Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
COVID-19 and kidney transplantation: Results from the TANGO International Transplant Consortium

Kidney transplant recipients may be at a high risk of developing critical coronavirus disease 2019 (COVID-19) illness due to chronic immunosuppression and comorbidities. We identified hospitalized adult kidney transplant recipients at 12 transplant centers in the United States, Italy, and Spain who tested positive for COVID-19. Clinical presentation, laboratory values, immunosuppression, and treatment strategies were reviewed, and predictors of poor clinical outcomes were determined through multivariable analyses. Among 9845 kidney transplant recipients across centers, 144 were hospitalized due to COVID-19 during the 9-week study period. Of the 144 patients, 66% were male with a mean age of 60 (±12) years, and 40% were Hispanic and 25%...
Since its initial detection in Wuhan, China, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is responsible for coronavirus disease 2019 (COVID-19), has rapidly emerged as an international pandemic. As of June 2020, >6 million cases have been reported worldwide, leading to >400,000 deaths. Clinical symptoms associated with COVID-19 are variable, although the most common include fever, cough, shortness of breath, diarrhea, anosmia, and lack of taste. Those with advanced age and medical comorbidities, including diabetes mellitus, hypertension, cardiovascular disease, pulmonary disease, and malignancy, are at increased risk for severe disease, including diabetes mellitus, acute respiratory distress syndrome, septic shock, multiorgan failure, and death. In addition, a hyperinflammatory state, known as cytokine storm syndrome, has been described with COVID-19 infection that is associated with rapidly worsening clinical features leading to multiorgan failure. Increased levels of circulating inflammatory cytokines, including interleukin (IL)-1, IL-6, and interferon-γ, have been shown in those patients.

Theoretically, solid organ transplant recipients are at particularly higher risk of developing critical COVID-19 due to chronic immunosuppression. European experience in Italy regarding 20 kidney transplant recipients with COVID-19 pneumonia documented a fast progression in >75% of their patients with 25% mortality during a median follow-up of 7 days. In Spain, 18 solid organ recipients diagnosed with COVID-19 had a mortality rate of 28%. In the United States, the initial experience was reported by transplant centers in New York. A single-center experience at Montefiore Medical Center reported 28% mortality in 36 consecutive adult kidney transplant recipients. Seventy-eight percentage required hospital admission, 96% of hospitalized patients had imaging findings of viral pneumonia, 39% required mechanical ventilation, and 21% required renal replacement therapy. Columbia and Cornell medical centers in New York reported clinical outcomes of 90 transplant recipients (46 kidney, 17 lung, 13 liver, 9 heart, and 5 dual-organ transplants). Among the 68 hospitalized patients, 12% required nonrebreather and 35% required intubation. Sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU patients) and 37 (54%) were discharged. Northwell center reported 30% mortality and 50% acute kidney injury in 10 kidney transplant recipients.

The aim of our report is to present the clinical outcomes of a large multicenter cohort of 144 kidney transplant recipients who were hospitalized due to COVID-19 at 12 transplant centers in North America and Europe to identify predictors of poor clinical outcomes.

## 2 | Patients and Methods

### 2.1 | Study design and participants

This retrospective cohort study included kidney transplant recipients admitted with COVID-19 in 12 centers participating in the international TANGO consortium (www.tangoxstudy.com). We included all adult (≥18 years) kidney transplant recipients with a functioning kidney allograft who were admitted to a hospital between March 2 and May 15, 2020. Medical records were reviewed by TANGO investigators in the collaborating centers. Since testing criteria for SARS-CoV-2 vary among locations, we decided to exclude patients with presumed or diagnosed COVID-19 who did not require hospital admission. We also excluded any patients who had been reported in prior publications by any of the participating centers. The study was approved by the Brigham and Women’s Hospital Research Ethics Commission (2015P000993).

### 2.2 | Data collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records using...
2.3 | Laboratory procedures

SARS-CoV-2 infection was determined in nasopharyngeal swabs with the use of real-time RT-PCR. Routine blood examinations performed included complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase [LDH], and electrolytes), myocardial enzymes, IL-6, serum ferritin, C-reactive protein, D-dimer, and procalcitonin. Frequency of examinations was determined by the treating physician in each center. Fever was defined as an axillary temperature of at least 37.3°C. Dyspnea was defined as a subjective experience of breathing discomfort reported by the patient. Acute kidney injury was diagnosed according to the KDIGO clinical practice guidelines.

