

ORIGINAL ARTICLE

Kidney transplantation in the time of COVID-19: Dilemmas, experiences, and perspectives

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Abstract

Introduction: Hospital do Rim is a high-volume kidney transplant (KT) center located in São Paulo, a city with 12.2 million inhabitants. Over the last 18 years, we performed 11 436 KT, 70% of which from deceased donors. To mitigate the effects of reduction in the number of transplants on the waiting list, sequential measures were implemented when COVID-19 was declared pandemic.

Methods: The first step was to provide SARS-COV-2 RT-PCR testing for all symptomatic employees and patients and the compulsory use of personal protective equipment in the hospital facilities. Living donor KT were postponed, and all deceased donors and recipients were tested before the transplantation. The immunosuppressive protocols were maintained, and telehealth strategies were developed.

Results: Among the 1013 employees, there were 214 cases of COVID-19, nine required ward hospitalization, and no deaths occurred. In 26%, the probable source of contamination was occupational. From the first patient diagnosed with COVID-19 in 03/20/2020 till 10/21/2020, 523 deceased KT were performed, a 21% increase compared with 2019, with no confirmed donor-derived SARS-CoV-2 infection. Four patients were transplanted with a positive pretransplant SARS-CoV-2 test, but none of them developed the disease. Overall, of 11 875 KT followed in our center, 674 developed COVID-19. Among the hospitalized, 53% required mechanical ventilation, and 45% required hemodialysis. Their overall mortality rate was 27.5%.

Conclusion: This experience shows the challenges that transplant centers faced as the pandemic unfolded and illustrates the effectiveness of the sequential measures implemented to provide a safe environment for transplantation.

KEYWORDS

COVID-19, kidney transplant, strategic planning

1 | INTRODUCTION

On March 11, 2020, roughly 3 months after the first confirmed case in Hubei province, China, coronavirus disease (COVID-19) caused by severe acute respiratory syndrome virus (SARS-CoV-2) was declared a pandemic by the World Health Organization.¹ In Brazil, the first confirmed case was registered on February 26 in São Paulo. On March 16, social distancing measures were adopted, with schools and offices closed, followed by bars and restaurants. The first death occurred on March 17.

Based on the early developments in the European region, it was possible to anticipate the significant impact that the pandemic would have in the local health-care system and, ultimately, in the care of patients with chronic kidney disease. According to the data from the Brazilian Dialysis Census, there are currently 133464 patients on chronic dialysis treatment, with an average annual increase of 5587 patients in the last 10 years.² In 2019, there were 25163 were active in the waiting list for a kidney transplant. Of them, 13194 were newly listings, and 6283 eventually received a kidney transplant.³

The metropolitan region of São Paulo has around 12.2 million inhabitants and over 9000 patients on the waiting list for a kidney transplant. Hospital do Rim is a high-volume kidney transplant center located in São Paulo. During the last 18 years, we performed 11436 kidney transplants, an average of 70 kidney transplants per month, 70% of which from deceased donors.⁴ The present analysis describes the sequential coordinated measures and outcomes that were gradually implemented and perfected to mitigate the effects of the pandemic on organ donation and transplantation.

2 | METHODS

This is an ongoing single-center observational prospective study. It describes the timelines and details of the contingency plan instituted in our center to reduce the negative impact of the COVID-19 pandemic on the transplant volume and quality. The outcome measures were SARS-CoV-2 infection rates and outcomes among employees and among patients either receiving a kidney transplant amid the pandemic or on long-term follow-up. This analysis involves data obtained from 01/13/2020 to 10/21/2020. This study was approved by the local ethics committee (CAEE 35 321 020.9.0000.8098). Informed consent was obtained from all employees and patients, but waiver was granted for patients who died in other hospital.

3 | RESULTS

3.1 | Development of the COVID-19 contingency plan

On January 13, 2020, the institution established the COVID-19 managing committee and started to disseminate pedagogical actions on

concepts, forms of contamination, and institutional and community behavior measures related to avoid virus spreading among employees and patients. The usual consent form, obtained before the kidney transplant, was reviewed in order to incorporate information regarding coronavirus.

