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Coronavirus Disease 2019 (COVID-19) in Solid Organ Transplant Recipients: A Case-Control Study

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: It is unclear whether solid organ transplant (SOT) patients have more severe coronavirus disease 2019 (COVID-19) and worse outcome than the general population.

Material/Methods: We conducted a case-control study on 32 SOT recipients and 84 non-SOT controls matched for age and sex admitted for confirmed COVID-19. The primary endpoint was in-hospital all-cause mortality rate. Secondary endpoints included severe acute respiratory distress syndrome (ARDS), use of high-flow oxygen therapy, and length of hospital stay.

Results: The median (IQR) Charlson comorbidity index (CCI) at admission was significantly higher in SOT recipients (6 [3-8] vs 3 [2-4]; $P < 0.01$). Fever was less frequent in SOT recipients (78% vs 94%, $P = 0.01$). SOT recipients had a higher median SaO₂/FiO₂ at admission (452 [443-462] vs 443 [419-452], $P < 0.01$) and reached the worst SaO₂/FiO₂ value later during hospitalization 15 (10-21) vs 11 (9-14) days, $P = 0.01$). Both groups had a similar severe ARDS rate during hospitalization (33% vs 28%) ($p = 0.59$). There were no significant differences during hospitalization in terms of highest level of respiratory support needed, or length of hospital stay: 8.5 (5.5-21) vs 11.5 (6.5-16.5) days; $P = 0.34$ in SOT recipients when compared to controls. In-hospital all-cause mortality rates were significantly higher in SOT recipients (21.9% vs 4.7%, $P < 0.01$; OR 1.08; 95% CI 0.10-10.98), but among patients who died, median CCI was similar between groups (8 [6-8] vs 7 [6-8]).

Conclusions: In our experience, hospitalized SOT recipients for COVID-19 had higher in-hospital mortality compared to non-SOT patients, probably due to the greater number of underlying comorbidities, and not directly related to chronic immunosuppression.

Keywords: Liver Transplantation • Heart Transplantation • Kidney Transplantation • COVID-19 • Lung Transplantation • Severe Acute Respiratory Syndrome Coronavirus 2

Abbreviations: COVID-19 – coronavirus disease 2019; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2; ARDS – acute respiratory distress syndrome; SOT recipients – solid organ transplant recipients; non-SOT patients – non-solid organ transplant patients; rt-PCR – real-time reverse transcriptase polymerase chain reaction assay; LDH – lactate dehydrogenase; CRP – C-reactive protein; IL-6 – interleukin-6; SaO₂/FiO₂ – arterial oxygen saturation and inspiratory oxygen fraction ratio; PaO₂ – partial pressure of arterial oxygen; MMF/MPA – mofetil/mycophenolic acid; IQR – interquartile ranges; ORs – odds ratio

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Background

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 when a new strain of coronavirus was isolated and named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. Due to the alarming levels of spread and severity of the outbreak, the World Health Organization characterized COVID-19 as a pandemic on March 11th, 2020 [3]. To date, it is reported that 202 608 000 people have been infected with SARS-CoV-2 worldwide and 4 290 000 people have died due to COVID-19 [4]. Studies on the general population suggest that factors linked to severe disease include advanced age, male sex, and underlying comorbidities such as hypertension, obesity, diabetes, chronic kidney disease, chronic lung disease, and coronary heart disease [1,5-9].

Solid organ transplant (SOT) recipients are also at risk of SARS-CoV-2 infection. Whether SOT recipients are at particularly high risk for severe COVID-19 and worse outcome compared with non-transplant (non-SOT) patients is unclear, as the impact of post-transplant chronic immunosuppression on the natural history of COVID-19 is uncertain. On one hand, chronic immunosuppression can increase the viral load, leading to more severe disease, but on the other hand, these drugs can attenuate the inflammatory response linked to cytokine release syndrome [10,11]. Many of the comorbid conditions linked to severe COVID-19 frequently occur among SOT recipients and it is unclear whether these or other potential confounding features, rather than chronic immunosuppression itself, contribute to the risk.

