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# Immune-Suppression Modulation in Solid Organ Transplant Recipients Admitted for COVID-19

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**Abstract**

SARS-CoV-2 infection has significantly impacted solid organ transplant (SOT) recipients, who are at high risk of disease and worse outcomes. Moreover, therapeutic management in this population is not precise yet. Our study aimed to evaluate the overall survival of SOT recipients and predictive factors for mortality. We also aimed to assess the impact of antiviral treatments and immunosuppressant changes on overall mortality and to evaluate the length of hospital stay of SOT compared to the general population. This is a retrospective monocenter study. We included all SOT recipients with laboratory-confirmed SARS-CoV2 infection admitted at Niguarda Hospital in Milan from February 2020 through January 2022. We enrolled 74 solid organ transplant recipients with a median age of 59. The overall mortality rate was 19%. Older age, male sex, diabetes, and high LDH values were associated with an increasing fatality rate. The median length of stay (LoS) was 17 days. Low white blood count and lymphocyte levels were associated with 19 days LoS. Changes in immunosuppression and

SARS-CoV-2 antiviral therapies had no impact on mortality and LoS. In this study, we confirm previously described risk factors for worse outcomes. We did not observe beneficial therapies in terms of mortality rate and LoS. Seven patients received antiviral treatment. More studies are needed to assess the best therapeutical options, including immunosuppressant modulation, in SOTs.

**Keywords**
SARS-CoV-2; COVID-19; immunosuppressor; solid organ transplant; SOT

## 1. Introduction

Immunocompromised hosts, e.g., solid organ transplant (SOT) recipients, are at higher risk of SARS-CoV-2 infection and of a more severe course of COVID-19 disease. In this population, the role of immunosuppressants is not entirely understood as these may favor viral infection and decrease immune response against viruses while lowering the inflammatory burden that sustains clinical disease. Furthermore, several different therapeutic options have been used during the pandemic, and their role in SOT recipients is unclear.

Our study aimed to evaluate the overall survival of SOT recipients and predictive factors for mortality. We also aimed to assess the impact of antiviral treatments and immunosuppressant changes on overall mortality and to evaluate the length of hospital stay of SOT compared to the general population.

## 2. Methods

A retrospective monocentric analysis included all SOT recipients with laboratory-confirmed SARS-CoV-2 infection admitted to a tertiary hospital in Milan, Northern Italy, from February 18, 2020, to January 18, 2022.

Data were collected from hospital electronic records.

Microbiologic diagnosis of SARS-CoV-2 infection was a positive real-time polymerase chain reaction (RT-PCR) test from respiratory specimens (nasopharyngeal swabs or bronchoalveolar lavage).

Clinical severity at hospitalization was recorded according to the WHO-COVID classification and $SpO_2/FiO_2$ ratio [1]. A “severe” case was defined as the presence of respiratory distress (respiratory rate ≥30 per min), oxygen saturation on room air at rest ≤93% or P/F (or Horowitz Index, partial pressure of oxygen in arterial blood/fraction of inspired oxygen) ≤300 mmHg; a “critical” case was defined as the presence of respiratory failure needing ventilation (either invasive or not), septic shock or any other organ dysfunction requiring intensive care unit (ICU) monitoring and treatment.

Median and interquartile range (IQR) were used to describe continuous variables' absolute and relative (%) values for categorical variables. Non-parametric tests were applied to compare the groups: one-way ANOVA for independent measures for constant and Fisher's exact test for categorical variables. Median hospital length of stay (LoS) was compared to that defined by Wang Z. et al. (19 days, IQR 14-23) [2]. The Kaplan-Meier method evaluated patient overall survival and LoS; the curves obtained were compared using the log-rank test. Demographic, clinical, and

biochemistry parameters were tested as predictors of outcome using unadjusted and adjusted Cox proportional hazards models. The Cox proportional hazards assumption was assessed using the Breslow method to handle tied failures [3]. Two-tailed p-values were calculated, and a value below 0.05 was considered statistically significant. Data management and analysis were performed using the STATA package, version 16.1 (College Station, TX, StataCorp 2019).