The first and decisive step was taken on March 16, with SARS-CoV-2 real-time polymerase chain-based (RT-PCR) testing for all symptomatic employees and patients, with test results available within 24 h. In parallel, personal protective equipment was made available for employees and patients, for compulsory use whenever within the hospital facilities, along with thorough temperature and symptoms screening at the entrances of the building. Asymptomatic employees with known positive contacts remained isolated for a period recommended by the Brazilian Ministry of Health and did not undergo testing. If any suspicious symptoms developed, that employee was subjected to RT-PCR.

Elective living donor kidney transplants were postponed since March 28, and all deceased donors were tested for SARS-CoV-2 infection before organ recovery since April 6. No organ was recovered from donors before the RT-PCR result. In the face of a positive result, organ harvesting was aborted, and the potential deceased donor was discarded. A similar screening strategy was implemented for all potential recipients since April 20, but not until June 12, we were able to obtain the test result before the transplant surgery. We decided to maintain our immunosuppressive protocols, based on a single 3 mg/kg dose of antithymocyte globulin induction followed by tacrolimus, prednisone, and azathioprine/mycophenolate. In parallel, a centralized admission unit, previously prepared to receive patients with suspected contagious respiratory conditions (tuberculosis, H1N1, etc), was designated for kidney transplant recipients with suspected COVID-19, and all patients requiring elective admissions for other complications were tested for SARS-CoV-2, regardless of symptoms. Telehealth strategies were developed to educate, evaluate, and assist all kidney transplant recipients in follow-up, reducing the number of in-person outpatient visits.

3.2 | COVID-19 among employees

There were 220 (22%) out of 1013 employees diagnosed with COVID-19 from the 03/08/2020 to 10/21/2020 (Figure 1). Of them, 214 (97%) were confirmed by RT-PCR in nasopharyngeal sample, and six cases had negative RT-PCR but respiratory symptoms, positive epidemiology, and chest tomography scan with abnormal findings compatible with viral pneumonia. In 56 (26%), the probable source of contamination was occupational at our institution, mostly during the first weeks of the pandemic (Figure 2). The median age (IQR) of the individuals was 37 (30-43) years; 68 (31%) had overweight and 32 (15%) were obese; hypertension and diabetes were present in 15 (7%) and 3 (1.4%) individuals, respectively. The predominant symptomatology was headache (68%), myalgia (67%), cough (57%), and fever (46%). Nine required hospitalization

