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COVID-19 and solid organ transplantation: Finding the right balance

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\textbf{ABSTRACT}

\textbf{Background:} The COVID-19 pandemic has a great impact on solid organ transplant (SOT) recipients due to their comorbidities and their maintenance immunosuppression. So far, studies about the different aspects of the impact of the pandemic on SOT recipients are limited.

\textbf{Objectives:} This systematic review summarizes the risk factors that make SOT patients more vulnerable for severe COVID-19 disease or mortality and the impact of immunosuppressive therapy. Furthermore, their clinical outcomes, mortality risk, immunosuppression, immunity and COVID-19 vaccination efficacy are discussed.

\textbf{Methods:} A systematic search on PubMed was performed to select original articles on SOT recipients concerning the following four topics: (1) mortality and clinical course; (2) risk factors for mortality and composite outcomes; (3) maintenance immunosuppression; (4) immunity to COVID-19 infection and (5) vaccine immunogenicity. Relevant data were extracted, analyzed and summarized in tables.

\textbf{Results:} This systematic review includes 77 articles. Mortality was associated with advanced age. Post-transplantation time or comorbidities were variably identified as independent risk factors for mortality or severe disease. However, generally, no comorbidity was reported as a major risk factor. SOT recipients have a higher risk of acute kidney injury, but no higher rate of mortality compared to non-transplanted patients was found. Immunosuppression was individually adjusted, without leading to high rates of graft dysfunction. Generally, no association between type of immunosuppression and mortality was found. SOT patients established humoral and cellular immune responses after COVID-19 disease comparable to immunocompetent people. At last, SOT patients experience a diminished immune response after two-dose vaccination with SARS-COV-2-mRNA-vaccines.

\textbf{Conclusion:} More research is needed to address the direct effect of COVID-19 disease on the graft in lung transplant recipients, as well as the factors ameliorating the immune response in SOT recipients.

\section{1. Introduction}

\subsection{1.1. COVID-19 disease}

COVID-19 disease, caused by severe acute respiratory syndrome coronavirus-2 (SARS-COV-2), has affected the whole world leading to a pandemic \cite{1}. This pandemic affects the landscape of transplantation as well as the management of transplant patients. Consequently, a lot of changes, recommendations and guidelines for management, prevention and treatment of COVID-19 infection in solid organ transplant (SOT) patients were made. Progress has been made in understanding the impact of these early changes in clinical practice in the field of solid transplantation. A lot of changes, recommendations and guidelines for management, prevention and treatment of COVID-19 infection in solid organ transplant (SOT) patients were made. Progress has been made in understanding the impact of these early changes in clinical practice in the field of solid transplantation.

\textit{Abbreviations:} Abs, antibodies; ACE-I, angiotensin converting enzyme inhibitor; ACE-2, angiotensin-converting enzyme 2; Anti-NCP Abs, antibodies against the nucleocapsid protein subunit; Anti-RBD Abs, antibodies against the receptor binding domain; Anti-S1 Abs, antibodies against Spike protein subunit S1; ARB, angiotensin II receptor blocker; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; AM, antimetabolites; CCI, Charlson Comorbidity Index; CI, calcineurin inhibitors; COVID-19, Coronavirus Disease 2019; CKD, chronic kidney disease; DIC, disseminated intravascular coagulation; DP, dialysis patients; FACS, Fluorescence-Activated Cell Sorting; HTR, heart transplant recipients; ICU, intensive care unit; IGRA, interferon-gamma release assay; IS, immunosuppression; KTR, kidney transplant recipients; LTR, liver transplant recipients; mTOR-i, mammalian target of rapamycin inhibitors; NR, not reported; NS, not significant; RAAS-I, renin-angiotensin-aldosterone system inhibitors; RRT, renal replacement therapy; SARS-COV-2, severe acute respiratory syndrome coronavirus-2; SOT, solid organ transplant; WL, waiting list.

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organ transplantation, including the risk, the pathophysiology of COVID-19 and the effect of therapeutic strategies on morbidity and mortality of transplant recipients. [2-6]

1.2. Pathophysiology

COVID-19 has been recognized as a disease that affects multiple organ systems, resulting in a wide range of symptoms. The severity of these symptoms varies from asymptomatic to mild or to a life-threatening illness. The progress of COVID-19 disease and its symptoms can be divided in two phases.

First, the virus enters the target organ cells during the viral phase. The spike (S) protein of SARS-COV-2, a protein characteristic for coronaviruses, has a crucial role in determining the host-pathogen interaction by mediating receptor binding and membrane fusion. The S-protein interacts with ACE-2-receptors resulting in viral RNA-release inside respiratory epithelial cells for replication in the cytoplasm. [7,8] After replication, the virus is released for further invasion of cells and causes a vascular integrity defect, resulting in pulmonary oedema, activation of disseminated intravascular coagulation (DIC), pulmonary ischemia, hypoxic respiratory failure and progressive lung damage. [9] Additionally, the virus interacts with other ACE-2-receptors, found on different organ tissues such as the heart, liver, kidney, intestine, vascular structures and other tissues. Alveolar type II cells constitute 83% of all ACE-2-presenting cells. [7,10,11]

After the viral phase, some patients develop worse symptoms. This can be described as a secondary phase, called the hyperinflammatory phase. During this phase, also described as cytokine storm syndrome, increased levels of circulating inflammatory cytokines are observed, including interleukin (IL) -1, IL-6 and IFN-gamma [7,9,10,12]. Furthermore, binding of the virus to ACE-2-receptors expressed on arterial and venous endothelial cells can cause endothelial dysfunction and vascular inflammation, leading to dysregulation of coagulation pathways and potential development of DIC [7,9,12]. This hypercoagulative and hyperinflammatory response can ultimately lead to acute respiratory distress syndrome (ARDS) and multiorgan failure [7,9,12]. However, little is known about the origin of this dysregulated response and how it specifically affects immune suppressed SOT recipients.

Furthermore, during disease progression, the binding of the virus to ACE-2 receptors, also found on renal epithelial cells, results in acute kidney injury (AKI) as a frequent complication of COVID-19. [13,14] This AKI is caused by multiple factors, including reduced renal perfusion, cytokine storm and multiorgan failure. [14,15] Since the majority of SOT patients are kidney transplants, they might be more vulnerable for severe kidney failure as a result of COVID-19 infection.

1.3. Risk factors and mortality

Many comorbidities contributing to the severity of COVID-19 disease have been studied. Several risk factors have been associated with a higher risk for severe forms of COVID-19 or mortality. [16,17] In particular, SOT recipients are elderly patients with chronic underlying conditions such as hypertension, obesity, diabetes and cardiovascular disease, placing them at higher risk for severe disease. In addition, SOT patients are identified as a risk group for COVID-19 because of their chronic immunosuppressive therapy. [18] In contrast, it is not clear if these medications could be beneficial by decreasing the severity of cytokine storm and/or reducing viral replication. [5,19]

1.4. Medication

Since the start of the pandemic, there has been a worldwide effort to discover the best treatment options for COVID-19. A wide range of therapeutic options has been studied, including steroids, antiviral drugs, anti-inflammatory drugs and other treatment [10]. However, data in SO recipients is still lacking. Furthermore, immunosuppressive therapy is frequently adapted for SOT patients suffering from COVID-19. [19] A tailored approach is needed for management of their therapy, taking into account the potential drug interactions and rejection risk.