## 3. Results

The analysis included 74 SOT recipients: 29 (39%) kidney (KT), 29 (39%) liver (LT), 9 (12%) heart (HT), and 7 (10%) combined transplants (CT) (Table 1). Median age was 59 (51-66) years and 66% were males. The most common immunosuppressive regimen at the time of hospital admission was a calcineurin inhibitor (CNI): 51% were on cyclosporine A (CyA) and 43% on tacrolimus (FK506). Steroids and mycophenolate mofetil (MMF) were associated in 60% and 62% of cases. The second immunosuppressive agent was different among the type of transplant groups ($p < 0.001$), as was the number of immunosuppressants currently assumed: 45% of patients were on triple immunosuppressive therapy, with a more considerable prevalence in KT recipient ($p < 0.001$). Groups had heterogenous CyA plasmatic concentration two hours after drug intake, with higher levels in LT and CT ($p = 0.023$), as well as the dosage of steroids and MMF ($p < 0.001$ and $p = 0.042$, respectively). The study population exhibited several comorbidities: the most common was arterial hypertension followed by chronic renal failure (creatinine 2.3 [1.4-2.6] mg/dL) and diabetes, without difference among groups.

**Table 1** Clinical and demographic characteristics.

| **Parameter** | **Liver transplant (29)** | **Kidney transplant (29)** | **Hearth transplant (9)** | **Combine transplant (7)** | **Overall cohort (74)** | **p** |
|---|---|---|---|---|---|---|
| **Age(y) median, (IQR)** | 61 (53-68) | 58 (54-63) | 59 (55-63) | 56 (50-70) | 59 (51-66) | 0.948 |
| **Gender %, (N)** | | | | | | |
| **Man** | 69 (20) | 62 (18) | 55 (5) | 86 (6) | 66 (49) | 0.652 |
| **Previous Medical History %, (N)** | | | | | 92 (68) | |
| BMI (kg/m$^2$) median, (IQR) | 27 (22-28) | 27 (25-29) | 29 (28-31) | 25 (25-25) | 27 (24-30) | 0.284 |
| Diabetes | 45 (13) | 21 (6) | 22 (2) | 43 (3) | 32 (24) | 0.192 |
| Hypertension | 41 (12) | 55 (16) | 11 (1) | 57 (4) | 45 (33) | 0.112 |
| COPD | 10 (3) | 3 (1) | 11 (1) | 0 | 7 (5) | 0.652 |
| Chronic renal failure | 34 (10) | 31 (9) | 33 (3) | 71 (5) | 36 (27) | 0.730 |
| Smoking | 3 (1) | 3 (1) | 0 | 14 (1) | 4 (3) | 0.520 |
| **Charlson median (IQR)** | 4.28 (2-6) | 2.77 (1-4) | 3.89 (3-5) | 4.8 (2-7) | 3.6 (2-5) | 0.415 |
| **Re-TX %, (n)** | 10 (2) | 17 (5) | 0 | 14 (1) | 11 (8) | 0.399 |
| **SARS-CoV-2 variant %, (n)** | | | | | | 0.177 |
| Wilde type sars-cov-2 | 66 (19) | 73 (21) | 33 (3) | 86 (6) | 66 (49) | |
| Alpha variant (12.20) | 24 (7) | 21 (6) | 45 (4) | 14 (1) | 24 (18) | |
| Delta variant (07.21) | 10 (3) | 3 (1) | 0 | 0 | 6 (4) | |
| Omicron variant (12.21) | 0 | 3 (1) | 22 (2) | 0 | 4 (3) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Pandemic wave %, (n)** | | | | | | 0.175 |
| First pandemic wave (02.2020-05.2020) | 34 (10) | 35 (10) | 0 | 57 (4) | 33 (24) | |
| Second pandemic wave (10.2020-04.2021) | 45 (13) | 48 (14) | 56 (5) | 43 (3) | 47 (35) | |
| Non pandemic period | 21 (6) | 17 (5) | 44 (4) | 0 | 20 (15) | |
| **Main Immunosuppressor at Baseline (Drugs) %, (n)** | | | | | | |
| Cyclosporine | 38 (11) | 59 (17) | 56 (5) | 72 (5) | 51 (38) | 0.246 |
| Tacrolimus | 59 (17) | 35 (10) | 44 (4) | 14 (1) | 43 (32) | |
| None | 3 (1) | 6 (2) | 0 | 14 (1) | 6 (4) | |
| **Second Immunosuppressor (Drugs) %, (n)** | 10 (3) | 73 (21) | 56 (5) | 57 (4) | 45 (33) | <0.001 |
| mTOR inhibitors | 3 (1) | 0 | 11 (1) | 14 (1) | 4 (3) | |
| Steroids | 17 (5) | 13 (4) | 0 | 29 (2) | 15 (11) | |
| Mycophenolate | 35 (10) | 7 (2) | 33 (3) | 0 | 20 (15) | |
| None | 35 (10) | 7 (2) | 0 | 0 | 16 (12) | |