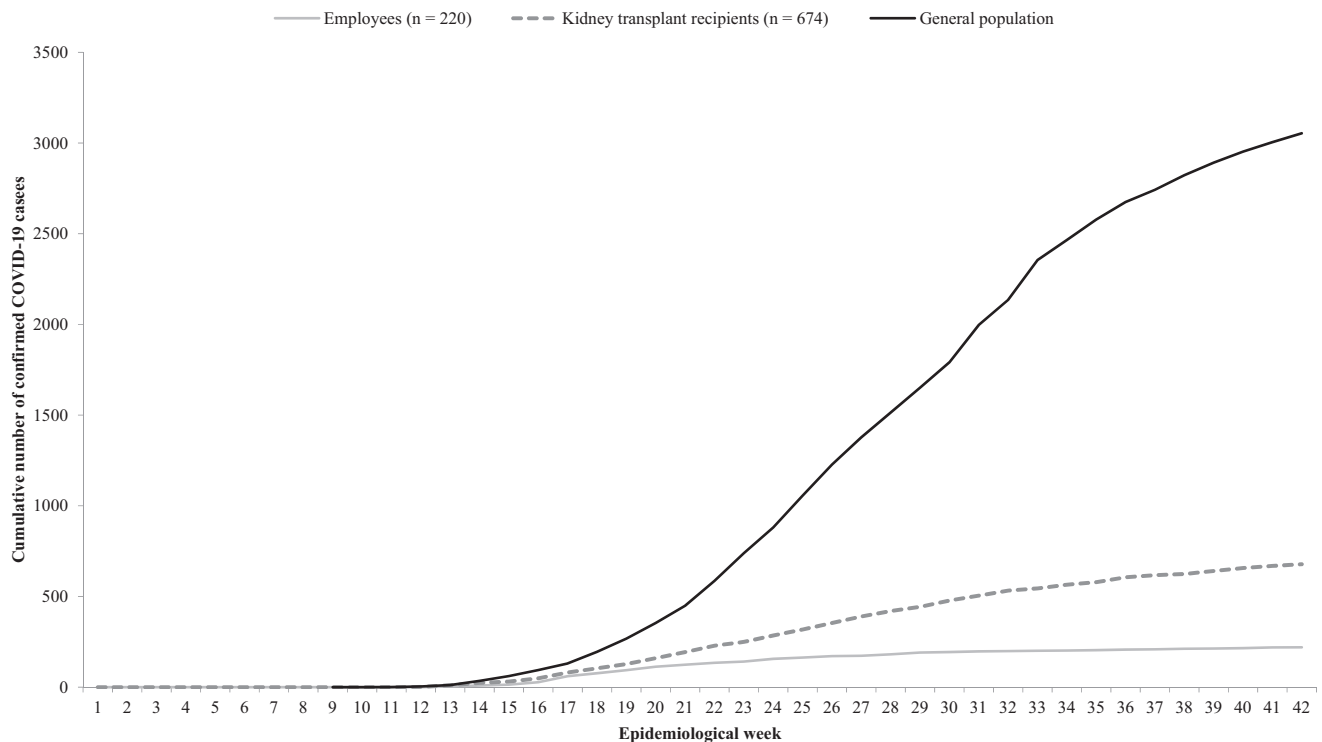


FIGURE 1 Cumulative number of COVID-19 cases among employees and kidney transplant recipients and in the general population of the city of São Paulo ($\times 100$). First employee diagnosed COVID-19 (+) on March 8, 2020. First patient diagnosed COVID-19 (+) on March 20, 2020

in ward, only one required oxygen supplementation, and all of them showed full recovery and were discharged home. From these 220 individuals, 218 had already returned to work without sequels at the time of this analysis.

3.3 | COVID-19 among kidney transplant donors and recipients

3.3.1 | Deceased donor screening

From March 20 to October 21, the city of São Paulo showed an exponential increase in the number of confirmed COVID-19 cases (Figure 1).⁵ During this period, there were 309 potential donors yielding 100 effective donors (32%) in the local Organ Procurement Organization region. From these 100, three (3%) were discarded after confirmation of SARS-CoV-2 infection, before the organ recovery. As a result, there were no patients who received organs from donors who had suffered the SARS-CoV-2 infection.

3.3.2 | COVID-19 among kidney transplant recipients

Of the 11875 kidney transplant recipients in follow-up, 674 developed COVID-19 (Figure 1, Table 1). The first kidney transplant recipient was diagnosed with COVID-19 on 20th of March. In 299

(44%) cases, a close contact with a confirmed case was identified; there were 49 nosocomial infections, and in the other 326 cases, the precise source was not found, and acquisition was deemed communitarian (Figure 3). Overall, 372 patients required hospitalizations, 58 in our hospital and 314 in 91 hospitals throughout the country. Several therapies directed to COVID-19 were prescribed to 383 (57%) patients (Table 1). None of them received either remdesivir or tocilizumab. One patient received convalescent plasma in addition of azithromycin, steroids, and ivermectin. Discontinuation of all immunosuppressive drugs except steroids was necessary in 199 (29%) critically ill patients. From the hospitalized patients, 196 (53%) required mechanical ventilation, and 167 (45%) required hemodialysis. There were 173 deaths, resulting in an overall fatality rate of 27.5%. The fatality was 39% among the 372 patients who required hospitalization, 84% among those who required mechanical ventilation, and 85% when on mechanical ventilation and hemodialysis. Acute allograft rejection was diagnosed in one of four patients who completely discontinued immunosuppression and underwent a kidney biopsy. Similarly, acute cellular rejection was found in four of the 12 patients who were kept on full immunosuppressive therapy and underwent a kidney biopsy. One of the five patients who developed acute rejection was recently transplanted, having the diagnosis of SARS-CoV-2 infection on the RT-PCR performed immediately before the surgery. The other patients had more than one year of transplant and were not sensitized. Three percent of the survivors returned definitively to dialysis.

