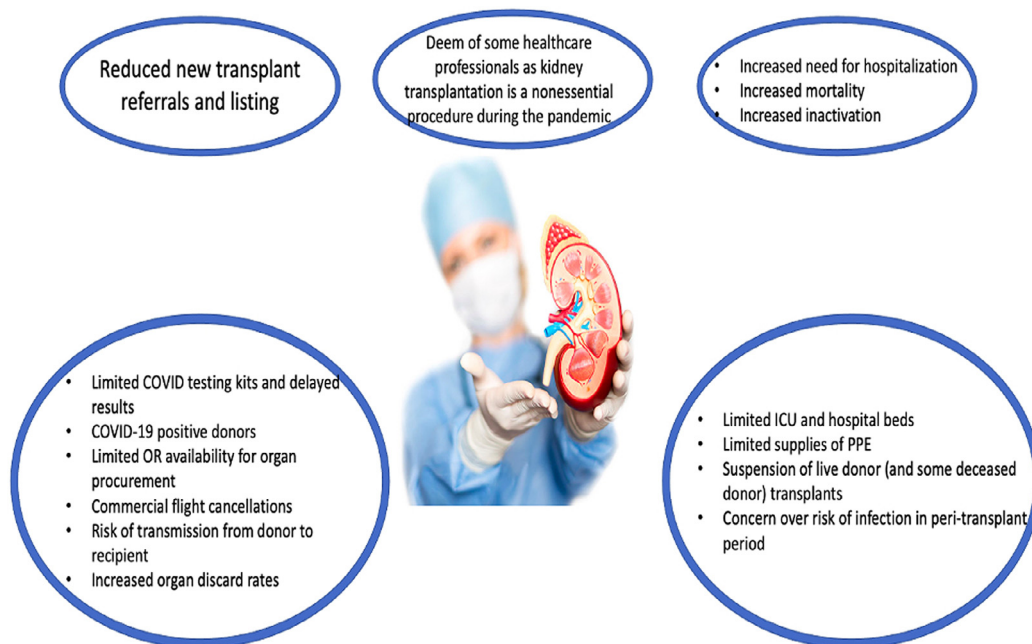


Fig 3. Factors affecting kidney transplant rates during the SARS-CoV-2 pandemic.

ICU: intensive care unit; PPE: personal protective equipment. *Due to SARS-CoV-2 infection

the recipient or donor patients to the infectious disease department if they show signs of SARS-CoV-2 infection; these patients should not reach the transplant center [20].

So far, several nations have announced a heterogeneous distribution of the SARS-CoV-2 pandemic across their countries, with foci of the high frequency of contagion producing significant confusion in social life and health care systems. Recent research by Loupy et al showed that transplant procedures decreased in public and private health care institutions, but to a differing extent (91% in France and 51% in the United States) [4]. Michaels et al proposed redistributing cases on the organ waiting list in endemic areas to less affected regions [3]. Such a strategy gives the benefit of not penalizing patients on the waiting list just because of their geographic distribution; however, in a quickly shifting scenario, less affected regions may need to keep their sources ready for potential unexpected increments in hospital bed demand, or this demand cannot be afforded, which may cause possible contamination of the less affected region.

The European Renal Association–European Dialysis and Transplant Association data suggested that the rate of SARS-CoV-2 infection in patients with kidney replacement therapy was low. Nevertheless, as 2.9% of the dialysis patients and 1.4% kidney graft recipients were infected by SARS-CoV-2, and this infection seems to have a more significant influence on the patients receiving kidney replacement therapy than on the general population [21], which may be due to their older age or

perhaps the consequence of more frequent testing. However, data of SARS-CoV-2 cases were obtained from population-based registries; these data may not describe all dialysis patients infected with SARS-CoV-2. Most infected people do not show any symptoms or have mild symptoms and do not need hospitalization, possibly not even examined by a general practitioner. Additionally, the majority of the patients may not have been tested and may therefore have remained undiagnosed. The ability of specific countries, such as Germany and particular regions in the United States, to maintain transplantation numbers despite the necessity of controlling the SARS-CoV-2 pandemic shows an essential model for coming waves of SARS-CoV-2 infection. Moreover, Belgium and Italy showed strong efforts to maintain transplantation numbers, notwithstanding the higher number of deaths per 1 million population. Notably, the SARS-CoV-2 pandemic might spread to different regions to substantially various degrees. Producing autonomy to individual hospital systems to adapt to specific conditions could facilitate lifesaving procedures such as transplant to proceed, even as other vital restrictions, such as limiting travel or closing non-essential commercial businesses, are imposed.

Transplant surgeons have encountered different epidemics/pandemics. The case report of Al Ghamdi et al, published in 2014, during the Middle East respiratory syndrome (MERS)-CoV outbreak, stated that solid organ recipients potentially increase the risk of viral transmission to contacts, including health care professionals, due to immunosuppression. The authors say that although a few

modifications to the transplant program were established in response to the MERS-CoV outbreak, transplant procedures were eventually suspended during the epidemic [22]. In Canada, in 2003, during the SARS epidemic, all programs in Toronto were temporarily suspended. Before restarting the transplant program, a SARS screening program was initiated due to the risk of SARS virus transmission from undiagnosed donors [23]. Chui et al reported that throughout the 2003 SARS epidemic in Hong Kong, no liver transplant surgeries were performed, as the intensive care unit was assigned to the care of patients with severe SARS-CoV. The authors remind us that “the SARS outbreak demonstrated the vulnerability of an organ transplantation service” [24]. While nearly associated with SARS-CoV and MERS-CoV, the mortality related to SARS-CoV-2 may be lower than reported. However, caution is still needed, as we do not yet know the full impact of the SARS-CoV-2 infection as it spreads to more diverse populations.

Limitations of the study

The most critical limitation of this study is the inability to fully access health data for all countries. Although the WHO clearly presents all the statistics, it is noteworthy that the number of cases in some countries is extremely low compared with their general population. Notably, our findings are restricted to a short follow-up time, and long-term observations are needed to better clarify the outcome of kidney transplant during the SARS-CoV-2 pandemic.

CONCLUSIONS

SARS-CoV-2 pandemic has direct and indirect impacts on kidney transplant centers. This report outlined global trends in kidney transplants throughout the SARS-CoV-2 outbreak. While the overall kidney transplantation numbers have increased in the year to date, kidney transplants decreased drastically at the onset of the pandemic. Although there is no single, globally accepted solution, we believe delaying or halting kidney transplants is not a reliable option for patients with end-stage renal disease. Because they still need lifesaving dialysis during the SARS-CoV-2 pandemic, these vulnerable patients are unable to practice social distancing rules and must travel to dialysis facilities. Therefore, we should carefully consider the risks and advantages of pursuing or postponing kidney transplant, considering immediate medical circumstances.

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