We report the clinical characteristics and outcomes of a cohort of SOT recipients admitted to hospital with COVID-19 compared with a concomitant cohort of non-SOT COVID-19 patients.

Material and Methods

Design of the Study

This was a single-center retrospective study of consecutive SOT recipients admitted to hospital for confirmed COVID-19 from March 1 to May 31, 2020. Non-SOT patients admitted to hospital due to COVID-19 during the same study period, matched according to sex and age, were used as controls. According to the World Health Organization (WHO) COVID severity scale, patients to be included in the study must have ≥ 3 points in the scale [12].

SARS-CoV-2 infection was confirmed by real-time reverse transcription polymerase chain reaction assay (rt-PCR) in nasopharyngeal swabs specimens. The study was approved by the hospital review board (PI134-20) and informed consent was obtained from all patients to include their clinical information within a database for epidemiological and clinical studies.

Data Collection

Data were retrospectively collected from electronic medical records, and included demographic variables, past medical history, comorbidities, clinical symptoms, physical examination findings, laboratory and diagnostic imaging tests at admission, treatments, in-hospital complications, length of hospital stay, and outcomes (hospital discharge or death).

Age was divided into 3 groups: ≤ 60 years, 61-70 years, and ≥ 71 years. Maximum body temperature was stratified as follows: $\leq 37.3^{\circ}\text{C}$, $37.4\text{-}38^{\circ}\text{C}$, $38.1\text{-}39^{\circ}\text{C}$, and $\geq 39.1^{\circ}\text{C}$. Highest level of respiratory support was categorized attending to the maximum request during admission: room air, oxygen supplementation, use of high-flow oxygen therapy or BiPAP, need for mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). In SOT recipients, time from transplant to COVID-19 diagnosis was expressed in years and categorized into 3 groups: < 1 year, 1-5 years, and > 5 years.

Arterial oxygen saturation and inspiratory oxygen fraction ratio ($\text{SaO}_2/\text{FiO}_2$) was calculated by pulse oximetry. $\text{SaO}_2/\text{FiO}_2$ has a good correlation with the partial pressure of arterial oxygen ratio ($\text{PaO}_2/\text{FiO}_2$) [13]. The worst registry of respiratory situation on medical records during hospitalization was defined by the highest level of respiratory support that the patient needed. Time from symptom onset to the highest respiratory support date was measured in days.

Outcomes and Study Definitions

The primary endpoint was in-hospital all-cause mortality. Secondary endpoints included severe acute respiratory distress syndrome (ARDS) defined as $\text{SaO}_2/\text{FiO}_2$ ratio of 148 ($\text{PaO}_2/\text{FiO}_2$ ratio of 100) [14,15], and length of hospitalization. The outcomes from SOT recipients were compared with those of non-SOT patients.

Immunosuppressive Treatment Approach

According to the general approach in our center, blood levels of tacrolimus, cyclosporine, everolimus, and sirolimus levels were reduced or maintained, and mycophenolate mofetil/mycophenolic acid was reduced or temporally discontinued according to the criteria of the treating physician. The baseline dose of steroids was not modified.

Statistical Analysis

Quantitative variables are expressed as medians with interquartile ranges (IQR) and qualitative variables as counts and percentages. The Mann-Whitney U test and chi-square test were used to compare differences between the SOT recipient group

and the non-SOT recipient group, as appropriate. The association of transplantation and the primary endpoint was assessed through conditional logistic regression to compute odds ratios (ORs) and their 95% confidence intervals (CI). The statistical significance level was set at two-sided *P* value of <0.05. Statistical analyses were performed using the STATA system.

Results

We identified 1494 consecutive adult patients hospitalized with confirmed COVID-19 in our center during the study period. Thirty-two (2.1%) of the 1494 patients were SOT recipients (78.1% males, median age 66.5 years [IQR 63.5-72]). Of the remaining 1462 patients, 84 non-SOT patients that were not under immunosuppressive therapy, matched according to sex and age, were used as controls (79.8% males, median age 65.5 years [IQR 60.5-70.5], *P*=0.40). Characteristics of patients are shown in **Table 1**.