1.5. Aim of this study

This systematic review aims to summarize the current literature about COVID-19 in SOT recipients. This study will elaborate on the risk factors that make SOT patients more vulnerable for severe disease or mortality and the impact and effect of immunosuppressive therapy. Furthermore, their clinical outcomes, mortality risk, immunity after COVID-19 infection and the COVID-19 vaccination efficacy will be discussed.

2. Methods

2.1. Search methods

A systematic literature review was conducted identifying PubMed articles published in English between May 2021 and September 25th, 2021. Systematic selection was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [20].

We focused our search on 4 areas in adult SOT recipients infected with SARS-COV-2: (1) mortality and clinical course; (2) demographics and risk factors for mortality and composite outcome; (3) maintenance immunosuppression; (4) vaccination response after 2 doses of SARS-COV-2-mRNA vaccines. A second article search was performed in June 2022, concerning natural immunity after COVID-19 infection. A comprehensive electronic literature search was conducted using Mesh terms “COVID-19”[Mesh], Transplants”[Mesh], “SARS-CoV-2”[Mesh] and “Organ Transplantation”[Mesh]. Additionally, a search using the free terms 'covid 19,” “covid-19”, “transplant”, “risk factors”, “treatment”, “mortality”, “immunity”, “vaccine” was performed to identify additional eligible studies. After an initial screening of titles and abstracts, the full text was analyzed based upon established inclusion criteria.

2.2. Inclusion and exclusion criteria

Original articles were considered. In addition, other relevant articles were examined from the reference list of the included studies and extracted from the reference list of systematic reviews. Articles comparing outcomes of SARS-COV-2 infected SOT patients with infected non-transplanted patients on the 5 described topics were included, as well as articles comparing COVID-19 incidence and mortality to waiting list patients.

Articles were excluded if they were not published in English, contained patients with age < 18y, consisted of <50 participants or not concerned the 4 areas described above. Articles not identifying SARS-COV-2 positive patients by laboratory-confirmed PCR-test were excluded. Single dose vaccination studies were not included. Case reports, case series, commentaries, letters to the editor, editorials and congress reports were excluded. After the second article search concerning immunity articles, twelve articles were included containing >10 SOT patients.

2.3. Data extraction and processing

We collected the following data:

- Demographics and comorbidities
  - Age
  - Gender
  - Comorbidities
3. Results

3.1. Search results

Based on title and abstract, 2314 articles were screened on PubMed, of which 89 articles were further analyzed. After full text screening, 65 articles were used in this systematic review (Fig. 1). Of all the included studies, 28 analyzed only kidney transplant recipients (KTR), 8 studies only liver transplant recipients (LTR), 2 only heart transplant recipients (HTR), 2 only lung transplant recipients and 25 studies included a mixed SOT population. Tables 1-5 summarize the study outcomes. Comparative studies, comparing SOT recipients to non-transplanted patients, were sorted next to non-comparative studies. Studies concerning different topics were included in multiple tables. Figure summarizes the subdivision of the 65 articles based on topic and type of SOT. After an additional article search, 12 articles concerning natural immunity after COVID-19-infection were included, resulting in 77 included articles in this systematic review.

Fig. 1. PRISMA flow diagram.
3.2. Risk factors

Thirty-one studies described demographic characteristics and comorbidities of SOT patients infected with COVID-19, which are summarized in Tables 1a and 1b. [21–51]

3.2.1. Comorbidities as risk factors for disease severity or mortality

In general, compared to non-transplanted patients, comorbidities were more prevalent in SOT recipients. [21,22,24–26,28,31] Among these SOT patients, hypertension, diabetes mellitus and obesity were commonly reported as prevalent comorbidities in SOT. [27,29,32,35,38,41,42,46] More specific, several studies found different comorbidities to be independent risk factors for mortality or composite outcome. In the study of Heldman et al., heart failure, obesity and chronic lung disease were independent risk factors for mortality in hospitalized SOT patients (Heart failure: OR 2.3 [95% CI 1.3–3.9], p = 0.007; Obesity: OR 1.7 [95% CI 1.2–2.4], p = 0.005; Chronic lung disease: OR 2.7 [95% CI 1.5–4.6], p < 0.001). [34] Three other studies confirmed these comorbidities to be significant. [35,43,46] Additionally, other smaller studies showed diabetes mellitus or cardiovascular disease to be risk factors for mortality. [22,23,42]

In contrast, Caillard et al. indicated that only cardiovascular disease is a risk factor for severe COVID-19 after matching with non-transplanted patients (HR 1.35 [95% CI 1.03–1.76], p = 0.028). [27] For mortality, no comorbidity was found to be an independent risk factor in this study. This was confirmed by Hilbrands and Webb et al., who could not find hypertension, chronic lung disease, coronary artery disease or diabetes mellitus to be independent risk factors for mortality. [29,32] A large part of other smaller studies confirmed that no specific association was found for the multiple comorbidities. [22,25,26,31,37,40,49,50]

Other less prevalent characteristics such as smoking status, chronic liver disease, malignancy and their effect on mortality or composite outcome were described in only a few studies. [21,22,24,27,29,31,32,42,43,46,48]

3.2.2. Number of comorbidities

Besides the specific comorbidities mentioned above, Kates et al. showed that infected SOT recipients had an increased risk for mortality when having a number of these comorbidities, suggesting a cumulative effect (Number of high risk comorbidities: 1 vs 0, OR 3.0 [95% CI 1.4–6.3], >2 vs. 0, OR 11.0 [95% CI 5.0–24.0]). [35] The association between the cumulative number of comorbidities and mortality was confirmed by Cristelli, showing an increase in 28-day fatality rate by higher number of comorbidities [42].