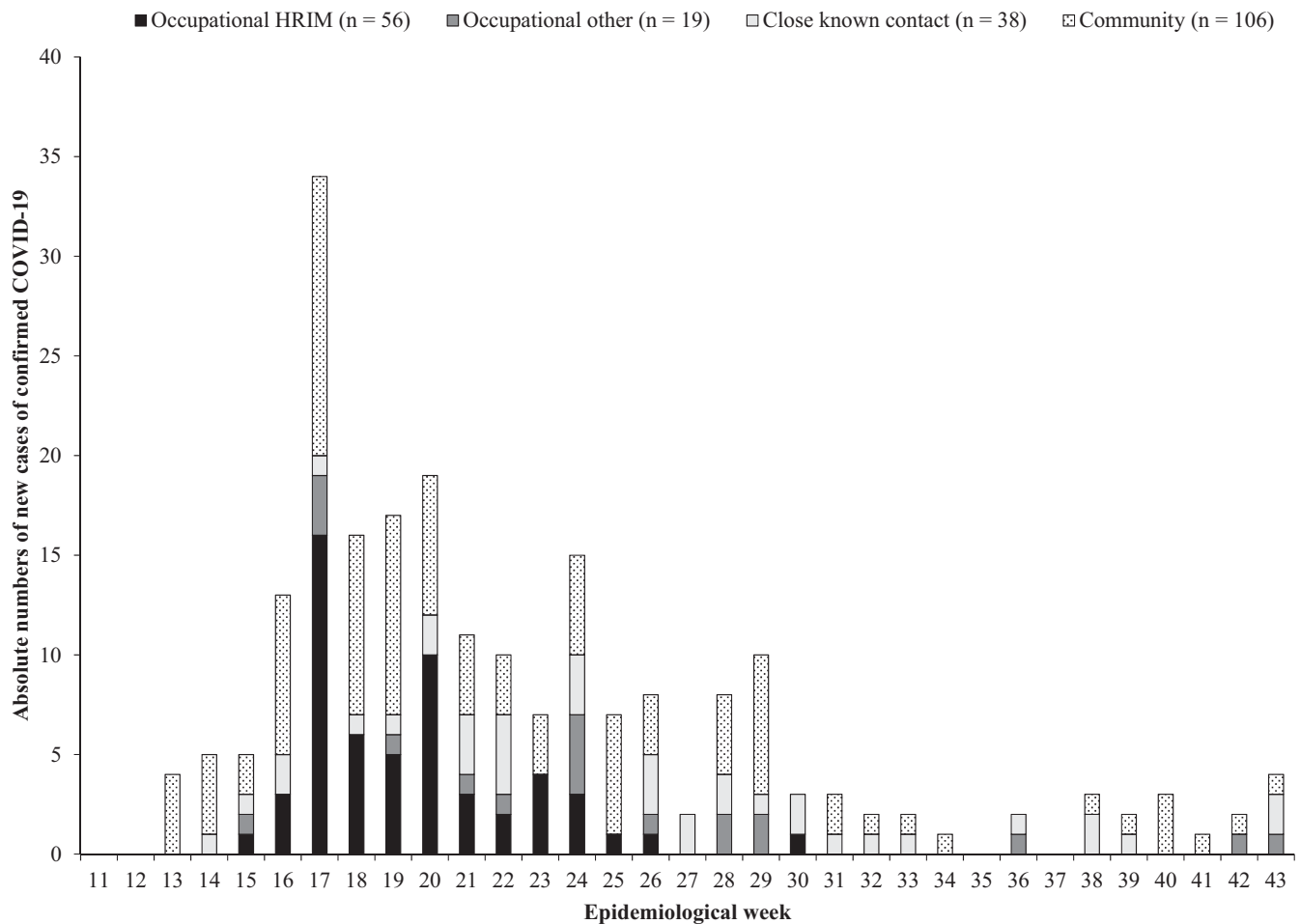


FIGURE 2 Temporal distribution of the 220 cases of COVID-19 among employees, per epidemiological week, according the source of contagion

3.3.3 | COVID-19 in deceased donor kidney transplants performed during the pandemic time

There were 882 potential recipients screened during the allocation process. Of them, 31 tested positive, and only four were transplanted because the test result was not available in time. Overall, 523 deceased donor kidney transplants were performed during the pandemic time, a 21% increase compared with the same period in 2019 (Figure 4). The institutional immunosuppressive protocol was not preemptively changed: all of them kept receiving methylprednisolone plus a single 3 mg/kg dose of rabbit antithymocyte globulin followed by tacrolimus, prednisone, and either azathioprine or mycophenolate.

Of those 523 recipients discharged from the initial transplant hospitalization, 24 developed COVID-19 (representing 3.5% of the global cohort of patients with the disease; Table 1). All of them received a deceased donor kidney transplant. Four (17%) were deemed as nosocomial infections. Specific therapies directed to COVID-19 were used in 11 (46%) patients. Discontinuation of all immunosuppressive drugs except steroids was necessary in four (17%) critically ill patients. Twenty (83%) individuals required hospitalization. From the hospitalized, six (30%) needed mechanical ventilation, and seven (35%) required dialysis. Coinfection was observed in seven (35%)

patients (cytomegalovirus infection in four, urinary tract infection in three). There were three deaths, resulting in an overall fatality rate of 12.5%. From the survivors, two evolved with allograft loss.

Four of the 24 patients were transplanted with positive RT-PCR for SARS-CoV-2 from the nasopharyngeal swab obtained immediately before surgery, but with delayed results. The respective values of RT-PCR cycle old (Ct) were 27, 28, 17, and 27, suggesting a recent infection instead of a previous event. At the time of the surgery, all of them were asymptomatic, with no history of