| **Third Immunosuppressor (Drugs) %, (N)** | | | | | | <0.001 |
| Steroids | 10 (3) | 66 (19) | 56 (5) | 57 (4) | 42 (31) | |
| mTOR inhibitors | 0 | 6 (2) | 0 | 0 | 3 (2) | |
| None | 90 (26) | 28 (8) | 44 (4) | 43 (3) | 55 (41) | |
| **Immunosuppression levels at baseline Median (IQR)** | | | | | | |
| CyA level C2 | 407.5 (194-628) | 303.5 (168-439) | 166.5 (140-191.5) | 540 (540-540) | 248 (168-540) | 0.023 |
| FK level | 6.6 (3.9-8.9) | 7.6 (6.1-9.6) | 11.15 (6.45-14.15) | 7.8 (7.8-7.8) | 7.3 (5-8.9) | 0.402 |
| Steroid dose MPND or equivalent (mg) | 8 (6-16) | 4 (4-4) | 16 (12-32) | 4 (2-4) | 4 (4-10) | <0.001 |
| MMF dose | 1500 (1000-2000) | 1000 (1000-1440) | 1500 (860-1500) | 1220 (680-1720) | 1080 (1000-1750) | 0.042 |
| **Interval since tx and infection (n months) median, (IQR)** | 90 (16-146) | 76 (32-137) | 42 (26-122) | 119 (59-226) | 80 (29-145) | 0.013 |
| **Clinical presentation of COVID-19 %, (n)** | | | | | | |
| Fever | 69 (20) | 86 (25) | 89 (8) | 57 (4) | 78 (58) | |
| Cough | 24 (7) | 59 (17) | 11 (1) | 86 (6) | 42 (31) | |
| Anosmia/disgeusia | 3 (1) | 7 (2) | 0 | 14 (1) | 7 (4) | |
| Gastrointestinal | 21 (6) | 10 (3) | 11 (1) | 0 | 14 (10) | |
| Asymptomatic | 17 (5) | 0 | 11 (1) | 0 | 11 (6) | |
| **Interval since symptoms** | 3 (0-6) | 7 (2-10) | 3 (1-6) | 4 (2-10) | 4 (1-7) | 0.642 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **and admission (n days) median, (IQR)** | | | | | | |
| **Length of hospitalization (n days) median, (IQR)** | 27 (13-46) | 17 (9-35) | 13 (11-15) | 16 (14-33) | 17 (12-35) | <0.001 |
| **Covid-19 Specific Therapy %, (n)** | | | | | | |
| Steroid | 45 (13) | 66 (19) | 67 (6) | 71 (5) | 58 (43) | 0.359 |
| LWMH | 17 (5) | 38 (11) | 22 (2) | 57 (4) | 30 (22) | 0.116 |
| Remdesivir | 10 (3) | 7 (2) | 22 (2) | 0 (0) | 9 (7) | 0.509 |
| Inadequate(lopinavir-ritonavir, hydroxychloroquine, azithromycin) | 21 (6) | 28 (8) | 0 | 43 (3) | 23 (17) | |
| None | 41 (12) | 10 (3) | 22 (2) | 0 | 23 (17) | |
| Convalescent plasma | 7 (2) | 7 (2) | 0 | 14 (1) | 7 (5) | 0.724 |
| Tocilizumab | 0 | 3 (1) | 0 | 29 (2) | 4 (3) | 0.027 |
| mAbs | 7 (2) | 7 (2) | 22 (2) | 0 | 8 (6) | 0.373 |
| **Interval Since Symptoms and Start Therapy (N Days) Median, (IQR)** | 6 (3-7) | 6 (3-10) | 6 (3.5-8.5) | 7.4 (3-11) | 6 (3-10) | 0.001 |
| **Immunosuppression modification %, (n)** | 31 (9) | 90 (26) | 67 (6) | 86 (6) | 64 (47) | <0.001 |
| **Type Of Immununosuppression Modification %, (n)** | | | | | | |
| Stop/reduce MMF | 24 (7) | 66 (19) | 67 (6) | 71 (5) | 50 (37) | 0.001 |
| No MMF modification | 66 (19) | 10 (3) | 33 (3) | 14 (1) | 35 (26) | |
| **Chest CT scan %, (n)** | | | | | | |
| Ground glass opacities | 100 (14) | 100 (27) | 86 (6) | 100 (7) | 98 (54) | 0.255 |
| Normal | 0 | 0 | 14 (1) | 0 | 2 (1) | |
| Lobar opacities | 16 (3) | 13 (4) | 0 | 40 (2) | 6 (10) | |
| **Severity classification %, (n)** | | | | | | 0.426 |
| Mild | 31 (9) | 10 (3) | 34 (3) | 0 | 20 (15) | |
| Moderate | 34 (10) | 35 (10) | 34 (3) | 58 (4) | 37 (27) | |
| Severe | 21 (6) | 35 (10) | 22 (2) | 42 (3) | 28 (21) | |
| Critical | 14 (4) | 20 (6) | 11 (1) | 0 | 15 (11) | |
| **Respiratory support %, (n)** | 55 (16) | 93 (27) | 56 (5) | 86 (6) | 73 (54) | 0.003 |
| **Type of respiratory support %, (n)** | | | | | | 0.044 |
| None | 38 (11) | 7 (2) | 45 (4) | 14 (1) | 24 (18) | |
| Low flow | 21 (6) | 51 (15) | 11 (1) | 43 (3) | 34 (25) | |
| NIV | 31 (9) | 21 (6) | 33 (3) | 29 (2) | 27 (20) | |
| Mechanical ventilation | 10 (3) | 21 (6) | 11 (1) | 14 (1) | 15 (11) | |