2.4 | Statistical analysis

Descriptive statistics for Table 1 include frequency analysis (counts and percentages) for categorical variables and medians and IQRs for continuous measures. Distributions were visually inspected for all continuous measures, and potential influence points/outliers double-checked with respective sites for validity. Due to the small sample, we used the nonparametric Mann-Whitney U test for all continuous variables and χ² test or Fisher exact test (for cell size <5) for all categorical variables. All variables evaluated for missing data and the Little test for the overall sample did not reject the null hypothesis confirming MCAR (missing completely at random). Sensitivity analysis by repeating all tests without missing data verified no change in results. Univariate and multivariate logistic regression models were used to explore associations of baseline laboratory and clinical characteristics and the risk for death. At the outset, it was decided to exclude any COVID-19–related case management characteristics for investigating predictors of survival outcomes (e.g., CNI withdrawal, hydroxychloroquine). Therefore, only clinical or laboratory variables demonstrating significant differences from the baseline were candidates for univariate regression models predicting survival (Table 1).

With the intention of parsimony due to the limited sample size, we attempted a multivariable risk-prediction model using only 5 vital predictors from the univariable models. Although a strong predictor, dyspnea was excluded due to collinearity with respiratory rate. Model fit and superiority for the multivariable model were evaluated by using the Akaike information criterion and the Nagelkerke pseudo $R^2$. A type 1 error rate of .05 was considered statistically significant for all analyses. Statistical analysis was performed using the R software (version 3.6.1 [2019-07-05]).

3 | RESULTS

3.1 | Patient characteristics

One hundred forty-four kidney transplant recipients with a diagnosis of COVID-19 were identified. Of 144 patients, 95 (66%) were male with a median age of 62 (IQR 52-69) (56.2% > 60) years old, and 40% were Hispanic, 31% were white, and 25% were African American (Table 1). Hypertension was the most common comorbidity affecting 95% of patients, followed by diabetes (52%), obesity (49%), heart disease (28%), and lung disease (19%). Twenty-eight percent of the patients had a prior or current history of smoking tobacco, whereas 15% had a history of cancer. Twenty-four patients (17%) were receiving angiotensin II receptor antagonists at the time of diagnosis, and 20 (14%) were taking angiotensin-converting enzyme (ACE) inhibitors.

Time to diagnosis of COVID-19 after transplant ranged from <1 year to 31 years (median 5 years); 16% were diagnosed during the first year after transplant. Causes of original kidney disease included diabetes (30%), glomerular disease (17%), hypertension (14%), and polycystic kidney disease (9%). Most patients had undergone a deceased kidney transplant (78%) and received induction therapy with T cell depletion at the time of transplant (62%). Maintenance immunosuppression consisted of tacrolimus (91%), antimetabolite (mycophenolate) (77%), mTOR inhibitor (7.5%), and steroids (86%).

3.2 | Clinical outcomes

The most common symptoms on admission were fever and dyspnea (67%), followed by myalgia (53%) and diarrhea (38%) (Table 2). During a median follow-up of 52 days (IQR: 16-66 days) after the diagnosis of the first COVID-19 patient, 74 patients developed acute kidney injury (51%), 42 patients required mechanical ventilation (29%), and 46 patients had died, totaling 32% mortality in this cohort. Twenty-two of the patients who entered the ICU died (51%). The median time from illness onset (i.e., before admission) to discharge was 22 days (IQR 15-35 days), whereas the median time to death was 15 days (IQR: 8-22 days; Table 1). Extracorporeal membrane oxygenation was used in 3 patients, none of whom survived.