The median time from symptoms onset to hospital admission was 6 days (IQR 4-9), without differences between groups. The median Charlson comorbidity index (CCI) for the overall study population was 3 (IQR 2-5.5). Median CCI was significantly higher in the SOT recipients (6 [IQR 3-8] vs 3 [IQR 2-4]; *P*<0.01).

The most common presenting symptoms were fever, cough, and dyspnea. Fever was less frequent in SOT recipients (78% vs 94%, *P*=0.01). No significant differences between SOT recipients and controls were found for cough (62.5% in SOT recipients vs 76%; *P*=0.14) and dyspnea (44% in SOT recipients vs 54%, *P*=0.34). All patients presented pneumonia at admission. SOT recipients had a higher median SaO₂/FiO₂ at admission (452 [IQR 443-462] vs 443 [IQR 419-452], *P*<0.01) and reached the worst SaO₂/FiO₂ value later during hospitalization (15 days [IQR 10-21] vs 11 days [IQR 9-14], *P*=0.01).

Biochemical findings upon admission are shown in **Table 2**. Significant differences between SOT recipients and controls were found for serum creatinine (1.7 mg/dl [1.1-3.0 mg/dl]) vs 0.8mg/dl [0.6-1.0 mg/dl], *P*<0.001). Blood cell count and inflammatory biochemical parameters (CRP, serum ferritin, and IL-6) were comparable.

Severe ARDS was developed in 37 (31.9%) patients overall and was similar between the 2 groups (SOT recipients 28.1% vs 33.3%, *P*=0.59). There were no significant differences during hospitalization in terms of highest level or respiratory support needed or length of hospital stay in SOT recipients when compared to controls (**Table 3**).

The in-hospital all-cause mortality rate was significantly higher in SOT recipients than in the control group (21.9% vs 4.7%,

P<0.01). It is noteworthy that among patients who died, the median CCI score was similar between groups (SOT recipients 8 [IQR 6-8] vs 7 [IQR 6-8]). Four out of the 7 SOT recipients who died were older than 70 years compared with 2 out of the 4 controls (*P*=0.819). COVID-19-related lung disease was the main cause of death in both groups. The relatively small sample size of SOT recipients did not allow further risk stratification analysis. Conditional logistic regression was performed, but due to the low number of events, it cannot be inferred that immunosuppression and/or being a SOT recipient are conditioning factors of higher risk of mortality (OR 1.08; 95% CI 0.10-10.98).

Among SOT recipients, 11 (34%) received a liver, 9 (28%) received a kidney, 7 (22%) received a heart, and 5 (16%) received a lung. The median time from transplant to hospital admission for COVID-19 was shorter in lung transplant recipients (3.13 years [IQR 0.68-9.85]) and longer in liver transplant recipients (13.25 [IQR 3.71-15.94] years). Baseline immunosuppression regimen and management of immunosuppressive drugs after COVID-19 diagnosis are described in **Table 4**. Tacrolimus (n=21; 65.6%), mycophenolate mofetil (n=21; 65.6%), and steroids (n=21; 65.6%) were the predominant immunosuppressants. Among COVID-19 diagnosis, immunosuppressive regimens were modified in all patients. Tacrolimus dose was reduced in 10 of the 21 patients, discontinued in 4 patients, and remained unchanged in 7 patients. Cyclosporine A dose was reduced in 1 out of 5 patients, discontinued in 1 patient, and unchanged in 3 patients. Mycophenolate mofetil dose was reduced in 6 patients and discontinued in 15 of the 21 patients (71%). There were no graft rejection episodes during the study period.

Discussion

In the present study, days elapsed from symptoms onset to hospital admission were comparable between groups, which allowed us to compare COVID-19 disease evolution over time in SOT recipients and in controls. SOT recipients were less likely to have fever at admission (78% vs 94%) and had lower body temperature values during hospitalization. This fact is well known in SOT recipients, and it is related to the anti-inflammatory effect of immunosuppressive drugs. Dyspnea, cough, inflammatory biochemical parameters values at admission, and risk of developing severe ARDS in SOT recipients were similar to controls. Elapsed time from admission to worst SaO₂/FiO₂ value during hospitalization was greater in SOT recipients (15 days [IQR 10-21] vs 11 days [IQR 9-14]; *P*=0.01). These data suggest that the clinical course among patients hospitalized due to COVID-19 is similar and evolves slower compared with a general population matched according to sex and age, contrary to the results of other series [16].