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|---|---|---|---|---|---|---|
| **Added Lung Infections %, (n)** | 34 (10) | 17 (5) | 11 (1) | 29 (2) | 24 (18) | 0.348 |
| **Death %, (n)** | 21 (6) | 14 (4) | 33 (3) | 14 (1) | 19 (14) | 0.581 |

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; Re TX, re transplanted; CyA C2, two- hours post-dose cyclosporine level; FK 506, Tacrolimus; mAbs, monoclonal antibodies; NIV, non-invasive ventilation.

Most of the patients experienced SARS-CoV-2 infection several months post-transplantation: median time from transplant to disease was longer in LT (90 [16-146] months) and shorter in HT (42 [26-122] months) (p = 0.013). No difference in severity score at hospital admission was observed (p = 0.426).

Forty-seven patients (67%) modified their immunosuppressive regimen during hospitalization, although the type of change was not homogeneous among groups (p < 0.001). MMF withdrawal was the most common intervention (50%, p = 0.001). Despite the reduction of immunosuppressive therapy and the concomitant immune activation due to COVID-19 disease, no patients experienced graft rejection.

Time from symptoms to therapy administration differed among groups (p = 0.001): CT recipients started SARS-CoV-2 treatment slightly later than the other transplants (7 vs 6 days, p = 0.001). Lymphocyte lowest count (p < 0.001), D-dimer (p < 0.001), lowest platelets value (p = 0.004), procalcitonin (PCT) (p < 0.001), aspartate aminotransferase (AST) (p < 0.001) and interleukin-6 (IL 6) (<0.001) were different during hospitalization among groups.