3.3 | Risk factors associated with death from COVID-19

There was no difference in mortality across the transplant centers. Patients who died were older than survivors (66 vs 60 years old; $P < .001$), with 71% of patients over the age of 60 among nonsurvivors (Table 1). There was no significant difference in outcomes between recipients of organs from living or deceased donors or between patients with < 1 year since transplant compared with those with longer time
| TABLE 1 | Baseline demographics, comorbidities, and medications of hospitalized kidney transplant recipients with COVID-19 |
|---------|---------------------------------------------------------------------------------------------------------|
|         | Total (N = 144) | Survivors (n = 98) | Nonsurvivors (n = 46) | P value |
| **Baseline characteristics** | | | | |
| Age | 62.00 [52.00, 69.00] | 60.00 [48.00, 66.75] | 66.50 [60.00, 72.00] | <.001 |
| >60 y | 81 (56.2%) | 48 (49.0%) | 33 (71.7%) | .012 |
| Male | 94 (65.3%) | 65 (66.3%) | 29 (63.0%) | .711 |
| Race | | | | |
| Hispanic | 56 (39.7%) | 39 (40.2%) | 17 (38.6%) | .99a |
| Caucasian | 43 (30.5%) | 29 (29.9%) | 14 (31.8%) | |
| African American | 35 (24.8%) | 24 (24.7%) | 11 (25.0%) | |
| Others | 7 (5.0%) | 5 (5.2%) | 2 (4.5%) | |
| **Causes of kidney disease** | | | | |
| Diabetes mellitus | 43 (30.1%) | 28 (28.9%) | 15 (32.6%) | .96a |
| Glomerular | 25 (17.5%) | 17 (17.5%) | 8 (17.4%) | |
| Hypertension | 20 (14.0%) | 14 (14.4%) | 6 (13.0%) | |
| Others | 24 (16.8%) | 17 (17.5%) | 7 (15.2%) | |
| Polycystic kidney disease | 13 (9.1%) | 10 (10.3%) | 3 (6.5%) | |
| Unknown | 18 (12.6%) | 11 (11.3%) | 7 (15.2%) | |
| **Type of kidney transplant (deceased vs living donor)** | | | | |
| Deceased | 112 (77.8%) | 75 (76.5%) | 37 (80.4%) | .756 |
| Time from transplant to COVID-19 symptom onset (y) | 5.00 [2.00, 9.25] | 4.00 [2.00, 8.00] | 5.00 [2.25, 11.00] | .281 |
| <1 y since transplant to COVID-19 symptom onset | 23 (16.0%) | 17 (17.3%) | 6 (13.0%) | .629 |
| **Transplant center** | | | | |
| Bronx, NY | 47 (32.6%) | 28 (28.6%) | 19 (41.3%) | .4a |
| New York, NY | 29 (20.1%) | 21 (21.4%) | 8 (17.4%) | |
| Palo Alto, CA | 4 (2.8%) | 4 (4.1%) | 0 (0.0%) | |
| Denver, CO | 11 (7.6%) | 8 (8.2%) | 3 (6.5%) | |
| Boston, MA | 11 (7.6%) | 10 (10.2%) | 1 (2.2%) | |
| Barcelona, Spain | 24 (16.7%) | 15 (15.3%) | 9 (19.6%) | |
| Navarra, Spain | 3 (2.1%) | 3 (3.1%) | 0 (0.0%) | |
| Parma, Italy | 5 (3.5%) | 2 (2.0%) | 3 (6.5%) | |
| Padova, Italy | 3 (2.1%) | 2 (2.0%) | 1 (2.2%) | |
| Ancona, Italy | 5 (3.5%) | 3 (3.1%) | 2 (4.3%) | |
| Verona, Italy | 2 (1.4%) | 2 (2.0%) | 0 (0.0%) | |
| **Comorbidities** | | | | |
| Hypertension | 137 (95.1%) | 93 (94.9%) | 44 (95.7%) | 1 |
| Diabetesb | 75 (52.1%) | 50 (51.0%) | 25 (54.3%) | .724 |
| Obesity | 71 (49.3%) | 45 (45.9%) | 26 (56.5%) | .284 |
| Heart disease | 41 (28.5%) | 23 (23.5%) | 18 (39.1%) | .074 |
| Lung disease | 27 (18.8%) | 18 (18.4%) | 9 (19.6%) | 1 |
| Cancer | 22 (15.4%) | 12 (12.4%) | 10 (21.7%) | .213 |
| Smoker (current or past) | 39 (28.5%) | 25 (26.9%) | 14 (31.8%) | .55 |
| HIV/AIDS | 3 (2.5%) | 1 (1.2%) | 2 (5.4%) | .224 |
| **Medications** | | | | |
| T cell depletion at time of transplant | 85 (62.5%) | 60 (65.9%) | 25 (55.6%) | .263 |