Kute et al. stated that non-survivors have more comorbidities [44]. Three studies used the Charlson comorbidity index (CCI) as a variable to check for mortality. The smallest study, containing only 46 mixed types of SOT patients, declared that higher CCI is an independent risk factor for mortality in SOT. [26] Softeland et al., studying 230 SOT patients, showed CCI 1–2 to be a significant predictor of hospitalization compared to SOT having CCI 0. [38] In contrast, no association was found for mortality and no significance was found for patients with a higher CCI-scorer than 2. [38] Colmenero documented that higher CCI was an independent risk factor for severe COVID-19 among hospitalized patients (RR 1.28 [95% CI 1.05–1.56]). [50]

3.2.3. Gender

Although most infected SOT recipients in the included studies were male, male sex was not found to be an independent risk factor for mortality [26,27,29–35,40,42,43,49]. Additionally, no association between sex and severe disease or ICU admission was found. [27,31,32,36,37,39,40,42]

3.2.4. Age

In the majority of the studies, age was found to be an important risk factor for mortality and composite outcome. For instance, Hilbrands et al. identified age as a small significant risk factor for mortality in KTR specifically. (HR 1.07 [95% CI 1.04–1.10], p < 0.001) [29] Several other studies confirmed age to be a significant risk factor for mortality in SOT patients in general. [22,23,25–27,31–35,37,38,40,42–44,46,47,49,51] Most studies used age above 60y or higher as an independent variable in their analysis. However, some studies used age subcategories, showing that older age is associated with higher mortality risk (Jager: Age 65–74y: HR 2.54 [95% CI 1.96–3.29]; Age > 75y: HR 3.85 [95% CI 3.06–4.86]). [25,29,30,34] Furthermore, older SOT recipients are more at risk for severe disease or hospitalization. [27,36–38,46]

3.2.5. Type of SOT

Some studies used type of SOT as an independent variable for mortality. Heldman et al. analyzed that hospitalized lung transplant recipients have a higher mortality risk compared to other hospitalized SOT patients (OR 1.7 [95% CI 1.0–2.8], p = 0.04). [34] This was confirmed by Coll et al. (Lung vs other: OR 2.5 [95% CI 1.4–4.6], p = 0.035). [33] However, two smaller studies containing less lung transplant recipients could not confirm a different mortality risk based on type of SOT. [26,35] Furthermore, type of SOT did not influence disease severity or hospital admission. [30–38]

3.2.6. Time after transplantation

Studies investigating the association between post-transplantation time of SOT infected with COVID-19 and mortality risk show variable results. The large study of Villanego et al., containing 1011 KTR, reported increasing mortality risk in 4 subgroups according to age and time after KTR, concluding both age and KTR < 6 months to be independent mortality risk factors (KTR < 6 m: HR 1.64 [95% CI 1.07–2.5], p = 0.021) [47] Only two smaller studies confirmed this result, showing a shorter post-transplantation time to be associated with poor clinical outcome. [37,46] Hilbrands et al. stated that patients in the first year after kidney transplantation have an increased mortality risk compared to waiting list patients [29]. However, no analysis was performed to compare the mortality risk between the post-transplantation time subgroups. In contrast, the fourteen other studies analyzing years after transplantation did not find an association with mortality or composite outcome. [26,30,32,33,35,36,38,41–43,48–51]

3.3. Mortality and clinical course

Thirty-two studies described mortality rates and composite outcomes (hospital admission, ICU admission, AKI, need for mechanical ventilation) of SOT patients infected with COVID-19, of which results are summarized in Tables 2a and 2b. [21–32,34–38,40,44,46–48,50–56]

3.3.1. Mortality of SOT recipients – non-comparative studies

Requiao-Moura et al. reported a 90-day cumulative incidence of death of 21% in KTR. [46] The overall mortality of LTR was 18%, reported by Colmenero et al. [50] One study about HTR indicated a mortality of 16% in symptomatic patients and a hospital mortality of 24%. [51]

3.3.2. Mortality of SOT recipients compared to non-transplanted patients

Multiple studies did not find a difference in in-hospital mortality risk, comparing different types of SOT recipients with non-transplanted patients. [21,22,24–26,53] Additionally, Molnar et al. reported no difference in mortality risk in ICU-admitted SOT and non-SOT patients. [52] The cohort study of Fisher et al., comparing 128 SOT patients to 9907 matched controls, were the only to describe a higher mortality risk in SOT (OR 1.93 [95% CI 1.18–3.15], p < 0.01) [23]. Furthermore, Caillard et al. showed that mortality was higher in KTR compared to non-transplanted patients. [27] However, kidney transplantation was not an independent risk factor for mortality after multivariate analysis. [27] Two other multicentre KTR-studies
### Table 1a

| Type of study               | Study population/type of SOT                                                                 | Median age | Gender | Comorbidities$^a$                                                                 | Time after transplantation | Outcome                                                                 |
|-----------------------------|----------------------------------------------------------------------------------------------|------------|--------|---------------------------------------------------------------------------------|---------------------------|------------------------------------------------------------------------|
| Mixed type of SOT           | Avery et al. [21] Retrospective multicentre cohort study 2472 patients: 45 SOT, 2427 non-transplant patients | Median age: 59 SOT, 59 non-SOT Male: 53.3% SOT, 51.9% non-SOT | Renal failure: 83.7% SOT, 19.4% non-SOT Hypertension: 68.9% SOT, 44.3% non-SOT Diabetes: 60.0% SOT, 33.8% non-SOT Former smoker: 40.0% SOT, 18.5% non-SOT Liver disease: 34.9% SOT, 8.5% non-SOT History of malignancy: 23.3% SOT, 10.9% non-SOT Chronic pulmonary disease: 18.6% SOT, 22.6% non-SOT Peripheral vascular disorders: 18.6% SOT, 7.8% non-SOT History of peptic ulcer disease: 7.0% SOT, 1.5% non-SOT HIV: 7.0% SOT, 1.4% non-SOT Median BMI: 27.3 SOT, 28.6 non-SOT | | Comorbidities SOT vs non-SOT: Diabetes: 60.0% vs. 33.8%, p < 0.001 Hypertension: 68.9% vs. 44.3%, p = 0.001 Peripheral vascular disorders: 18.6% vs. 7.8%, p = 0.018 History of peptic ulcer disease: 7.0% vs. 1.5%, p = 0.029 HIV: 7.0% vs. 1.4%, p = 0.02 |
|                             | Chaudhry et al. [22] Retrospective single-centre cohort study 147 patients: 47 SOT, 100 non-transplant recipients | Median age: 62 SOT, 60 non-SOT Male: 65.7% SOT, 50.0% non-SOT | Hypertension: 94.3% SOT vs 72% non-SOT CKD: 88.6% SOT, 57% non-SOT Diabetes: 65.7% SOT, 33% non-SOT Congestive heart failure: 28.6% SOT, 14% non-SOT Smoking history: 25.7%, 25% non-SOT Chronic lung disease: 17.1% SOT, 13% non-SOT Coronary artery disease: 14.3% SOT, 12% non-SOT Malignancy: 11.4% SOT, 13% non-SOT | | Comorbidities SOT vs non-SOT: Median BMI: 27.3 SOT vs 28.6, p = 0.02 CKD: 89% vs 57% P = 0.0007 Diabetes: 66% vs 33% P = 0.0007 Hypertension: 94% vs 72%, P = 0.006 |
|                             | Fisher et al. [23] Retrospective multicentre matched cohort study 4035 patients: 128 SOT (106 KTR (82.8%), 9 LTR (7.0%), 6 HTR, 4 combined kidney/pancreas (3.1%), and 3 combined kidney/liver (2.3%)), 3907 matched non-transplant patients | Median age: 60 SOT, 60 matched non-SOT Male: 61.7% SOT, 61.7% matched non-SOT | After matching in SOT: Hypertension: 59.4% CKD: 57.8% Diabetes mellitus: 56.2% Obesity: 8.6% Congestive heart failure: 3.1% Coronary artery disease: 2.3% Chronic obstructive pulmonary disease: 2.3% Cirrhosis: 1.6% Cancer: 0% Smoking status: former smoker 13.3%, current smoker 0%, never smoker 71.1% | | Comorbidities SOT vs non-SOT: Male sex: OR 1.6 [95% CI 1.3–2.0], p < 0.01 Age: OR 2.11 [95% CI 1.8–2.5], p < 0.01 Diabetes mellitus: OR 5.06 [95% CI 3.8–6.7], p < 0.01 Hypertension: OR 0.79 [95% CI 0.64–0.96], p = 0.02 |