Overall mortality was 19%: no difference was observed between groups (p = 0.581, log-rank = 0.291). In the Cox regression analysis, diabetes mellitus and female sex were significantly associated with mortality in the multivariate model (Table 2). Specific COVID-19 therapies are underlined in Table 1, and only seven patients were exposed to remdesivir (10%). Neither COVID-19-specific treatment nor the time to any COVID-19 therapy initiation was significantly related to mortality, as was the change in immunosuppression at the time of hospital admission. Inflammatory indexes (C reactive protein (CRP), IL6, PCT, white blood cell (WBC), lymphocyte count, and lactic dehydrogenase (LDH) were significantly associated with mortality in the univariate analysis. At the same time, only LDH maintained a statistically significant correlation with mortality (p = 0.051) in the multivariate model.

**Table 2** Clinical predictors for overall mortality.

| | **Univariate** | | | **Multivariate** | | |
|---|---|---|---|---|---|---|
| **Clinical characteristic** | HR | 95%CI | p | aHR | 95%CI | p |
| **Age(y)** | 1.12 | 1.05-1.19 | <0.001 | 1.32 | 1.03-1.70 | 0.025 |
| **Sex** | | | | | | |
| *Male* | 1 (ref) | | | | | |
| *Female* | 0.27 | 0.59-1.20 | 0.085 | 0.001 | 1.23-0.59 | 0.034 |
| **SARS-CoV-2 variant** | | | | | | |
| *Wilde type* | 1 (ref) | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| *Alpha* | 1.21 | 0.37-3.94 | 0.754 | | | |
| *Delta* | 1.38 | 0.17-11.03 | 0.760 | | | |
| *Omicron* | | | | | | |
| **Pandemic waves** | | | | | | |
| *First* | 1 (ref) | | | | | |
| *Second* | 1.28 | 0.42-3.91 | 0.669 | | | |
| *Non pandemic* | 0.37 | 0.04-3.17 | 0.364 | | | |
| **Post-vaccine availability infection** | 0.73 | 0.09-5.65 | 0.766 | | | |
| **Organ transplant type** | | | | | | |
| *Liver* | 1 (ref) | | | | | |
| *Kidney* | 0.75 | 0.23-2.47 | 0.637 | 33.74 | 1.53-743.20 | 0.026 |
| *Heart* | 2.85 | 0.68-11.90 | 0.151 | 402.49 | 3.70-43770.26 | 0.012 |
| **Re TX** | 2.10 | 0.46-9.67 | 0.341 | | | |
| **BMI** | 1.15 | 1.03-1.29 | 0.013 | 1.26 | 0.94-1.69 | 0.121 |
| **Diabetes** | 2.77 | 0.96-8.03 | 0.059 | 10.44 | 1.18-92.30 | 0.035 |
| **COPD** | 1.15 | 0.15-9.01 | 0.889 | | | |
| **Hypertension** | 0.68 | 0.23-2.02 | 0.484 | | | |
| **CHARLSON index** | 1.51 | 1.17-1.94 | 0.001 | 1.94 | 0.71-5.35 | 0.196 |
| **Immunosuppression at baseline** | | | | | | |
| CyA | 0.43 | 0.05-3.52 | 0.427 | | | |
| FK | 0.46 | 0.05-3.58 | 0.429 | | | |
| **Immunosuppression level at baseline** | | | | | | |
| *CyA C2* | 0.98 | 0.97-1.01 | 0.198 | | | |
| *FK* | 1.34 | 0.98-1.83 | 0.067 | | | |
| **$SPO_2/FIO_2$** | 0.99 | 0.99-1.00 | 0.115 | | | |
| **Respiratory support** | 3.91 | 0.51-30.02 | 0.190 | | | |
| **Lung superinfection** | 3.41 | 1.17-9.95 | 0.024 | 5.05 | 0.59-42.95 | 0.138 |
| **Interval since symptoms and start therapy** | 0.90 | 0.77-1.05 | 0.166 | | | |
| **Covid-19 specific therapy** | | | | | | |
| *Inadequate* | 0.32 | 0.02-3.58 | 0.356 | | | |
| *Steroid* | 1.27 | 0.15-10.12 | 0.820 | | | |
| *LMWH* | 0.81 | 0.25-2.56 | 0.710 | | | |
| *Remdesivir* | 1.21 | 0.40-3.67 | 0.725 | | | |
| *Plasma* | 1.16 | 0.14-9.03 | 0.140 | | | |
| *Tocilizumab* | 1.38 | 0.18-10.72 | 0.756 | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Immunosuppression change** | | 0.46 | 0.16-1.33 | 0.153 | | | |
| | *CyA* | 0.35 | 0.04-2.90 | 0.335 | | | |
| | *MMF* | 0.43 | 0.14-1.30 | 0.136 | | | |
| **Time to admission** | | 0.93 | 0.82-1.06 | 0.297 | | | |
| **Time since TX** | | 1.00 | 1.00-1.01 | 0.056 | 0.99 | 0.98-1.01 | 0.578 |