Table 1. Epidemiological and clinical characteristics.

| | All patients (N=116) | SOT-recipients (N=32) | No-SOT patients (N=84) | P |
|---|-------------------------|--------------------------|---------------------------|-------|
| Epidemiological characteristics | | | | |
| Age | | | | |
| Median (IQR) | 66 [61.5-71] | 66.5 [63.5-72] | 65.5 [60-70.5] | 0.40 |
| Distribution (%) | | | | |
| <60 years | 28 (24.1) | 6 (18.7) | 22 (26.2) | |
| 61-70 years | 58 (50) | 17 (53.1) | 41 (48.8) | |
| >71 years | 30 (25.9) | 9 (28.1) | 21 (25) | |
| Female gender (%) | 24 (20.7) | 7 (21.9) | 17 (20.2) | 0.84 |
| Hypertension (%) | 65 (56) | 21 (65.6) | 44 (52.4) | 0.2 |
| Diabetes (%) | 34 (29.3) | 14 (43.7) | 20 (23.8) | 0.03 |
| Chronic heart failure (%) | 15 (12.9) | 10 (31.2) | 5 (5.9) | <0.01 |
| Coronary heart disease (%) | 11 (9.5) | 5 (15.6) | 6 (7.1) | 0.16 |
| Chronic obstructive pulmonary disease (%) | 16 (13.8) | 8 (25) | 8 (9.5) | 0.03 |
| Chronic renal disease (%) | 23 (19.8) | 20 (62.5) | 3 (3.6) | <0.01 |
| Median Charlson Index (IQR) | 3 [2-5.5] | 6 [3-8] | 3 [2-4] | <0.01 |
| Clinical characteristics | | | | |
| Days from clinical onset to admission (IQR) | 6 (4-9) | 6.5 [3-9.5] | 6 [4-8] | 0.79 |
| Fever on admission (%) | 104 (89.7) | 25 (78.1) | 79 (94.1) | 0.01 |
| Maximum temperature during hospitalization | | | | |
| <37.3°C (%) | 15 (12.9) | 7 (21.9) | 8 (9.5) | |
| 37.4-38°C (%) | 37 (31.9) | 12 (37.5) | 25 (29.8) | |
| 38.1-39°C (%) | 55 (47.4) | 12 (37.5) | 43 (51.2) | |
| >39°C (%) | 19 (7.7) | 1 (3.1) | 8 (9.5) | |
| Dry cough | 84 (72.4) | 20 (62.5) | 67 (76.2) | 0.14 |
| Dyspnea | 59 (50.9) | 14 (43.7) | 45 (53.6) | 0.34 |
| Diarrhea | 24 (20.7) | 10 (31.2) | 14 (16.7) | 0.08 |
| Myalgia or arthralgia | 42 (36.2) | 11 (34.4) | 31 (36.9) | 0.8 |
| SaO ₂ /FiO ₂ on admission | 447.62 [428.6-457.1] | 452.38 [442.9-461.9] | 442.86 [419.1-452.4] | <0.01 |
| Severe ARDS during admission (%) | 37 (31.9) | 9 (28.1) | 28 (33.3) | 0.59 |
| Highest level of respiratory support (%) | | | | |
| Room air | 28 (24.1) | 12 (37.5) | 16 (19.1) | 0.07 |
| Nasal cannula | 45 (38.8) | 11 (34.4) | 34 (40.5) | |
| Non-rebreather-mask | 20 (17.2) | 3 (9.4) | 17 (20.2) | |
| High flow or BiPAP | 9 (7.7) | 5 (15.6) | 4 (4.8) | 0.12 |
| Intubation | 14 (12.1) | 1 (3.1) | 13 (15.5) | 0.13 |
| Days to worst respiratory parameters since clinical onset | 11 [9-15] | 15 [10-21] | 11 [9-14] | 0.01 |

Results are expressed as mean±standard deviation and number (percentage). SOT – solid organ transplant; IQR – interquartile ranges; SaO₂/FiO₂ – arterial oxygen saturation and inspiratory oxygen fraction ratio; BiPAP – bilevel positive airway pressure.

