INTRODUCTION
Since it was declared a pandemic by the World Health Organization on March 11, 2020, >520 million people have been affected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection around the world.1 Besides the associated mortality and unprecedented use of healthcare resources, the persistence of clinical effects for weeks or months beyond the acute phase of the infection is a growing public health concern.2

Currently named as “Long–coronavirus disease (Long-COVID),” this unclear condition is reported by up to 87% of convalescents, depending on the definition, the population studied, and the instrument used for assessment.3 Its pathophysiology is still being understood but appears to be the interaction between viral cytopathic effects and dysregulation of the immune system into a pro-inflammatory state.3-5 In the general population, advanced age, female gender, number of symptoms in the acute phase, and

Background. Kidney transplant recipients are at a higher risk to develop more severe clinical forms of coronavirus disease 2019 (COVID-19), perhaps increasing the risk of presenting its long-term clinical complications, labeled as Long-COVID. Methods. This single-center, observational, prospective study included adult kidney transplant recipients with COVID-19 confirmed by reverse transcription polymerase chain reaction between March 20, 2020, and May 31, 2021, who were alive and with functioning graft 3 mo after the onset of symptoms. The prevalence of Long-COVID was investigated by a phone survey using a structured questionnaire of organic symptoms. Adjusted multivariable logistic regression models were used to investigate independent risk factors. Results. Of 1741 patients who developed COVID-19, 465 died, and 37 returned to dialysis. Of the 1239 eligible patients, 780 (63%) answered the survey during the window period. The mean age was 48 ± 12 y, 41% were women, and the mean time from transplantation was 8 ± 6 y. During acute illness, 45% needed hospitalization. Long-COVID was identified in 214 (27%) of the subjects, with body aches being the most prevalent symptom (44%). Of 233 who provided working status, 17% did not return to work within 3 mo. No baseline characteristics or infection-related variables predicted Long-COVID; actually, the number of symptoms in the acute illness was the only independent risk factor identified (hazard ratio, 1.12; 95% confidence interval, 1.02-1.22). Conclusion. In this cohort of kidney transplant recipients, Long-COVID was prevalent and associated with a reduced return to work. The burden of acute phase symptoms was the only risk factor associated with Long-COVID. (Transplantation 2022;106: 2408–2415).

High Prevalence of Long-COVID Among Kidney Transplant Recipients: A Longitudinal Cohort Study
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Received 27 July 2022. Revision received 5 August 2022. Accepted 7 August 2022.

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The authors declare no funding or conflicts of interest.

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ISSN: 0041-1337/20/10612-2408
DOI: 10.1097/TP.0000000000004359

verified the underlying data; M.P.C., L.A.V., V.L.T.G., H.d.L.C., G.B.B.L., F.S.d.S.S., G.S.d.C.e.L., and T.d.S.R. participated in data analysis; J.M.-P., M.P.C., L.A.V., C.E.N.A., V.L.T.G., and H.T.-S. participated in the writing of the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal’s Web site (www.transplantjournal.com).

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severity of COVID-19 had been identified as independent risk factors. However, its progressive description in convalescents from mild to moderate disease has made this subject even more challenging.

Kidney transplant patients are at higher risk of unfavorable outcomes from COVID-19, showing at least 10 times higher fatality rates, probably associated with the chronic use of immunosuppressive drugs and a higher number of comorbidities. Considering this more aggressive course of the acute illness, it is reasonable to hypothesize that long-term effects could be more prevalent than in the general population.

Until now, 3 groups investigated the clinical complications following COVID-19 among renal transplant recipients. Basic-Jukic et al evaluated 104 convalescent patients after a median of 64 d after the initial diagnosis and found that 45.2% presented at least 1 post–COVID-19 symptom, including, but not limited to, shortness of breath, tiredness, peripheral neuropathy, venous thromboembolism, de novo diabetes mellitus, cardiorenal syndrome, and self-reported cognitive impairments. Malinowska et al enrolled 67 kidney transplant recipients for a questionnaire interview 6 mo after acute COVID-19 and reported that 70.1% of the patients presented at least 1 of persistent COVID-19-related symptoms, such as fatigue, hair loss, myalgia, headaches, memory disturbances, or increased severity of dyspnea. Older age and the Charlson comorbidity index were predictors for the clinical complications at 6 mo from the acute illness. Finally, Chauhan et al applied sequential assessments in 142 kidney transplant recipients who had been hospitalized because of COVID-19 and found at least 1 persistent symptom in 37.5% of convalescents after 1 mo, in 15% after 3 mo, and in 8% of them beyond 6 mo from acute COVID-19. However, these studies lacked uniformity in terms of definition and minimum symptom duration. Moreover, they addressed a small number of patients, thus being underpowered to investigate the risk factors associated with this condition.