contact with a suspicious or confirmed case and with a normal thorax computerized tomography. After transplantation, none of them developed the disease. All four patients were alive and with graft function 28 days after the SARS-CoV-2 infection diagnosis and at the time this manuscript was prepared. Detailed information regarding these four patients is published elsewhere.⁶

3.3.4 | Living donor kidney transplants performed during the pandemic time

The number of kidney transplants with living donors was reduced from a monthly average of 28 to four procedures, resulting in

TABLE 1 Characteristics of COVID-19 among the entire cohort of 674 kidney transplant recipients (global) and among the 24 patients transplanted during the pandemic time (recent)

| Variable | Global n = 674 | Recent n = 24 |
|-------------------------------------------------------------------|-------------------|------------------|
| Median age, years (IQR) | 52 (42-60) | 47 (42-55) |
| Male gender, n (%) | 412 (61) | 14 (58) |
| Source of acquisition, n (%) | | |
| Nosocomial | 49 (7) | 4 (17) |
| Close contact with a confirmed case | 299 (44) | 15 (62) |
| Communitarian | 326 (49) | 5 (21) |
| Any treatment directed to COVID-19, n (%) | 383 (57) | 11 (46) |
| Azithromycin (\pm another antibiotic) | 155 (23) | 4 (17) |
| Azithromycin plus steroids (\pm another antibiotic) | 68 (10) | 2 (8) |
| Azithromycin + hydroxychloroquine | 53 (8) | 1(4) |
| Steroids (\pm another antibiotic) | 28 (4) | 2 (8) |
| Hydroxychloroquine (\pm another antibiotic) | 7 (1) | 1 (4) |
| Other antibiotics | 72 (10) | 0 |
| Missing information | 27 (4) | 1 (4) |
| Management of immunosuppression, n (%) | | |
| No changes | 357 (53) | 13 (54) |
| Complete suspension, except for steroids | 199 (29) | 4 (17) |
| Suspension of the antiproliferative drug or calcineurin inhibitor | 118 (18) | 7 (29) |
| Need for hospitalization, n (%) | 372 (55) | 20 (83) |
| Mechanical ventilation | 196 (53) | 6 (30) |
| Need for dialysis | 167 (45) | 7 (35) |
| Fatality, n (%) | 173 (27.5) | 3 (12.5) |
| Graft loss among the survivors, n (%) | 17 (3) | 2 (8) |