Abbreviations: Re TX, re transplantation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; $SpO_2/FiO_2$, peripherical oxygen saturation/inhaled oxygen fraction; WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; ALT, alanine transaminase; LDH, lactic dehydrogenate; IL6, interleukin 6.

The adjusted multivariate analysis identified KT and HT as risk factors for adverse outcomes.

The length of hospitalization was different among transplants ($p < 0.001$): LT experienced a more extended hospitalization with a median of 27 (13-46) days. The lowest lymphocyte value was inversely related to hospital discharge within days 14 and 19 from admission, while inflammatory index (CRP, PCT, ferritin and IL6) was not associated with hospital discharge. No correlation was observed between hospitalization length and COVID-19-specific therapy or respiratory support requirements. Immunosuppression changes did not directly affect hospitalization on day 19th.

No relationship was observed between SARS-CoV-2 variants nor between different pandemic waves and fatality rates.

## 4. Discussion

Studies across a variety of COVID-19 waves indicate significantly higher morbidity and mortality among SOT recipients compared with non-immunocompromised populations [3].

The mortality rate in our study was high (19%) but in line with that observed in large metanalysis [4]. Interestingly, we did not find correlations between mortality and disease severity, comorbidities, or immunosuppression management. We confirmed risk factors for adverse outcomes, such as male gender, older age, higher body mass index, elevated Charlson index score, and diabetes mellitus, as previously described [5].

Moreover, we did not notice any correlation between the mortality rate and the different viral variants that followed during the months encompassed in this study. Most patients were infected during the first period when wild-type (66%) and Alpha (24%) variants were predominant. Indeed, during the Delta and Omicron variant pandemic, fewer SOT recipients were hospitalized thanks to vaccination and early administration of monoclonal antibodies, which have been associated with reduced disease severity [6].

In the large study, a trend of reduction in mortality rate has been observed in SOTs, with a decrease in mortality from 19.6% to 13.7% [7]. Although this tendency was not observed in our analysis, the low proportion of Delta and Omicron infections in our study sample could have prevented the detection of this variation to keep any difference in mortality between different variants.

In our cohort, HT and KT were risk factors for increased mortality due to COVID-19. The higher immunosuppression in HT and KT at disease occurrence (higher steroid dose at baseline, $p < 0.001$) compared to LTs may have played a role. Contrarily, a long time between transplant and infection

occurrence – generally associated with a lower burden of immunosuppression – was confirmed as a protective factor for a negative outcome [3].

The impact of immunosuppression on COVID-19 disease severity in SOT recipients remains unclear. The pathogenesis of COVID-19 appears to represent an interplay between direct viral injury and the consequent host response, with experimental data suggesting that a dysregulated and hyperintense immune response may mediate more severe disease. Since immunosuppressive agents modulate several aspects of host immune response, the severity of COVID-19 could be affected by the type, combinations, and intensity of immunosuppression [8]. Few immunosuppressive medications causing lymphopenia (i.e., antimetabolites such as mycophenolate mofetil) increase the risk for severe infection due to the imbalanced response consisting of low expression of interferons and high expression of pro-inflammatory cytokines [9]. Conversely, data suggest that mTOR inhibitors may allow the development of humoral response and appear to exert some biological activity against SARS-CoV-2 [10].