This present study aimed to determine the prevalence of and the risk factors for Long-COVID in a large cohort of kidney transplant recipients.

MATERIALS AND METHODS

This is a prospective, single-center cohort study was designed to assess the prevalence and risk factors of Long-COVID among kidney transplant recipients.

Eligible patients were those kidney transplant recipients aged over 18 y, diagnosed with symptomatic SARS-COV-2 infection by the reverse transcription polymerase chain reaction test between March 20, 2020, and May 31, 2021, who were alive and with functioning allograft at 3 mo after the onset of symptoms. The patients who returned to dialysis were excluded because all of them were withdrawn from immunosuppressive regimens, which could constitute a bias in the interpretation of the findings.

The definition of Long-COVID followed those published by the National Institute for Health and Care Excellence on December 18, 2020, as the signs and symptoms that develop during or after an infection consistent with COVID-19, continue for >12 wk, and are not explained by an alternative diagnosis.

A dedicated team of pharmacists and biomedicals was trained and performed the telephone calls, under medical supervision, for all the eligible patients in the visit of interest, which was at 3 mo (+30 d) after the onset of COVID-19 symptoms. Call attempts were made for up to 5 consecutive days, and other means of communication such as text messaging were extensively used to locate the nonresponders within the stipulated time window.

A short questionnaire was constructed from the information available in the literature at that time about the most frequent organic symptoms persisting after acute COVID-19 (Figure S1, SDC, http://links.lww.com/TP/C578). It was decided to restrict the questionnaire to physical complaints, excluding those related to mental health and quality of life, in an attempt to decrease the subjectivity of the phone interview. From June 10, 2021, questions about the work status were added to the survey. Data regarding the development of IgG-anti-SARS-CoV-2 after acute COVID-19 were not available for analysis. The study was approved by the local research ethics committee (CAAE 30631820.0.1001.8098). All the patients signed an informed consent form at the in-person consultation, which is regularly performed per institutional protocol around 28 d after COVID-19 diagnosis.

Statistical Analysis

Descriptive characteristics are presented as means and SD unless otherwise noted. The Kolmogorov-Smirnov and Levene tests were used to verify the nature of data distribution and homogeneity, respectively. Chi-square tests were performed to compare categorical variables, whereas continuous variables were compared by performing an independent Student t test. We performed a backward elimination stepwise binary regression to investigate independent risk factors for Long-COVID. At each step, the variable that is the least significant is removed (based on the significant level at P < 0.1). This procedure continues until no nonsignificant variables remain. All statistical analyses were performed using, released 2013, IBM SPSS Statistics for Windows, version 26.0 (IBM Corp, Armonk, NY), and GraphPad Prism, version 8.0.0, for Windows (GraphPad Software, San Diego, CA).

RESULTS

Between March 20, 2020, and May 31, 2021, 1741 kidney transplant recipients in follow-up were diagnosed with COVID-19 by the reverse transcription polymerase test. Of those, 465 died, and 37 lost their graft: the remaining 1239 patients were eligible for the survey. After all the attempts of contact, there were 459 (37%) nonresponders, yielding a final cohort of 780 (63%) patients included for analysis (Figure 1). To investigate the possibility of selection bias, we compared the demographic data of responders (780) and nonresponders (GraphPad Software, San Diego, CA).

Demography and Acute COVID-19

Among the 780 included patients, the mean age was 48 ± 12 y, 317 (40%) were women, and the most common comorbidities were hypertension and diabetes, with a frequency of 70% and 25%, respectively. Besides that, 479 (61%) of the patients had received a deceased donor...
transplant, the mean time from transplantation to COVID-19 diagnosis was 8 ± 6 y, and the mean of the baseline creatinine was 1.6 ± 0.7. None of our patients had been vaccinated before COVID-19 or in the period of study (Table 1).