Table 2. Laboratory findings.

| | All patients (N=116) | SOT-recipients (N=32) | No-SOT patients (N=84) | P |
|---|-------------------------|--------------------------|---------------------------|-------|
| Laboratory findings on admission (IQR) | | | | |
| Creatinine – mg/dl | 0.9 [0.7-1.2] | 1.7 [1.1-3.0] | 0.8 [0.6-1.0] | <0.01 |
| Bilirubin – mg/dl | 0.5 [0.4-0.8] | 0.5 [0.4-0.6] | 0.5 [0.3-0.8] | 0.64 |
| AST – U/L | 35.5 [27-44] | 31.5 [22.5-42] | 36.5 [29-51] | 0.03 |
| ALT – U/L | 24.5 [18-36] | 24 [17-33] | 25 [19-39] | 0.28 |
| GGT – U/L | 45.5 [32-87] | 54 [36-66.5] | 44.5 [31-93] | 0.62 |
| ALP – U/L | 65 [56-88] | 72 [55-93] | 64 [56.5-78.5] | 0.21 |
| LDH – U/L | 277 [225-343.5] | 263 [226-336] | 279 [224-347] | 0.58 |
| Serum ferritin ng/ml | 797 [458-1156] | 700.5 [404-1146.5] | 813 [480-1261] | 0.47 |
| CRP – mg/L | 73.4 [34-156.7] | 68.1 [31.3-139.3] | 85 [34.3-160] | 0.38 |
| IL6 – pg/ml | 44.5 [17.9-93.4] | 38.85 [16.8-100.9] | 46.86 [17.4-93.4] | 0.86 |
| Leukocytes 10 ³ /μL | 6.3 [4.4-7.9] | 6.56 [4.3-7.6] | 6.06 [4.5-8.3] | 0.73 |
| Lymphocytes 10 ³ /μL | 0.9 [0.6-1.2] | 0.9 [0.6-1.6] | 0.96 [0.7-1.2] | 0.86 |
| Platelets 10 ³ /μL | 169 [136-220] | 153.5 [131-206] | 171 [142-223] | 0.19 |
| D-dimer – μg/ml | 0.7 [0.5-1.3] | 0.7 [0.4-1.1] | 0.7 [0.5-1.3] | 0.61 |
| INR | 1.1 [1.0-1.2] | 1.0 [1.0-1.3] | 1.1 [1.0-1.1] | 0.03 |
| Laboratory findings on 7th day of hospitalization (IQR) | | | | |
| Creatinine (mg/dl) | 0.8 [0.7-1.1] | 1.3 [1-1.9] | 0.8 [0.6-1] | <0.01 |
| Bilirubin (mg/dl) | 0.7 [0.4-0.9] | 0.4 [0.3-0.7] | 0.7 [0.5-0.9] | <0.01 |
| AST – U/L | 35 [26.5-49] | 33 [27-47] | 35.5 [26-49] | 0.80 |
| ALT – U/L | 35 [22.5-58.5] | 34.5 [16-46] | 36 [24-66] | 0.23 |
| GGT – U/L | 65 [42-125] | 68 [46-111] | 65 [42-125] | 0.88 |
| ALP – U/L | 60 [53-92] | 60 [56-93] | 60 [49-91] | 0.58 |
| LDH – U/L | 300 [239-431] | 264 [235-438] | 306 [242-417] | 0.83 |
| Serum ferritin ng/ml | 915 [486-1453] | 962 [417-1608] | 915 [491-1439] | 0.95 |
| CRP – mg/L | 34.5 [15.4-107] | 29.15 [13.1-80.7] | 35.3 [16.2-117.1] | 0.35 |
| IL6 – pg/ml | 119.4 [10-570.3] | 226 [4.7-660] | 91.75 [10-511.6] | 0.32 |
| Leukocytes 10 ³ /μL | 7.0 [4.7-10.3] | 4.6 [3.5-7.1] | 7.9 [5.3-10.8] | <0.01 |
| Lymphocytes 10 ³ /μL | 0.9 [0.6-1.3] | 0.7 [0.4-1.3] | 1 [0.7-1.4] | 0.07 |
| Platelets 10 ³ /μL | 267 [198-339.5] | 184 [143-291] | 278 [228-347] | <0.01 |
| D-dimer – μg/ml | 1.0 [0.5-1.8] | 0.8 [0.5-1.5] | 1 [0.5-2] | 0.44 |
| INR | 1.1 [1-1.2] | 1.1 [1-1.2] | 1.1 [1-1.1] | 0.35 |