(Continues)
since transplant (Table 1). Time from onset of symptoms to admission was slightly shorter in patients who died. Neither race, comorbidities, induction therapy with depleting agents, maintenance immunosuppression, nor therapy with Renin Angiotensin System inhibitors differed significantly between survivors and nonsurvivors (Table 1).

3.4 | Presentation and laboratory results according to mortality from COVID-19

The respiratory rate at admission was significantly higher in nonsurvivors compared with survivors (Table 2), and diarrhea was less frequent in nonsurvivors (23.9% vs 44.9%). None of the other clinical characteristics at presentation differed significantly between the 2 groups. Major laboratory markers were tracked from illness onset. Lymphopenia (<0.8) was present in 42% of patients. Baseline lymphocyte count was significantly higher in survivors than in nonsurvivors (1.2 vs 0.7, \( P = .004 \)) as well as estimated glomerular filtration rate (eGFR; 53 vs 38 mL/min) (Table 2). There was no statistically significant difference between the 2 groups in terms of white blood cell, hemoglobin, platelet, alanine aminotransferase, and creatine phosphokinase levels but nonsurvivors had higher aspartate transaminase (30 vs 24 U/L) and LDH (406 vs 296 U/L, \( P < .001 \)) levels. In terms of inflammatory markers, levels of procalcitonin (0.61 vs 0.2 ng/mL, \( P = .003 \)) and IL-6 (79.94 vs 24.80 ng/mL, \( P = .007 \)) were significantly elevated in nonsurvivors compared with survivors (Table 2), whereas ferritin, D-dimer, and C-reactive protein levels were not significantly different between groups.

3.5 | Treatment of COVID-19 in kidney transplant recipients

In most cases, mycophenolate (MMF/MPA) or everolimus was reduced or discontinued (68%), whereas calcineurin inhibitor was discontinued in 32 patients (23%) (Table 3). There was no significant association between immunosuppression withdrawal and mortality. Most patients received hydroxychloroquine (71%) and antibiotics (74%), and a smaller subset of patients received tocilizumab (13%) or antivirals (14%) (Figure 1). There was no significant difference in mortality among different treatments of COVID-19 with the exception of a slightly greater use of antibiotics in nonsurvivors.

3.6 | Predictors of mortality

In univariable analysis, the odds of in-hospital death was higher in older patients and patients with higher respiratory rates, LDH, IL-6, and procalcitonin levels, whereas mortality risk was lower in patients with diarrhea or higher eGFR levels. These variables were used for the multivariable logistic regression model. In addition to age, we found that higher respiratory rate, lower eGFR, and higher IL-6 at admission were associated with increased odds of death (Table 4).

4 | DISCUSSION

Our large international registry demonstrated a high early mortality rate of 32% in hospitalized kidney transplant recipients with COVID-19, similar to previous single-center reports, which observed death rates between 24% and 30%.\(^6\)-\(^{10}\) Our kidney transplant patients had multiple risk factors for COVID-19–related mortality, other than chronic immunosuppressive treatment, that have been shown to be important predictors in the general population. These risk factors include older age, hypertension, diabetes mellitus, and cardiovascular disease.\(^1\),\(^3\),\(^4\) It is still not clear if immunosuppressive treatment is an independent risk factor on top of all the other medical comorbidities. Mortality rate from
COVID-19 in the general population has been reported at 8% in New York, 14% in Italy, and 12% in Spain (https://coronavirus.jhu.edu/map.html). In hospitalized patients, the mortality rate in the general population varies. In initial study from China, a 28% mortality rate was reported in 191 patients. Clinical outcomes were assessed for 2634 patients who were discharged or had died among 5700 hospitalized patients in the New York area. The authors reported 21% mortality with 12.2% of patients receiving invasive mechanical ventilation and 3.2% treated with kidney replacement therapy. Mortality for those requiring mechanical ventilation was 88.1%. In another cohort of 1150 adults who were admitted with laboratory-confirmed COVID-19 in a New York hospital, of whom 257 (22%) were critically ill, 39% of patients had died, 79% patients received mechanical ventilation, and 31% received renal replacement therapy. Older age, chronic heart and lung disease, and high IL-6 and D-dimer levels were associated with mortality. Last, an initial report from Seattle documented 50% mortality in 24 patients admitted to the ICU, similar to our mortality rate (51%).