During the acute phase of COVID-19, fever/chills were the most common initial manifestation, reported by 55% of the patients, followed by cough (54%) and body aches (51%), and the mean number of symptoms during the acute illness was 4 ± 2. Forty-five percent of the patients were hospitalized, 30% required oxygen therapy, 17% were admitted to an intensive care unit, and 5% were submitted to mechanical ventilation (Table 1). After hospital discharge, about 1% of our patients needed domiciliary oxygen therapy.

**Long-COVID**

After 3 mo from COVID-19, 214 patients reported at least 1 of the investigated symptoms of Long-COVID, resulting in a prevalence of 27%. Figure 2A illustrates the occurrence of each one of the inquired symptoms among the prevalent patients. The most frequent one was body aches (44%), followed by weakness (41%) and headache (38%). Among those 214 patients, 26% developed 2 complaints, and 32% reported 3 or more symptoms (Figure 2B).

The baseline patient characteristics were similar, except for a higher number of symptoms during the acute phase among the patients who presented Long-COVID versus those who did not (Table 2). There was no difference in the prevalence of Long-COVID comparing individuals who were hospitalized versus those patients managed at home (30% versus 25%, $P = 0.118$).

In 233 out of the 780 patients, information about working status and returning to work was obtained. Of these 233 individuals, 90 (39%) were employed before COVID-19, and 15 of them (17%) had not returned to their original work because of Long-COVID. Among the subjects who were unable to return to work, 8 (53%) were hospitalized (75% of them in the intensive care unit), 7 (46%) needed oxygen therapy, 5 (33%) needed dialysis, and 4 (26%) required mechanical ventilation during the acute phase.

In the univariable analysis, history of pulmonary disease, the chronic use of mycophenolate versus other antiproliferative drugs, and the total number of symptoms during acute illness were associated with Long-COVID. Among the subjects who were unable to return to work, 8 (53%) were hospitalized (75% of them in the intensive care unit), 7 (46%) needed oxygen therapy, 5 (33%) needed dialysis, and 4 (26%) required mechanical ventilation during the acute phase.

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**DISCUSSION**

In this prospective cohort study, 27% of the kidney transplant recipients who survived from COVID-19 in
the prevaccination and pre-Omicron era reported at least 1 organic symptom of Long-COVID-19 persisting for 12 wk after the acute illness. The total number of symptoms during the acute phase was the only independent predictor for its prevalence. Furthermore, this condition seemed to affect the ability to return to normal activity, considering that 17% of the formerly employed people could not return to work because of Long-COVID.

The prevalence found in our study was different from previous reports both in the general population and in transplant recipients. The main reason for this discrepancy is the definition of Long-COVID, which is a widely recognized challenge. In terms of the minimum duration, we followed the National Institute for Health and Care Excellence guidelines requiring the persistence of symptoms for 12 wk. In terms of the symptoms included, we chose to restrict the questionnaire to those organic symptoms most commonly reported in the literature, not considering psychological complaints. On one hand, this strategy increased the specificity of our research because mental health disorders are extremely prevalent among transplant recipients. In the present analysis, the only risk factor was the total symptom burden in the acute phase of the disease, which was observed in other studies in the general population.

An important finding of our study was that 17% of employed patients did not return to their work activities as a consequence of Long-COVID. Although a more detailed investigation of the reasons for nonreturn was not the scope of our work, this finding is in line with publications that are concerned with the deleterious effects of COVID-19 on labor productivity and indicates the need for a broader approach to people of working age in order to identify and treat the symptoms early and in a multiprofessional manner for their complete rehabilitation.

Our study was conducted in the prevaccination and pre-Omicron era. The effect of vaccination and new variants on the prevalence of Long-COVID is still a matter of debate. A British study involving 28,356 participants with a short observation period of 67 d demonstrated a reduction in the risk of Long-COVID among vaccinated individuals, especially in those with 2 vaccine doses. Contrarily, an American study with a large database analysis, involving 10,024 individuals from the general population, reported a consistent prevalence of Long-COVID among vaccinated and unvaccinated people,23 which was not confirmed in subsequent analyses with larger numbers of patients.24 Among kidney transplant recipients, one study suggested that older age and a high comorbidity index could be associated with clinical complications. In the present analysis, the only risk factor was the total symptom burden in the acute phase of the disease, which was observed in other studies in the general population.