Results are expressed as mean±standard deviation. AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGT – gamma-glutamyl transferase; ALP – alkaline phosphatase; LDH – lactate dehydrogenase; CRP – C-reactive protein; IL-6 – interleukin 6; INR – international normalized ratio.

Table 3. Primary and secondary outcomes.

| | All patients (N=116) | SOT-recipients (N=32) | No-SOT patients (N=84) | P |
|-------------------------|-------------------------|--------------------------|---------------------------|-------|
| Mortality (%) | 11 (9.5) | 7 (21.9) | 4 (4.8) | <0.01 |
| Severe ARDS (%) | 37 (31.9) | 9 (28.1) | 28 (33.3) | 0.59 |
| Days of hospitalization | 10.5 [6-17] | 8.5 [5.5-21] | 11.5 [6.5-16.5] | 0.34 |

Results are expressed as mean±standard deviation and number (percentage). ARDS – acute respiratory distress syndrome.

Table 4. Baseline characteristics of solid organ transplant recipients.

| | All transplant recipients N=32 | Liver recipients N=11 (34.37) | Kidney recipients N=9 (28.12) | Heart recipients N=7 (21.87) | Lung recipients N=5 (15.62) |
|---|--------------------------------------|----------------------------------|----------------------------------|---------------------------------|--------------------------------|
| Median age (IQR) | 66.5 [63.5-72] | 68 [63-69] | 68 [64-74] | 67 [56-72] | 64 [64-66] |
| Years from transplant to diagnosis | | | | | |
| <1 year (%) | 4 (12.5) | 1 (9.1) | 1 (11.1) | 0 | 2 (40) |
| 1-5 years (%) | 9 (28.1) | 2 (18.9) | 3 (33.3) | 3 (42.8) | 1 (20) |
| >5 years (%) | 19 (59.4) | 8 (72.7) | 5 (55.6) | 4 (57.1) | 2 (40) |
| Baseline Immunosuppressant (%) | | | | | |
| Tacrolimus | 21 (65.6) | 6 (54.5) | 7 (77.8) | 3 (42.8) | 5 (100) |
| Ciclosporine A6 | 5 (15.6) | 1 (9.1) | 1 (11.1) | 3 (42.8) | 0 |
| Mycophenolate | 21 (65.6) | 5 (45.45) | 8 (88.9) | 5 (71.4) | 3 (60) |
| Everolimus | 5 (15.6) | 3 (27.3) | 0 | 1 (14.3) | 1 (20) |
| Steroids | 21 (65.6) | 0 | 9 (100) | 7 (100) | 5 (100) |
| Changes in immunosuppression (%) | | | | | |
| Decrease or hold CNI | 17/26 (65.4) | 4/7 (57.1) | 8/8 (100) | 2/6 (30) | 3/5 (60) |
| Decrease or hold mycophenolate | 15/21 (71.4) | 0 | 7/8 (87.5) | 5/5 (100) | 2/3 (66.7) |
| Decrease or hold steroids | 2/21 (9.5) | 0 | 0 | 0 | 2/5 (40) |
| Primary outcome | | | | | |
| Mortality (%) | 7 (21.9) | 2 (18.2) | 1 (11.1) | 3 (42.8) | 1 (20) |

Results are expressed as mean±standard deviation and number (percentage). IQR – interquartile ranges.