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### Table 1a (continued)

| Study population/type of SOT | Median age | Gender | Comorbidities | Time after transplantation | Outcome |
|-----------------------------|------------|--------|---------------|---------------------------|---------|
| Mean age: 54.3 SOT, 45.9 non-SOT | Male: 59.4% SOT, 44.5% non-SOT | Before matching: | Demographics before matching | | |
| | | Hypertension: 92.1% SOT, 25.9% non-SOT | SOT vs non-SOT: | Male gender: 59.4% vs 44.5% P < 0.01 | |
| | | Diabetes: 60.9% SOT, 13.5% non-SOT | Mean age: 54.3 vs 45.9 P < 0.01 | | |
| | | Ischemic heart disease: 43.9% SOT, 7.5% non-SOT | Obesity: 34.5% SOT, 14.2% non-SOT | | |
| | | Chronic lower respiratory disease: 29.6% SOT, 14.3% non-SOT | Nicotine dependence: 10.5% SOT, 6.9% non-SOT | | |
| Mean age: 58 SOT, 63 non-SOT | Male: 66% SOT, 66% non-SOT | Before matching: | Comorbidities SOT vs non-SOT: | Hypertension: 81% vs 45%, p < 0.001 | |
| | | Hypertension: 81% SOT, 45% non-SOT | CKD: 34% SOT, 5% non-SOT | Diabetes mellitus: 16% vs 32%, p = 0.013 | |
| | | Cardiovascular disease: 24% SOT, 13% non-SOT | COPD: 20% SOT, 17% non-SOT | CKD: 34% vs 5%, p < 0.001 | |
| | | Diabetes: 16% SOT, 32% non-SOT | | | |
| Mean age: 62.7 SOT, 66 non-SOT | Male: 71.7% SOT, 73.5% non-SOT | Before matching: | Risk factors for mortality: | Age > 63y: OR 1.14 [95% CI 1.08–1.19] | |
| | | Hypertension: 78.3% SOT, 56.5% non-SOT | Cardiovascular disease: HR 1.35 [95% CI 1.03–1.76], p = 0.028 | | |
| | | Chronic renal failure: 78.3% SOT, 18.1% non-SOT | Risk factors for mortality in SOT: | Age: HR 1.08 [95% CI 1.02–1.14], p = 0.016 | |
| | | Diabetes: 44.4% SOT, 35.2% non-SOT | CCI: HR 1.22 [95% CI 1.03–1.44]; p = 0.037 | | |
| | | Pneumopathy: 35.8% SOT, 20.5% non-SOT | | | |
| | | Solid tumour: 21.7% SOT, 24.1% non-SOT | | | |
| | | Obesity: 21.7% SOT, 22.6% non-SOT | | | |
| | | Atrial fibrillation: 11.1% SOT, 18.1% non-SOT | | | |
| | | Chronic heart failure: 10.9% SOT, 14.0% non-SOT | | | |
| | | Liver cirrhosis: 8.7% SOT, 1.8% non-SOT | | | |
| | | Median CCI: 5 SOT, 4 non-SOT | | | |
| Mean age: 62 KTR, 69 non-SOT | Male: 67.6% KTR, 58.6% non-SOT | Before matching: | Risk factors for severe disease: | Cardiovascular disease: HR 1.35 [95% CI 1.03–1.76], p = 0.028 | |
| | | Hypertension: 91.3% KTR, 49.8% non-SOT | | | |
| | | BMI > 25 kg/m²: 64.8% KTR, 66.3% non-SOT | | | |
| | | Cardiovascular disease: 38.8% KTR, 38.8% non-SOT | | | |
| | | Diabetes: 37% KTR, 35.9% non-SOT | | | |
| | | Respiratory disease: 13.9% KTR, 16.5% non-SOT | | | |
| | | Cancer: 12.5% KTR, 9.5% non-SOT | | | |
| Median time: 74.6 months | | | | | |

(continued on next page)
| Type of study | Study population/type of SOT | Median age | Gender | Comorbidities\(^a\) | Time after transplantation | Outcome |
|---------------|-----------------------------|------------|--------|----------------------|---------------------------|---------|
| Chavarot et al.\([28]\) | Retrospective multicentre matched cohort study | 2117 patients: 100 KTR, 2017 non-transplant patients | Median age: 64.7 KTR, 67.5 non-SOT | Male: 64% KTR, 57.9% non-SOT | Smoking: 12.7% KTR, 4.4% non-SOT Before matching: Hypertension: 85% KTR, 50% non-SOT Diabetes: 48% SOT, 29.4% non-SOT Cardiothoracic: 35% KTR, 21.3% non-SOT Atrial fibrillation: 29% KTR, 14.2% non-SOT Chronic lung disease: 11% KTR, 14.6% non-SOT Median BMI: 25.9 KTR, 27.0 non-SOT | Median years: 5.1y | Comorbidities, KTR vs non-SOT: BMI: 25.9 vs 27, \(p = 0.0003\) Age: 64.7 VS 67.5, \(p = 0.033\) Hypertension 85% vs 50%, \(p < 0.001\) Cardiothoracic: 35% vs 21.3% \(p < 0.001\) Diabetes 48% vs 29.4%, \(p < 0.001\) |
| Hilbrands et al.\([29]\) | Retrospective multicentre cohort study | 1073 patients: 305 KTR, 768 DP | Median age: 60 KTR, 67 DP | Male: 62% KTR, 60% DP | Smoking: 27.2% KTR, 10.7% DP Hypertension: 10.7% KTR, 5.3% DP Obesity: 7.5% KTR, 3.0% DP Coronary artery disease: 6.9% KTR, 3.9% DP Chronic lung disease: 3.0% KTR, 1.7% DP Heart failure: 2.6% KTR, 2.9% DP Active malignancy: 2.3% KTR, 0.8% DP Autoimmune disease: 1.6% KTR, 0.5% DP | \(<1y: 2.3\%\) | Risk factors for mortality in SOT: Age: HR 1.07 [95% CI 1.04–1.10], \(p < 0.001\) |
| Jager et al.\([30]\) | Retrospective multicentre cohort study | 4298 patients: 1013 KTR, 3285 DP | Mean age: 60.9 KTR, 71.7 DP | Male: 65.4% KTR, 69.3% DP | Smoking:72.2% KTR, 30% control, 78.9% HD, 89% CKD Diabetes mellitus: 25.3% KTR, 15.5% control, 48.3% HD, 43.8% CKD Ischemic heart disease: 17.1% KTR, 9.3% control, 45.4% HD, 46.7% CKD Heart failure: 2.6% KTR, 4.4% control, 25.1% HD, 25.9% CKD COPD: 6.5% KTR, 10.1% control, 13.9% HD, 21.2% CKD Cancer: 2.6% KTR, 4.6% control, 5.4% HD, 6.7% CKD Chronic liver disease: 0% KTR, 0.9% control, 1.4% HD, 0.4% CKD | NR | Median age 71.7 vs 60.9 dialysis, \(p < 0.001\) |
| Ozturk et al.\([31]\) | Retrospective multicentre cohort study | 1210 patients: 81 KTR, 289 CKD, 390 DP, 450 control | Median age: 48 KTR, 51 control, 64 HD, 71 CKD | Male: 59.3% KTR, 54.7% control, 51.5% HD, 56.7% CKD | Hypertension:72.2% KTR, 30% control, 78.9% HD, 89% CKD Diabetes mellitus: 25.3% KTR, 15.5% control, 48.3% HD, 43.8% CKD Ischemic heart disease: 17.1% KTR, 9.3% control, 45.4% HD, 46.7% CKD Heart failure: 2.6% KTR, 4.4% control, 25.1% HD, 25.9% CKD COPD: 6.5% KTR, 10.1% control, 13.9% HD, 21.2% CKD Cancer: 2.6% KTR, 4.6% control, 5.4% HD, 6.7% CKD Chronic liver disease: 0% KTR, 0.9% control, 1.4% HD, 0.4% CKD | NR | Median age 71.7 vs 60.9 dialysis, \(p < 0.001\) |