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population with SARS-CoV-2 infection, found no association between vaccination and a lower risk of Long-COVID. However, the authors themselves recognized a limitation in that the information was collected from databases not designed for this purpose, which may have led to not capturing relevant information. Initial analyses suggest that persistence of symptoms in the medium to long term is less frequent in the Omicron-predominant era. In the UK, for example, a study involving >100,000 people found a prevalence of 10.8% versus 4.5% of Long-COVID among people infected in the Delta-predominant versus Omicron-predominant era, respectively (relative risk, 0.41; 95% CI, 0.39-0.43).

Whether such a difference was because of biological variation of the virus, the effect of cumulative doses of vaccine, or both cannot be stated.

Some limitations must be acknowledged. Because this was a single-center study, the results do not allow extrapolation to other populations. The fact that 37% of the patients could not be contacted to answer the questionnaire may have constituted a selection bias, attenuated by the fact that the characteristics of the included population represented the total set of convalescents. A widely validated questionnaire on the specific set of defining symptoms has not been applied, but to date, this is not a consensus in the literature. The only risk factor identified was the total burden of symptoms in the acute phase. Although it may suggest a persistent pro-inflammatory state, which is one of the proposed mechanisms of Long-COVID, we recognize it may constitute an information bias, as the way in which the data were obtained depends on

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**FIGURE 2.** A, Frequency of each one of the reported symptoms of Long-COVID among the 214 prevalent patients identified by the survey. B, Distribution of the cumulative number of symptoms of Long-COVID reported by the prevalent patients. COVID, coronavirus disease.
### TABLE 2.
Baseline characteristics, clinical presentation, and major outcomes of acute infection of the studied population, stratified by the occurrence of Long-COVID

| Variables                                           | Long-COVID-19 (n = 214) | No Long-COVID-19 (n = 566) | P    |
|-----------------------------------------------------|-------------------------|----------------------------|------|
| Mean age ± SD, years                                | 48 ± 12                 | 48 ± 12                    | 1.000|
| Female sex, n (%)                                   | 88 (41)                 | 229 (40)                   | 0.865|
| Mean body mass index ± SD, kg/m²                    | 26 ± 6                  | 26 ± 7                     | 1.000|
| Comorbidities, n (%)                                |                         |                            |      |
| Smoking                                             | 49 (23)                 | 109 (19)                   | 0.762|
| Hypertension                                        | 152 (71)                | 396 (70)                   | 0.811|
| Diabetes                                            | 59 (27)                 | 139 (24)                   | 0.757|
| Cardiovascular disease                              | 7 (3)                   | 24 (4)                     | 0.902|
| Pulmonary disease                                   | 4 (2)                   | 3 (0.5)                    | 0.895|
| Hepatic disease                                     | 4 (2)                   | 7 (1)                      | 0.882|
| Neoplasia                                           | 3 (1)                   | 14 (2)                     | 0.908|
| Deceased donor transplant, n (%)                    | 141 (66)                | 338 (60)                   | 0.282|
| Mean time from transplant ± SD, years               | 8 ± 6                   | 8 ± 6                      | 1.000|
| Maintenance immunosuppressive regimen by drug, n (%)|                         |                            |      |
| Calcineurin inhibitors                              |                         |                            |      |
| TAC                                                 | 174 (81)                | 439 (77)                   | 0.722|
| CSA                                                 | 25 (12)                 | 78 (14)                    |      |
| None                                                | 11 (5)                  | 35 (6)                     |      |
| No information                                      | 4 (2)                   | 14 (2)                     |      |
| Prednisone                                          | 214 (100)               | 566 (100)                  |      |
| Antimetabolite                                       |                         |                            |      |
| MPA                                                 | 115 (54)                | 250 (44)                   | 0.135|
| Azathioprine                                         | 66 (31)                 | 211 (37)                   |      |
| mTOR inhibitors                                      | 23 (11)                 | 72 (13)                    |      |
| None                                                | 4 (2)                   | 14 (2)                     |      |
| Mean baseline creatinine ± SD                       | 1.6 ± 0.7               | 1.6 ± 0.7                  | 1.000|
| Baseline creatinine >1.6 mg/dl, n (%)               | 74 (35)                 | 224 (40)                   | 0.200|
| Initial symptoms, n (%)                             |                         |                            |      |
| Fever or chills                                      | 114 (53)                | 318 (56)                   | 0.703|
| Cough                                               | 129 (60)                | 297 (52)                   | 0.230|
| Dyspnea                                             | 59 (27)                 | 167 (29)                   | 0.762|
| Chest pain                                          | 2 (1)                   | 3 (1)                      | 1.000|
| Coryza                                              | 55 (26)                 | 127 (22)                   | 0.647|
| Headache                                            | 61 (28)                 | 151 (26)                   | 0.877|
| Nasal congestion                                    | 48 (22)                 | 89 (16)                    | 0.358|
| Fatigue                                             | 5 (2)                   | 18 (3)                     | 0.904|
| Myalgia                                             | 124 (58)                | 275 (48)                   | 0.243|
| Nausea or vomiting                                  | 7 (3)                   | 18 (3)                     | 0.997|
| Diarrhea                                            | 83 (39)                 | 146 (26)                   | 0.093|
| Anosmia                                             | 66 (31)                 | 178 (31)                   | 0.876|
| Ageusia                                             | 65 (30)                 | 158 (28)                   | 0.753|
| Mean number of symptoms ± SD                        | 4 ± 2                   | 3 ± 2                      | <0.0001|
| Outcomes during the acute phase, n (%)              |                         |                            |      |
| Hospitalization                                      | 106 (50)                | 246 (43)                   | 0.365|
| Intensive care unit                                 | 36 (17)                 | 95 (17)                    | 0.897|
| Oxygen therapy                                       | 70 (33)                 | 169 (30)                   | 0.632|
| Mechanical ventilation                              | 10 (5)                  | 29 (5)                     | 0.896|
| Dialysis                                            | 12 (5)                  | 48 (8)                     | 0.720|
| Immunosuppression suspended except for steroids     | 20 (9)                  | 53 (9)                     | 0.992|