30 living transplants (Figure 4). Both donor and recipients were screened before transplantation, with clinical evaluation, high-resolution computerized tomography thorax scan, and RT-PCR for SARS-CoV-2 within the 24 h preceding the procedure. None of those 30 living donor kidney transplant recipients discharged from the initial hospitalization developed SARS-CoV-2 infection.

4 | DISCUSSION

This experience substantiates the challenges and uncertainties that transplant centers faced as the pandemic unfolded and illustrates the effectiveness of the sequential measures implemented to provide a safe environment for organ donation and transplantation. Ultimately, it was possible to maintain a high-volume transplant program thanks to sequential measures implemented in each step of the process and to coordinated interactions with other hospitals and

transplant centers. In this complex scenario, screening of all potential donors, all recipients of transplants and patients readmitted to the hospital, and all health-care workers, with minimal or no symptoms, was decisive.

In the United States,⁷ in European countries,^{8,9} and in most Brazilian centers,¹⁰ the COVID-19 pandemic has resulted in a negative impact on organ donation and transplant activity. The maintenance of the transplant program at our center was only possible thanks to the set of strategies implemented. First, potential donors, recipients, and symptomatic patients were screened, with timely results for more appropriate decision making. The increase in transplant activity was only possible thanks to coordination between hospital units so that intensive care unit beds in our kidney transplant monographic center were not occupied with other SARS-CoV-2-infected patients. Newly diagnosed patients with COVID-19 were transferred to other hospitals. In turn, our institution received donors and recipients from other transplant centers with saturated hospital occupancy.

Among the employees, the outcome of the educational measures was reasonable, based on the low (26%) local occupational acquisition of the disease at the Hospital do Rim, that decreased further as the pandemic evolved, with no further occurrences since 07/25/2020. The young age group and the low frequency of comorbidities possibly contributed to the mild presentation of the disease, low hospitalization rate, and absence of fatal events. Among transplanted patients, however, lethality was high and comparable to multicenter studies already published.¹¹⁻¹⁴ Most likely, this population represents the opposite in terms of age group and comorbidities, in addition to the possible effect of immunosuppression on the evolution of the disease. A specific concern, yet not resolved, was whether the initial immunosuppressive intensity should be reduced in case a kidney transplant recipient developed COVID-19 after hospital discharge. We decided to maintain our immunosuppressive protocol, which is composed of a 3 mg/kg single dose of thymoglobulin, tacrolimus, prednisone, and mycophenolate/azathioprine, reasoning that an initial reduced intensity regimen would eventually lead to a higher incidence of acute rejection after hospital discharge. Moreover, returning to the local community and increased mobility due to scheduled visits at the transplant center would increase the risk of SARS-CoV-2 infection. Eventually, the need for treatment of acute rejection during this period could be associated with worse COVID-19 outcomes.