\(a\) Continued on next page.
confirmed this, finding no significant difference in mortality rate. [28,31]
In contrast, Webb et al. reported that mortality was higher in non-transplanted patients compared to LTR. [32]

3.3.3. Clinical course of SOT recipients compared to non-transplanted patients
The risk of ICU admission was similar in studies comparing mixed SOT patients or KTR with non-transplanted patients. [22–24,26,27] Webb et al. were the only to report a higher number of ICU-admission for LTR recipients. (28% LTR vs 8% non-LTR, \( p < 0.0001 \)) [32]. Furthermore, most studies did not find a higher risk for mechanical ventilation between SOT and non-SOT patients. [21,22,24,25,52,53] The matched studies of Fisher et al. and Webb et al., however, did report a higher need for invasive mechanical ventilation for respectively 128 mixed SOT recipients and 151 LTR. [23,32] In contrast, in the study of Fisher et al., SOT status was associated with higher risk of AKI compared to non-transplanted patients (OR 2.41 [95% CI 1.59–3.65], \( p < 0.001 \)). [23] This was confirmed by several other studies, showing a higher risk for AKI in SOT recipients. [22–24,27,52] Only two smaller studies including less SOT could not confirm this. [26,52]

3.3.4. Comparison with dialysis patients
The study of Jager et al. comparing 1013 KTR with 3285 dialysis patients (DP) showed that transplant patients have a higher mortality risk (HR 1.28 [95% CI 1.02–1.60]) [30]. This could not be confirmed by the smaller study of Hilbrands et al., finding no significant difference in death probability in the overall study population. [29] However, on one hand, the 28-day probability of death was 56% higher for DP considering hospitalized KTR and DP. (HR 1.56 [95% CI 1.17–2.07], \( p = 0.002 \)). [29] On the other hand, in-hospital mortality was again similar for KTR and DP after multivariate analysis (HR 0.81 [95% CI 0.59–1.10], \( p = 0.18 \)). [29]

3.3.5. Other
Some studies reported ARDS incidence or RRT requirement, but this was not systematically reported in the majority of the studies.

3.4. Waiting list studies
Table 3 summarizes 7 studies comparing the incidence and mortality of COVID-19 in SOT recipients to waiting list patients. [57–63]

3.4.1. Incidence of COVID-19
Thaunat et al. found an incidence of 1.4% in SOT compared to 2.9% for waiting list (WL) patients. [61] Other studies confirmed that the incidence of COVID-19 was lower for SOT recipients compared to candidates. [57,58,60,62]

3.4.2. Mortality due to COVID-19
COVID-19 related mortality in the study of Polak et al. was 18% among liver transplantation candidates and 15% among LTR. [62] The largest nationwide study of Thaunat et al. revealed that the excess of mortality in 2020 due to the COVID-19 pandemic was globally higher for candidates than for KTR. [61] Considering those hospitalized in the small study of Craig-Shapiro et al., the mortality rates of 25% for SOT recipients and 41% for candidates demonstrated that WL status was independently associated with mortality (OR 3.60 [95% CI 1.38–9.39], \( P = 0.009 \)). [59] However, the findings of these two studies could not be confirmed by three other large studies, indicating no significant difference in mortality between candidates and recipients. [57,60,62] The study of Mamode et al. documented that KTR and WL patients have similar mortality rates after hospital admission (KTR vs WL: RR 1.1 [95% CI 0.65–1.86]) [63]. Additionally, there were no significant differences for ICU admission or mechanical ventilation, although rates were high in both groups. [62,63]

3.5. Maintenance immunosuppression
Forty studies described the contribution of different immunosuppressive drugs on disease severity or mortality, the immunosuppressive modifications and therapy options in SOT patients, of which results are summarized in Tables 4a and 4b. [21–29,31–44,46–56,60,64–68]

3.5.1. Corticosteroids
Hilbrands et al. described that the use of prednisone prior to admission is associated with a higher 28-day fatality rate in KTR (HR 2.8 [95% CI 1.03–8.03], \( p = 0.04 \)). [29] Requiao-Moura et al. confirmed this (OR 1.53 [95% CI 1.06–2.21], \( p = 0.022 \)). [46] However, most studies did not confirm the association between steroid use and severe disease or mortality. [31,32,34,37,38,40,43,44,47,50,51,64,68]