In our cohort, 47 patients from Montefiore Medical Center, Bronx, had the highest mortality (40%). A previous report from the same center cited 29% mortality in 28 hospitalized patients during a shorter follow-up. The main difference from other centers is that 89% of Bronx transplant patients were African American or Hispanic. A recent study reported that the Bronx, which has the highest proportion of racial/ethnic minorities, a greater number of people living in poverty, and the lowest levels of educational attainment, had higher rates of hospitalization and death related to COVID-19 compared with other New York City boroughs, despite having the lowest proportion of patients with age > 65 years, indicating the potential importance of social and economic factors.

### TABLE 2  Symptoms, laboratory findings, and outcomes of hospitalized kidney transplant recipients with COVID-19

|                                | Total (N = 144) | Survivors (n = 98) | Nonsurvivors (n = 46) | P value |
|--------------------------------|-----------------|-------------------|-----------------------|---------|
| **Time from symptom onset to admission (d)** | 6.00 [3.00, 8.00] | 6.00 [3.00, 9.00] | 5.00 [2.00, 7.00] | .053    |
| **Fever** | 96 (67.1%) | 66 (68.0%) | 30 (65.2%) | .849 |
| **Myalgia** | 76 (53.1%) | 48 (49.5%) | 28 (60.9%) | .215 |
| **Dyspnea** | 97 (67.8%) | 59 (60.8%) | 38 (82.6%) | .012 |
| **Diabetes** | 55 (38.2%) | 44 (44.9%) | 11 (23.9%) | .017 |
| **Respiratory rate ≥20** | 86 (65.6%) | 50 (54.9%) | 36 (90.0%) | <.001 |
| **Heart rate** | 90.00 [80.00, 104.00] | 91.00 [80.00, 104.75] | 90.00 [84.50, 102.00] | .781 |
| **Systolic blood pressure** | 127.00 [115.25, 140.00] | 126.00 [117.00, 137.50] | 128.00 [114.50, 155.00] | .428 |
| **Diastolic blood pressure** | 72.00 [63.25, 80.00] | 72.00 [64.50, 80.00] | 72.00 [63.00, 82.00] | .978 |

**Laboratory values**

|                                | Total (N = 144) | Survivors (n = 98) | Nonsurvivors (n = 46) | P value |
|--------------------------------|-----------------|-------------------|-----------------------|---------|
| **White blood cell count, \(\times 10^9\)/L** | 6.40 [4.60, 8.31] | 5.95 [4.60, 7.77] | 7.00 [5.35, 9.62] | .162 |
| **Lymphocyte count, \(\times 10^9\)/L** | 0.94 [0.50, 3.08] | 1.20 [0.60, 4.08] | 0.71 [0.40, 1.10] | .004 |
| **Hemoglobin, g/dL** | 11.90 [10.30, 13.20] | 11.90 [10.60, 13.60] | 11.65 [10.25, 13.00] | .333 |
| **Platelet count, \(\times 10^9\) per L** | 178.00 [133.50, 236.75] | 183.50 [144.50, 236.75] | 166.00 [109.50, 237.00] | .157 |
| **Baseline creatinine, mg/dL** | 1.50 [1.10, 1.90] | 1.40 [1.00, 1.80] | 1.60 [1.30, 2.00] | .022 |
| **eGFR** | 48.88 [32.96, 66.21] | 53.54 [39.15, 70.48] | 37.97 [29.76, 52.03] | .001 |
| **Aspartate transaminase, U/L** | 26.00 [20.00, 36.25] | 24.00 [20.00, 34.00] | 30.00 [21.00, 45.75] | .045 |
| **Alanine aminotransferase, U/L** | 20.00 [12.00, 29.00] | 20.00 [12.00, 28.75] | 20.00 [14.25, 28.75] | .594 |
| **Lactate dehydrogenase, U/L** | 317.00 [261.00, 408.25] | 296.00 [245.00, 368.00] | 406.00 [292.00, 474.00] | <.001 |
| **Creatine phosphokinase, U/L** | 83.00 [47.00, 153.00] | 78.00 [47.00, 134.00] | 107.50 [46.25, 198.75] | .309 |
| **C-reactive protein, mg/L** | 41.00 [11.50, 125.35] | 41.00 [10.80, 103.00] | 44.40 [12.95, 170.90] | .21 |
| **Serum ferritin, μg/L** | 1260.00 [525.50, 2620.00] | 1257.50 [410.25, 2819.25] | 1544.00 [629.00, 2296.00] | .594 |
| **D-dimer, μg/mL** | 1.12 [0.62, 2.00] | 1.08 [0.54, 1.92] | 1.17 [0.80, 2.24] | .171 |
| **IL-6, ng/ml** | 36.92 [8.05, 125.35] | 24.80 [5.03, 64.10] | 76.94 [14.43, 194.35] | .007 |