The in-hospital mortality rate in SOT recipients in our series was 21.9%, similar to the rates of 4.8-37% described by others [16-36]. To date, several articles related with COVID-19 mortality in transplant patients have been published, but their results are variable and heterogeneous. Discarding the studies that analyzed a single organ type of transplant and hematopoietic transplant, most of them demonstrate high mortality rates [17-24]. However, it is noteworthy that some of these studies did not compare their results with the non-transplanted population [17-20], while others did not find such high mortality

rates or any differences compared with the non-transplanted population [16,25-30]. Mortality rates in these series were affected by age, number of underlying comorbidities, and by the population analyzed (hospitalized patients only [16,21,24,30] or also outpatients [17-20,22-23,25-28]). In our opinion, inclusion of outpatients can bias the comparison between both groups, since transplant patients are usually closely monitored, which makes it more likely to diagnose mild or asymptomatic cases. The study and follow-up periods were also heterogeneous among publications, which makes interpretation of

results difficult, especially considering how fast the protocols were changing for this group of patients in recent months. Some studies adjusted the comparison of groups according to their comorbidities but not to the Charlson index [23]. In our series, mortality during admission was almost 4 times higher in SOT recipients (21.9% vs 4.7%). The lower mortality rate observed in our study in non-SOT patients compared to other series could be explained by the low number of patients between 71 and 79 years (25%) and older than 80 years (4.16%) in our cohort. Mortality for these age groups is closer to that reflected in other series, at 12% and 40%, respectively [31].

To date, some studies suggested that elapsed time from transplantation is a risk factor linked to higher mortality in patients hospitalized for COVID-19 [32-34], with higher mortality in patients transplanted more than 10 years ago, with reduced immunosuppression, higher comorbidities, and age over 65 years [34]. In our series, of the 7 dead SOT patients, 29% had been transplanted less than 5 years ago, 14% 5-10 years ago, and 57% more than 10 years ago. This higher mortality in long-term survival SOT recipients could be explained by the high rate of comorbidities in this population, conditioned by chronic immunosuppressive treatment and other pathologies, some of which were the direct cause of the need for transplant. Some studies have shown a worse course of infection as the CCI increases [35]. In our series, among the 7 SOT recipients who died, the median CCI was 8 points (6-8) and 4 were older than 70 years. Non-SOT patients who died had a median of 7 points (6-8) in CCI, and 2 out of 4 were older than 70 years. All of them had severe ARDS.

The strengths of this study are that the same criteria were used for all the patients, for hospitalization and similar treatment strategy, and modifications in immunosuppressant treatment. Nevertheless, we are aware that our study suffers from some limitations, mainly due to the retrospective design and the small number of SOT recipients, which prevent forming strong conclusions on the efficacy of the optimal management of immunosuppression in SOT recipients with COVID-19.

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Conclusions

Despite the published literature, there are still many gaps in knowledge about the relationship between COVID-19 and solid organ transplantation. There is no doubt that these are high-risk patients due to their close contact with the hospital environment, but the role of immunosuppression and the best management options are still unknown. The results in different publications regarding mortality due to COVID-19 in transplant patients are heterogeneous, probably due to the difficulty of knowing the degree of immunosuppression of each patient and the different treatment regimens available. We contribute with a new series of admitted transplant patients compared with non-transplanted patients of the same age and sex during a period of time in which the admission criteria and the management protocol were the same for both groups.

In our experience, SOT recipients hospitalized for COVID-19 had higher in-hospital mortality compared to non-SOT patients, probably due to greater underlying comorbidities and not directly related to chronic immunosuppression. No differences were found between groups in clinical course, severe ARDS, length of hospital stay, and highest level or respiratory support needed. However, the patients who died in both groups had an elevated and similar CCI, suggesting the high mortality risk of comorbidity. In our series, the CCI was higher in transplant patients, which could explain the higher mortality in this group.

Patient Permission/Consent

The study was approved by the hospital review board (PI134-20) and informed consent was obtained from all patients to include their clinical information within a database for epidemiological and clinical studies.

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