3.5.2. Calcineurin inhibitors
The study of Belli et al. found the use of tacrolimus to be an independent protective factor for mortality in a study population of 243 LTR. (HR 0.55 [95% CI 0.31–0.99], \( p = 0.047 \)) [49] Additionally, patients treated at home received more tacrolimus in their baseline immunosuppressive regimen. [49] In the small study of Genuardi et al. containing 99 HT patients, use of tacrolimus was less prevalent in patients with severe disease, but calcineurin inhibitors were not independent risks factors after multivariate analysis. [51] Other studies did not report this protective effect of tacrolimus or the role of cyclosporin.
| Type of study | Study population/type of SOT | Median age | Gender | Comorbidities | Time after transplantation | Outcome |
|---------------|-------------------------------|------------|--------|---------------|--------------------------|---------|
| Coll et al. [33] | Retrospective multicentre cohort study | 778 SOT and HSCT: 423 KTR (54%), 113 HSCT (13%), 69 HTR (9%), 54 lung (7%), 8 pancreas (1%), 1 multivisceral (0.1%) | Median age: 61 | Male: 66% | NR | Median months: 59 |
| Heldman et al. [34] | Prospective multicentre cohort study | 1081 SOT: 120 Lung (11.1%), 131 HTR (13.6%), 154 LTR (16.0%), 72 KTR (70.0%), 3 other (0.3%) | Mean age: 60.6 | Male: 51.7% | CKD: 51.7% Lung, 35.0% non-lung SOT | NR |
| Kates et al. [35] | Retrospective multicentre cohort study | 482 SOT: 318 KTR or kidney/pancreas (56%), 73 LTR (15.1%), 57 HTR (11.8%), 30 lung (6.2%) | Mean age: 58 | Male: 61% | Hypertension: 77.4% Diabetes: 51% CKD: 37.3% Obesity: 35.1% Coronary artery disease: 21.8% Chronic lung disease: 10.4% Congestive heart failure: 8.3% | Median time: 5y |
| Pereira MR, Mohan S. et al. [36] | Retrospective multicentre cohort study | 90 SOT: 46 KTR (51%), 17 lung (19%), 13 LTR (14%), 9 HTR (10%), 3 heart-kidney (3%), 1 liver-kidney (1%), 1 kidney-pancreas (1%) | Mean age: 57 | Male: 59% | CKD: 60% mild/moderate disease, 70% severe disease Hypertension: 60% mild/moderate vs 78% severe Diabetes mellitus: 43% mild/moderate, 52% severe Chronic lung disease: 17% mild/moderate, 22% severe BMI >40: 5% mild/moderate, 7% severe HIV: 2% mild/moderate, 0% severe Active cancer: 0% mild/moderate, 11% severe | Median time: 6.6y |
| Salto-alejandre et al. [37] | Prospective multicentre cohort study | 2210 SOT: 108 KTR (51.4%), 50 LTR (23.8%), 33 HTR (15.7%), 15 Lung (7.1%), 4 kidney-pancreas (1.9%) | Mean age: 63 | Male: 70.5% | CKD: 31.3% FO, 44.4% UO Diabetes mellitus: 28.6% FO, 44.4% UO Chronic cardiopathy: 21.1% FO, 36.5% UO Chronic lung disease: 18.4% FO, 23.8% UO | Median time: 6.6y |

## Risk factors for mortality in univariate analysis:

**Type of transplant:**
- Lung vs Other: OR 2.5 [95% CI 1.4–4.6], p = 0.035
- Age > 60 years: OR 3.7 [95% CI 2.5–5.5], p < 0.001

**Risk factors for mortality in hospitalized SOT:**
- Lung transplantation: OR 1.7 [95% CI 1.0–2.8], p = 0.04
- Age > 65 years: OR 2.1 [95% CI 1.3–3.0], p < 0.001
- Heart failure: OR 2.3 [95% CI 1.3–3.9], p = 0.007
- Obesity: OR 1.7 [95% CI 1.2–2.4], p < 0.005
- Chronic lung disease: OR 2.7 [95% CI 1.5–4.6], p < 0.001

## Risk factors for mortality vs Other:

- Age > 65: OR 3.0 [95% CI 1.7–5.5], p < 0.001
- Congestive heart failure: OR 3.2 [95% CI 1.4–7.0], p = 0.004
- Chronic lung disease: OR 2.5 [95% CI 1.2–5.2], p = 0.018
- Obesity: OR 1.9 [95% CI 1.0–3.4], P = 0.039
- Number of high risk comorbidities: 1 vs 0, OR 3.0 [95% CI 1.4–6.3], P < 0.01
- ≥2 vs. 0: OR 11.0 [95% CI 5.0–24.0]

## Comorbidities, mild/moderate vs severe disease:

- Age: 54 mild/moderate disease vs 67 severe disease, p < 0.001
- Age > 60y: 38% vs 70%, p = 0.005
- Active cancer: 0% vs 11%, p = 0.01
- Hypertension: 60% vs 78%, p = 0.01

## Comorbidities FO vs UO:

- Age > 70y: 21.8% FO vs 46.6% UO, p = 0.001
- Time after transplantation: 7.1y vs 5.5y, p = 0.048

(continued on next page)
| Type of study | Study population/type of SOT | Median age | Gender | Comorbidities | Time after transplantation | Outcome |
|---------------|-----------------------------|------------|--------|---------------|--------------------------|---------|
| Sofeland et al. [38] | Retrospective multicentre cohort study | 230 SOT: 162 KTR (70.4%), 35 LTR (15.2%), 17 HTR (7.4%), 16 lung (7%) | Mean age: 54 | Male: 64% | Chronic liver disease: 12.2% FO, 17.5% UO | Median time: 78 months | Diabetes mellitus: 28.6% FO vs 44.4% UO, $p = 0.03$ |
| | | | | | Cancer: 10.2% FO, 15.9% UO | | Chronic cardiopathy: 21.1% FO vs 36.5% UO, $p = 0.02$ |
| | | | | | Morbid obesity: 6.1% FO, 1.6% UO | | Risk factors for UO: |
| | | | | | | Age $> 70y$: OR 3.01 [95% CI 1.30–7.00] | |
| | | | | | | Risk for 30-day mortality: Age $70+$: OR 62.06 [95% CI 7.97–1367.71], $p < 0.001$ | |
| | | | | | | Age 60–69: OR 10.95 [95% CI 1.58–222.25], $p = 0.037$ | |
| | | | | | | Sex male: OR 3.70 [95% CI 1.14–14.29], $p = 0.041$ | |
| | | | | | | BMI $> 30$: OR 5.93 [95% CI 1.29–35.19], $p = 0.031$ | |
| | | | | | | BMI 25–30: OR 5.83 [95% CI 1.37–28.70], $p = 0.026$ | |
| Kidney | AlOtaibi et al. [39] | Retrospective single-centre cohort study | 104 KTR | Mean age: 51 | Hypertension: 75.1% Diabetes: 30% BMI $> 30$: 23.9% Renal impairment: 16.1% Cardiovascular disease: 8.7% Malignancy: 2.6% CCI: CCI 0 (15.2%), CCI 1–2 (56.9%), CCI $\geq$3 (28.3%) | Median time: 72 months | Risk for 30-day mortality: Age $70+$: OR 62.06 [95% CI 7.97–1367.71], $p < 0.001$ |
| | | | | Mean age: 49.3 | | | Age 60–69: OR 10.95 [95% CI 1.58–222.25], $p = 0.037$ |
| | | | | Male: 75% | | | Sex male: OR 3.70 [95% CI 1.14–14.29], $p = 0.041$ |
| | | | | | | BMI $> 30$: OR 5.93 [95% CI 1.29–35.19], $p = 0.031$ | |
| | | | | | | BMI 25–30: OR 5.83 [95% CI 1.37–28.70], $p = 0.026$ | |
| | Bossini et al. [40] | Prospective single-centre cohort study | 53 KTR | Mean age: 60 | Hypertension: 79% Cardiac diseases: 19% Diabetes: 21% Other: 8% | NR | Risk factors for mortality: Age $> 60y$: OR 1.12 [95% CI 1.03–1.24]; $p = 0.01$ |
| | | | | Male: 79% | | | Age: 66 non-survivors vs 60 survivors; $P < 0.001$ |
| | Cravedi et al. [41] | Retrospective multicentre cohort study | 144 KTR | Mean age: 62 | Hypertension: 95% Diabetes: 52% Obesity: 49% Heart disease: 28% Lung disease: 19% | Mean time: 5y | Comorbidities ICU vs non-ICU: Diabetes mellitus: 42.5% non-ICU vs 64.5% ICU, $p = 0.04$ |
| | | | | Male: 66% | | | Hypertension: 57.5% non-ICU vs 80.7% ICU, $p = 0.024$ |
| | | | | | | Ischemic heart disease: 13.7% vs 35.5%, $p = 0.011$ | |
| | | | | | | Pulmonary disease: 4.1% vs 19.4%, $p = 0.011$ | |
| | Cristelli et al. [42] | 491 KTR | Mean age: 53 | Male: 60% | Hypertension: 68% Diabetes: 32% | Mean time: 6.6y <3 m: 3% | Comorbidities survivors vs non-
| | | | | | | (continued on next page) |