Note: All data reported are median (IQR), n (%), or n/N (%). P values reported result from the Mann-Whitney U test for continuous variables, and \(\chi^2\) test or Fisher exact test (for cell counts <5) for categorical variables.

Abbreviations: COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate.

*Omnibus \(\chi^2\)/Fisher exact test for all subgroups.

The bold values indicates statistically significant values.
Acute kidney injury is common in patients with COVID-19 due to multiple factors, including reduced renal perfusion, multiorgan failure, and cytokine storm. Although the range across centers is wide and later reports showed a higher incidence of acute kidney injury, our data indicate that mortality and the burden of AKI in the transplant population are substantial and at the highest end range of estimates. Interestingly, immunohistochemistry studies of postmortem analysis showed that SARS-CoV-2 NP antigen was accumulated in kidney tubules. Viral infection not only induces CD68+ macrophage infiltration into tubulointerstitium but also enhances complement C5b-9 deposition on tubules. It has been suggested that the virus may trigger direct cytopathic changes in the kidney, although it is unclear what proportions of patients may develop acute kidney injury due to direct SARS-CoV2 pathology vs a consequence of acute tubular injury from cytokine storm, reduction in effective arterial circulating volume, and multiorgan failure.

Supportive care remains the mainstay of treatment for COVID-19, and there are currently no antiviral therapies with proven efficacy. There is an absence of consensus about how to adjust immunosuppression in COVID-19 kidney transplant recipients. Reduction of the dosage of CNIs and reduction in or withdrawal of antimetabolite was considered in patients with COVID-19. However, reduction of immunosuppression could hypothetically exacerbate inflammation in the absence of anti-inflammatory agents. Most of our patients were treated with hydroxychloroquine, an antimalarial medication with in vitro activity against SARS-CoV-2. However, recent evidence from a large observational study and a randomized controlled trial generated after inclusion of patients in our registry does not support a significant benefit of this drug for treatment or prophylaxis of COVID-19. Lopinavir/ritonavir was also frequently used in patients with COVID-19, based on data suggesting efficacy against another coronavirus, Middle East respiratory syndrome. However, Cao et al found no benefit of lopinavir/ritonavir in hospitalized patients with COVID-19 infection. Another antiviral agent, remdesivir, is an adenosine analogue that has shown in vitro activity against other coronaviruses. A double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 documented faster recovery time (11 vs 15 days) and reduced mortality by 14 days (7.1% vs 11.9% in placebo; hazard ratio for death, 0.70; 95% CI, 0.47-1.04). However, another randomized trial conducted in China did not document any clinical benefit of remdesivir. Due to limited number of patients in our study (n = 9), we cannot assess any efficacy of this drug.