Despite the lack of solid evidence on optimal immunosuppression management in SOT recipients, a stepwise reduction of immunosuppression according to the severity of the clinical presentation may be appropriate [11]. In our cohort, 67% of subjects experienced a decline of immunosuppression during SARS-CoV-2 infection without impacting mortality and length of stay. Moreover, our study did not find any protective role of FK506, which is different from other reports [12]. It was generally maintained during the disease, given its role in the growth inhibition of other Coronaviruses and suppressing the early phase of T-cell activation and subsequent cytokine production [12]. Conversely, MMF dosing was lowered or withdrawn in half of patients as it may theoretically impair the ability to develop an adequate immune response to natural infection, even though this change did not impact mortality nor the length of stay in our cohort.

The apparent lack of association of immunosuppression-related factors on mortality should be interpreted cautiously, given the lack of well-defined clinical and biochemical surrogates to define the net state of immunosuppression. Neither the type of maintenance immunosuppression regimen nor the number of agents was associated with mortality, as was observed [13]. We described the use of specific SARS-CoV-2 therapy according to the therapeutic protocol that evolved during the pandemic waves, and we did not observe any impact on the fatality rate or the length of stay. Although this is expected for hydroxychloroquine, azithromycin, lopinavir/ritonavir, and hyperimmune convalescent plasma, which were subsequently found to be ineffective in COVID-19, it is surprising for remdesivir, currently recommended in hospitalized patients with mild to moderate respiratory failure. The limitation about the role of remdesivir is due to the small number of patients, only 10%. Although antiviral therapy started the same day of the hospitalization ($p < 0.001$), earlier compared to other treatments. Speaking of the severity of the disease in this sub-population, one patient showed mild disease, 5 patients moderate, and one critical condition. Nonetheless, a lower impact of antiviral therapy is anticipated in hospitalized patients with advanced disease compared to patients with early infection, as reported in another study on lung transplants [14]. Steroid and low molecular weight heparin did not have any role in reducing mortality or LOS.

The role of tocilizumab in this population is controversial. Some data reported a better overall survival with an increase in length of stay due to biochemical, respiratory, and infectious adverse events [15]. In contrast, others observed no differences in mortality rate or mechanical ventilation

requirement but shorter length of stay [16]. We did not find any impact on mortality rate and length of visit, similar to others [17].

Our study has several limitations: its retrospective design, the small and heterogeneous sample, and the low proportion of subjects infected by Omicron variants, which are currently predominant. Nonetheless, it provides additional data on the complexity of SARS-CoV-2 infection in SOT recipients, who may still experience severe and prolonged course of SARS-CoV-2 infection.

Overall, our analysis confirmed previous risk factors for mortality in SOT recipients. Even though no direct relationship between disease course, outcome, and immunosuppressive therapy was observed. Immune modulation plays a role in disease susceptibility and development and is often applied in this setting. However, we reported no impact on graft function when changing chronic immunosuppressive therapy. The definition of general guidelines for managing immunosuppressive regimens and immunomodulatory treatment might be complex. Considering the evolution of the epidemic, both in terms of virus characteristics and the host's susceptibility to disease (due to vaccination, repeated exposure, and early antiviral treatment) and given the extreme hosts' heterogeneity and the limited possibility to assess the state of immunosuppression. Although more extensive prospective studies will aid in a better assessment of the impacts of therapeutic efforts, the appropriate management will probably need to be tailored to each patient.

## Author Contributions

Peracchi Francesco, MD: Design and conceptualized study; drafted the manuscript for intellectual content. Major role in the acquisition of data. Same contribution to the study. Corresponding author. Travi Giovanna, MD: design and conceptualized study; drafted the manuscript for intellectual content. Same contribution to the study. Merli Marco, MD: revised the manuscript for intellectual content. Rossotti Roberto, MD: revised the manuscript for intellectual content. Puoti Massimo, MD: revised the manuscript for intellectual content.

## Competing Interests

The authors declare that they have no competing interests for this work.

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