In summary, daily, tireless, and concerted effort and determination of the health care professionals allowed the maintenance of the kidney transplant program and provided guidance for many other centers throughout the country. Consequently, the negative impact of the pandemic on the treatment of patients with chronic kidney disease could be reduced, maintaining the access to high-quality treatment options, considering the already existing local challenges and the anticipated shortage of supplies for dialysis.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

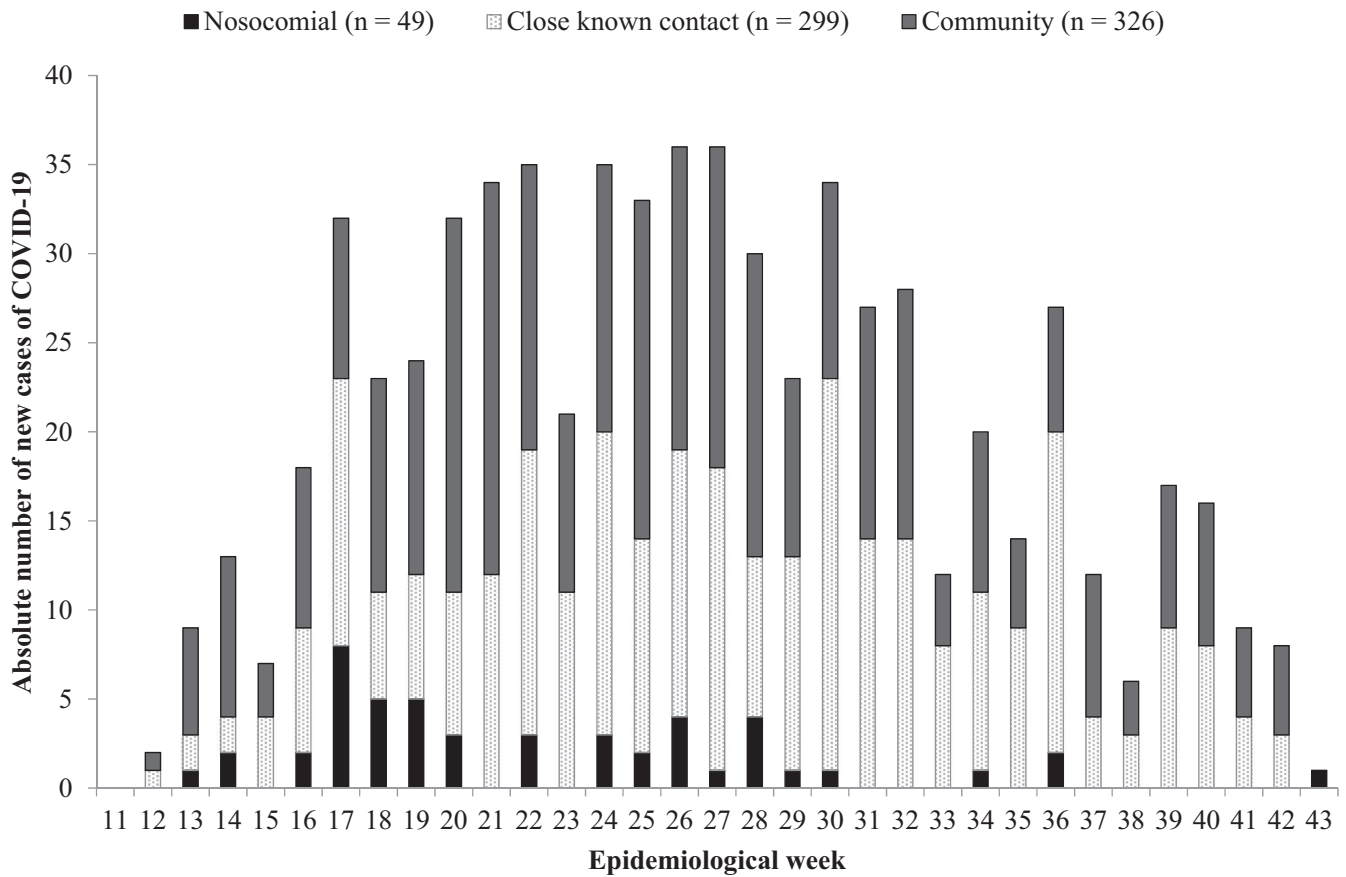


FIGURE 3 Distribution of the 674 cases of COVID-19 among kidney transplant recipients, per epidemiological week, according the reported source of contagion