**TABLE 3** Outcomes and management of hospitalized kidney transplant recipients with COVID-19

| Outcome/Therapy | Total (N = 144) | Survivors (n = 98) | Nonsurvivors (n = 46) | P value |
|-----------------|-----------------|-------------------|-----------------------|---------|
| Respiratory failure requiring intubation | 42 (29.2) | 19 (19.4) | 23 (50.0) | <.001 |
| Acute kidney injury | 74 (52.1) | 48 (49.0) | 26 (59.1) | .282 |
| Tacrolimus withdrawal | 32 (22.9) | 18 (18.9) | 14 (31.1) | .133 |
| MMF or everolimus withdrawal | 91 (67.9) | 59 (64.8) | 32 (74.4) | .324 |
| Increased steroids | 95 (66.0) | 64 (65.3) | 31 (67.4) | .852 |
| Hydroxychloroquine | 101 (70.6) | 65 (66.3) | 36 (80.0) | .115 |
| Antibiotics | 106 (74.1) | 66 (68.0) | 40 (87.0) | .023 |
| Tocilizumab | 19 (13.4) | 11 (11.3) | 8 (17.8) | .301 |
| Remdesivir | 9 (6.3) | 6 (6.1) | 3 (6.7) | 1 |
| Lopinavir-ritonavir | 7 (4.9) | 3 (3.1) | 4 (8.9) | .206 |
| Darunavir-ritonavir | 3 (2.1) | 2 (2.0) | 1 (2.2) | 1 |
| Darunavir-cobicistat | 1 (0.7) | 0 (0.0) | 1 (2.2) | .315 |

Note: All data reported are median (IQR), n (%), or n/N (%). % values reported exclude missing data. P values reported result from the Mann-Whitney U test for continuous variables, and χ² test or Fisher exact test (for cell counts <5) for categorical variables. Abbreviations: COVID-19, coronavirus disease 2019; MMF, mycophenolate mofetil. The bold values indicates statistically significant values.

**FIGURE 1** Percentages of patients receiving various COVID-19–related therapies stratified by survivors (red) and nonsurvivors (green). HCQ, hydroxychloroquine [Color figure can be viewed at wileyonlinelibrary.com]
IL-6 and procalcitonin levels were markedly elevated in transplant recipients with severe COVID-19. Many large observational studies including COVID-19 patients from the general population also identified IL-6 as a major risk factor for mortality. Tocilizumab is a humanized monoclonal antibody that blocks the IL-6 receptor, which is thought to help attenuate the overstimulated immune response associated with COVID-19 infection. However, published efficacy data of tocilizumab are limited to 21 COVID-19 patients. A multicenter phase 2 trial with tocilizumab is currently under way.

Procalcitonin is a peptide released in the setting of systemic inflammation, in particular bacterial infections, and the magnitude of elevation has correlated with infection severity. Procalcitonin synthesis is triggered by bacterial endotoxin and systemic cytokines such as tumor necrosis factor-α, IL-1β, and IL-6. While procalcitonin has been proposed by some as a biomarker to differentiate bacterial from viral infections, multiple recent studies in COVID-19 patients documented a correlation of procalcitonin with disease severity. It is highly likely that the increased procalcitonin levels correlate with the cytokine storm triggered by SARS-CoV-2. Another possibility is that it represents a bacterial coinfection, though further studies are needed to clarify that. The general recommendations are to not use procalcitonin to guide antibiotic use at this time.

A D-dimer level of >1 µg/mL has been associated with poor prognosis in the setting of COVID-19. In a retrospective study of 183 patients with COVID-19 pneumonia, 71.4% of nonsurvivors had high grade of disseminated intravascular coagulation, with 85.7% having a D-dimer level >3 µg/mL. In our study, D-dimer levels were, on average, >1 µg/mL but did not significantly differ between kidney transplant recipients who died and those who survived, possibly as a consequence of ongoing immunosuppression or intrinsic unique characteristics of this cohort of individuals.

Our multicenter study has several limitations. Individual centers had different approaches and access to medications for the treatment of COVID-19. Therefore, it is difficult to compare treatments, and our data reflect real-world use and outcomes of kidney transplant recipients with COVID-19. In addition, we have focused on a homogeneous cohort of hospitalized kidney transplant recipients, since criteria for diagnosis of COVID-19 in the ambulatory setting were variable and many patients did not have documented follow-up information from centers. Overall, this selection criteria limit the generalizability of our findings and prevent any conclusion about the overall mortality of all kidney transplant patients, only of hospitalized patients.