(continued on next page)
| Type of study | Study population/type of SOT | Median age | Gender | Comorbidities | Time after transplantation | Outcome |
|--------------|-----------------------------|------------|--------|---------------|--------------------------|---------|
| Prospective single-centre cohort study | Obesity: 25% Cardiac disease: 12% Neoplasia: 7% Lung disease: 2% | 4-12 m: 9% >12 m: 89% | survivors: Age: 49 survivors vs 59 non, \( p < 0.001 \) Diabetes: 26% survivors vs 44%, \( p < 0.001 \) Cardiac disease: 7% vs 23%, \( p < 0.001 \) Hypertension: 64% vs 76%, \( p = 0.010 \) Neoplasia: 5% vs 11%, \( p = 0.016 \) | Risk factors for mortality: Age: OR 3.08 [95% CI 1.86–5.09] Diabetes mellitus: OR 1.69 [95% CI 1.06–2.72] Cardiac disease: OR 2.00 [95% CI 1.09–3.68] | |

| Fava et al. [43] | Retrospective multicentre cohort study | 104 KTR | Mean age: 59.7 Male: 55.7% | Arterial hypertension: 86.5% Diabetes: 30.8% Heart disease: 29.8% Obesity: 26.9% Pulmonary disease: 15.4% Active neoplasms: 7.7% | Median time: 59 months \(<6 m: 14.4%\) | Risk factors for mortality: Age HR 1.10 [95% CI 1.05–1.16]; \( p < 0.001 \) |

| Kute et al. [44] | Retrospective multicentre cohort study | 251 KTR | Median age: 43 Male: 86% | Hypertension: 84% Diabetes: 32% BMI > 30: 23.9% Ischemic heart disease: 12% History of smoking: 12% Chronic lung disease: 4% | Median time: 3.5y | Comorbidities survivors vs non-survivors: Age: 42 survivors vs 54 non-survivors, \( p < 0.0001 \) BMI > 30: 16.7% survivors vs 55.2% non-survivors, \( p < 0.0001 \) ≥1 comorbidities: 39.3% survivors vs 96.5% non-survivors, \( p < 0.0001 \) Comorbidities mild disease vs moderate disease vs severe disease: Advanced age: 18% mild vs 62% severe, \( p = 0.03 \) Advanced age: 28% moderate vs 62% severe, \( p = 0.04 \) Diabetes mellitus: 45% mild vs 85% severe, \( p = 0.04 \) Diabetes mellitus: 45% moderate vs 85% severe, \( p = 0.02 \) | Risk factors for hospitalization: Age: OR 1.03 [95% CI 1.02–1.04]; \( p < 0.001 \) Hypertension: OR 1.42 [95% CI 1.08–1.87], \( p = 0.013 \) Cardiovascular disease: OR 1.65 [95% CI 1.08–2.52]; \( p = 0.021 \) | |

| Nahi et al. [45] | Retrospective single-centre cohort study | 53 KTR | NR | Hypertension: 100% Diabetes: 55% Obesity: 42% Heart disease: 26% | NR | |

| Requiao- moura et al. [46] | Retrospective multicentre cohort study | 1680 KTR | Mean age: 51.3 Male: 60.4% | Hypertension: 75.7% Diabetes: 34.0% BMI ≥ 30: 23.8% Cardiovascular disease: 12.3% Neoplasia: 5.0% Hepatic disease: 3.8% Pulmonary disease: 3.2% Autoimmune: 2.9% Neurologic disease: 1.2% | Median time: 5.9y | Risk factors for hospitalization: Age: OR 1.05 [95% CI 1.04–1.07]; \( p < 0.001 \) (continued on next page) |
| Type of study          | Study population/type of SOT | Median age | Gender | Comorbidities                                                                 | Time after transplantation | Outcome                                                                 |
|-----------------------|-----------------------------|------------|--------|-------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------------------------|
| Villanego et al. [47] | Retrospective multicentre cohort study | 1011 KTR   | Median age: 60 | Male: 62.8%                                                                 | Median months: 72 <6 m: 8.5% >6 m: 91.5% | Risk factors for mortality: Hypertension: OR 1.03 [95% CI 1.002–1.05], p = 0.020 |
| Liver Bacchetti et al. [48] | Prospective multicentre cohort study | 57 LTR     | Median age: 65y | Male: 70%                                                                     | Median time: 6y              | Comorbidities survivors vs non survivor: Arterial hypertension: 56% Clinical history of neoplasia: 42% Cardiovascular disease: 37% Diabetes: 37% CKD: 28% Concomitant respiratory diseases: 23% Active or former smoker: 12% |
| Belli et al. [49]     | Retrospective multicentre cohort study | 243 LTR    | Median age: 63 | Male: 70.4%                                                                   | Median time: 8y              | Risk factors for mortality: Hypertension: 45.7% Diabetes mellitus: 38.7% CKD: 20.2% BMI >30: 18.9% Chronic lung disease: 10.3% Chronic artery disease: 7.0% |
| Golimenero et al. [50] | Prospective multicentre cohort study | 111 LTR    | Median age: 65.3 | Male: 71.2%                                                                   | Median months: 105 15% first year post-transplantation | Risk factors for severe disease in hospitalized patients: Hypertension: 59.2% non-severe, 54.3% severe Diabetes: 43.4% non-severe, 57.1% severe Cardiomyopathy: 17.1% non-severe, 25.7% severe Bronchopulmonary: 11.8% non-severe vs 11.4% severe CCI: 3 non-severe, 5 severe |
| Heart Gemardi et al. [51] | Prospective multicentre cohort study | 99 HTR     | Median age: 60 | Male: 75%                                                                     | Median time post-transplant: 5.6y | Risk factors for mortality: Age > 60y: OR 7.6 [95% CI 1.9–51] |

a Favourable outcome: FO: full recovery and discharged or stable clinical condition
b Unfavourable outcome: UO: admission to ICU or death