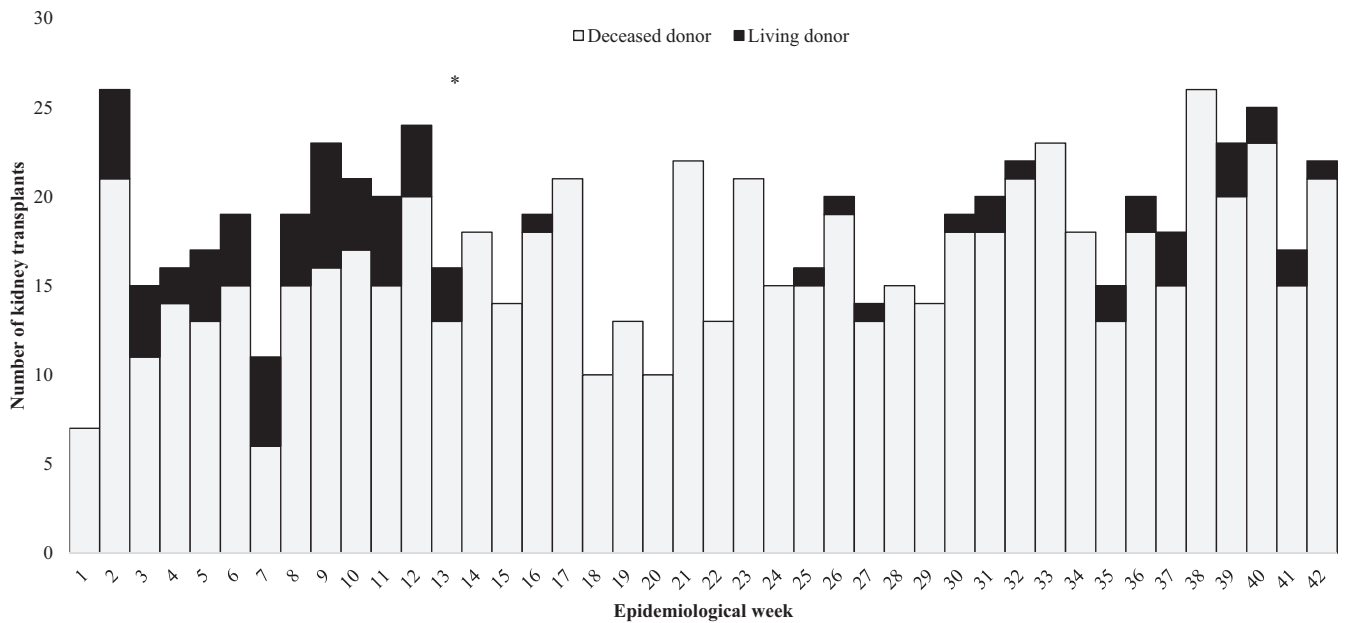


FIGURE 4 Number of new kidney transplants per epidemiological week, according donor source. The first case of COVID-19 in HRIM, in a late kidney transplant recipient, was diagnosed on March 20, 2020 (indicated with an asterisk)

AUTHORS' CONTRIBUTIONS

Cristelli MP: Design of the work, analysis and interpretation of data,

drafting the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to

be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Viana, LA: Design of the work, acquisition, analysis and interpretation of data, drafting the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Fernandes, RA: Interpretation of data for the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Nakamura, MR: Interpretation of data for the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Foresto, RD: Interpretation of data for the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Martins, SBS: Acquisition of data and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Alvarazi, JFL: Acquisition of data and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Leite, VC: Acquisition of data and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Oliveira, FR: Acquisition of data and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Carneiro, VA: Acquisition of data and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Santos, DWCL: Interpretation of data for the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Aguiar, WF: Interpretation of data for the work, revising it critically for important intellectual content, and final approval of the version to be published. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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