One other notable limitation of the study is the small sample and retrospective method, which may have resulted in false-positive results, or overestimation. We wish to emphasize the exploratory nature of the study, which was not driven by formal hypotheses but would instead hope that the findings presented here will inform larger studies going forward.

In conclusion, kidney transplant recipients should be closely monitored as they appear to have a high mortality and acute kidney injury rate. Investigation of the best strategy of immunosuppression adjustment on COVID-19 will be needed.

### Table 4 Baseline risk factors predicting survival

| Variable                  | Univariable odds ratio (95% CI) | P value | Multivariable odds ratio (95% CI) | P value |
|---------------------------|---------------------------------|---------|----------------------------------|---------|
| Age                       | 1.07 (1.03-1.11)                | <.001   | 1.07 (1.02-1.14)                | .022    |
| ≤60 y                      | 1 (ref)                         | —       | —                                | —       |
| >60 y                      | 2.64 (1.27-5.77)                | .012    | —                                | —       |
| Diarrhea                   | 0.38 (0.17-0.87)                | .017    | —                                | —       |
| Dyspnea                    | 3.06 (1.34-7.7)                 | .011    | —                                | —       |
| Respiratory rate, breaths/min |                                 |         |                                  |         |
| <20                        | 1 (ref)                         | —       | 1 (ref)                         | —       |
| ≥20                        | 7.38 (2.68-26.18)               | <.001   | 6.88 (1.63-41.98)               | .017    |
| Lactate dehydrogenase, U/L |                                 |         |                                  |         |
| ≤325                       | 1 (ref)                         | —       | 1 (ref)                         | —       |
| >325                       | 3.48 (1.62-7.83)                | .002    | 2.74 (0.8-10.11)                | .114    |
| IL-6, ng/mL                | 1.01 (1-1.01)                   | .013    | 1 (1-1.01)                      | .04     |
| Procalcitonin, ng/mL       |                                 |         |                                  |         |
| <0.5                       | 1 (ref)                         | —       | —                                | —       |
| ≥0.5                       | 3.04 (1.37-6.89)                | .007    | —                                | —       |
| Aspartate transaminase, U/L| 1.02 (1.01-1.04)                | .007    | —                                | —       |
| eGFR                       | 0.97 (0.95-0.99)                | .002    | 0.96 (0.93-0.99)                | .029    |

Abbreviation: eGFR, estimated glomerular filtration rate.

The bold values indicate statistically significant values.
DISCLOSURE
The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Paolo Cravedi https://orcid.org/0000-0001-7837-0923
Samira S. Farouk https://orcid.org/0000-0001-5598-5925
María J. Pérez-Sáez https://orcid.org/0000-0002-8601-2699
Xingxing S. Cheng https://orcid.org/0000-0002-0542-8749
Gianluigi Zaza https://orcid.org/0000-0002-6004-6196
Enver Akalin https://orcid.org/0000-0003-1341-5144
Leonardo V. Riella https://orcid.org/0000-0002-7636-3196

REFERENCES
1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10223):1054-1062.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
3. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-2059.
4. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763-1770.
5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. J Infect. 2020;80(6):607-613.
6. Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int. 2020;97(6):1083-1088.
7. Fernández-Ruiz M, Andrés A, Loinaz C, et al. COVID-19 in solid organ transplant recipients: a single-center case series from Spain. Am J Transplant. 2020;20(7):1849-1858.
8. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. N Engl J Med. 2020;382(25):2475-2477.
9. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant. 2020;20(7):1800-1808.
10. Nair V, Jandovitz N, Hirsch JS, et al. COVID-19 in kidney transplant recipients. Am J Transplant. 2020;20(7):1819-1825.
11. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the seattle region - case series. N Engl J Med. 2020;382(21):2012-2022.
12. Wadhera RK, Wadhera P, Gaba P, et al. Variation in COVID-19 hospitalizations and deaths across New York City Boroughs. JAMA. 2020;323(21):2192.