COVID-19, coronavirus disease 2019; CSA, cyclosporin A; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; TAC, tacrolimus.
TABLE 3.
Univariate and multivariate analysis for the occurrence of Long–coronavirus disease 2019

| Factors                                | Univariate analysis | Multivariate analysis |
|----------------------------------------|---------------------|-----------------------|
|                                        | P    | HR (95% CI) | P   | HR (95% CI) |
| Mean age, years                        | 0.920 | 0.984 (0.718-1.348) | -  | - |
| Female sex vs male                     | 0.867 | 1.028 (0.746-1.415) | -  | - |
| Hypertension vs no                     | 0.772 | 1.052 (0.745-1.487) | -  | - |
| Diabetes vs no                         | 0.389 | 1.169 (0.819-1.669) | -  | - |
| Cardiovascular disease vs no           | 0.538 | 0.764 (0.324-1.799) | -  | - |
| Pulmonary disease vs no                | 0.097 | 3.575 (0.793-16.106) | 0.079 | 4.265 (0.846-21.511) |
| Deceased donor vs living donor         | 0.125 | 1.293 (0.931-1.797) | -  | - |
| Calcineurin inhibitor                  | -    | -           | -  | - |
| Tacrolimus (ref.)                      | -    | -           | -  | - |
| Cyclosporine                           | 0.389 | 0.809 (0.499-1.311) | -  | - |
| None                                   | 0.516 | 0.793 (0.394-1.597) | -  | - |
| Antimetabolite                         | -    | -           | -  | - |
| Mycophenolate vs others                | 0.020 | 1.462 (1.063-2.012) | 0.069 | 0.728 (0.516-1.025) |
| Baseline creatinine                    | 0.536 | 0.932 (0.745-1.165) | -  | - |
| Burden of symptoms during the acute phase | 0.008 | 1.123 (1.030-1.224) | 0.015 | 1.116 (1.022-1.219) |
| Need of hospitalization vs no          | 0.118 | 1.286 (0.938-1.763) | -  | - |
| Hospitalization in ICU vs no           | 0.943 | 1.016 (0.667-1.547) | -  | - |

Cl, confidence interval; HR, hazard ratio; ICU, intensive care unit; ref, reference.

the individual’s perception of disease or health status. Finally, the exclusion of mental health complaints limited the present study’s investigation to the organic sphere of Long-COVID, which may have underestimated the prevalence of this condition.

In summary, in a large cohort of unvaccinated kidney transplant recipients who survived the acute phase of COVID-19 in the pre-Omicron era, there was a high prevalence of Long-COVID, with an impact on return to work. In addition to the number of initial symptoms, no risk factors for this condition could be identified. Further studies are needed to determine whether these symptoms will persist beyond three months of observation, what the impact will be on kidney function and graft survival, and whether there will be any influence of vaccination and the emergence of new variants on long COVID.

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