3.5. Anti-metabolites

Colmenero et al., a prospective multicentre cohort study on 111 LTR, reported that severe COVID-19 was independently associated with immunosuppression containing mycophenolate (OR 3.94 [95% CI 1.59–9.74]; \( p = 0.003 \)) [50]. Furthermore, in the multicentre study in 1680 KTR of Requiao-Moura et al., immunosuppressive regimen with calcineurin inhibitors and mycophenolate was independently associated with a higher mortality risk within 90-days compared to other regimens (CI-Mycophenolate: OR 1.20 [95% CI 1.02–1.40], \( p = 0.026 \)). [46] Nonetheless, no other studies suggested the independent role of anti-metabolites on disease severity or mortality. [31–38,40,43,47,49,51,64,66,68]

3.5.4. mTOR-inhibitors

The study of Heldman et al. stated that an mTOR-inhibitor regimen was associated with reduced mortality risk (OR 0.3 [95% CI 0.1–0.8], \( p = 0.03 \)) [34] Kates et al. also suggested this, but their analysis did not reach significance [35]. Additionally, mTOR-inhibitor use was an independent risk factor for severe COVID-19 disease, reported by the small study of Genuardi et al. (OR 6.80 [95% CI 1.30–41.00], \( p = 0.026 \)) [51]. These outcomes could not be found in other studies. [31,33,36–38,40,43,47,49,50,66,68]

3.5.5. Belatacept

Only 8 studies reported the use of belatacept as baseline immunosuppression. [27,28,36,38,53,55,56,66] No association with severe disease or mortality was found. [36,38,66]

3.5.6. Effect of baseline immunosuppression on clinical course

To conclude, type of baseline immunosuppression in SOT recipients was not associated with mortality or severe disease in the largest part of the studies. [28,31–38,40,43,47,49,55,66] Also, two studies documented that a higher number of maintenance immunosuppressive medications was not associated with mortality. [34,35]

3.6. RAAS-inhibitor use

Thirteen studies reported the use of renin-angiotensin-aldosterone-system-inhibitors (RAAS-I) as baseline treatment or as an additive treatment for COVID-19. [27,29,31,41,43,44,47–50,52,55,67] At the time of diagnosis, 21% received angiotensin-converting enzyme inhibitors (ACE-I) and 20% angiotensin II receptor antagonists (ARB), as described by Hillbrands et al. [29] KTR received more RAAS-I compared to non-transplanted patients. [27] No association was found between baseline RAAS-I intake and risk for severe disease, hospitalization or ICU admission [48,50,55]. Furthermore, baseline RAAS-I did not affect mortality or survival. [27,31,41,44,48] Belli et al. were the only that documented the use of ACE-I or ARB as an independent risk factor for mortality, but only after univariate analysis (OR 1.92 [95% CI 1.06–3.49], \( p = 0.033 \)). [49]

In the study of Villanego et al., 14.2% received ACE-I and 27.1% ARB as additional treatment for COVID-19. [47] RAAS-I treatment was not associated with mortality or survival. [47,68] Moreover, the application frequency of RAAS-I as additional treatment did not differ between SOT recipients and non-transplanted patients [41,52].

3.7. Modification of immunosuppression

3.7.1. Immunosuppressive change depending on care setting/disease severity

Immunosuppression withdrawal or reduction depended on care setting and disease severity. In general, immunosuppression decreased to a greater degree in relation to the increasing disease severity. [29,38,50,56,64,65,67] Steroids were an exception as they increased with worse disease severity [65,67].

For patients with mild disease treated at home, the overall part of the regimens was not adjusted [39,42,48,49,56,65,67]. Considering hospitalized patients, anti-metabolites (AM), mainly mycophenolate, were firstly and most often discontinued or reduced. [22,42,46,48,49,56,65] Sandal et al. reported decreasing or stopping anti-metabolites in 59.7% of the patients with mild disease managed at home, in 76.0% of the hospitalized patients with moderate disease and in 79.5% of ICU-admitted patients with severe disease [67]. Furthermore, calcineurin inhibitors (CI) were reduced or stopped in 23.2% of the patients managed at home, as reported by Sandal et al. [67] Other studies confirmed that they were continued for most patients with mild disease. [22,27,29,36,53–55,64,65,67] The dose was more frequently reduced or stopped in relation to increasing disease severity. (Sandal: 45.4% in moderate disease; 68.2% in severe disease). [36,65,67] For mild, moderate and severe disease, Sandal et al. analyzed that mTOR-inhibitors were reduced or withdrawn in 25.7%, 43.9% and 57.7% respectively. [67] Other studies confirmed the reduction or withdrawal of m-TOR-inhibitors, although this regimen was reported less than AM and CI based regimens [25–27,33,40,41,43,48,65,68]. For steroids, an increase in dose was documented by Sandal et al. for 2.1% of the patients with mild disease, for 30.6% with moderate disease and 46.0% with severe disease. [67]

3.7.2. Complete withdrawal of immunosuppression

Complete withdrawal of immunosuppression occurred mostly to patients with severe disease who were ICU-admitted. [29,42,50,64] In case of complete withdrawal, steroids were continued or the dose was increased. [29,42,50,64]

3.8. Treatment

Treatment options were dependent of the care setting. Due to the observational retrospective analysis of the treatment studies and the rapidly evolving treatment practices, analysis of the treatment data was not included in this article. The data concerning different treatment options are available in Table 4a and 4b.

3.9. Graft function

Twelve studies reported graft loss. [26,36–39,42,44,50,54,55,64,68] For instance, Salto-alejandre et al. documented 2.4% graft loss in 240 SOT and the single centre study of Cristelli et al. reported 4% graft loss in 491 KTR. [37,42] Graft loss was more prevalent among non-survivors compared to survivors. [68]

3.10. Natural immune response after COVID-19 infection

Twelve studies concerning natural immunity after COVID-19 infection have been included. [101–112]

3.10.1. Humoral response

Overall, the majority of SOT patients is able to mount a humoral response to SARS-COV-2. [101–108,111]

\* P-value not reported
\* d Severe disease: requirement of respiratory support, admission in intensive care unit and/or death
\* c Severe disease: requiring any of the following: mechanical ventilation, de novo renal replacement therapy, use of vasopressors, or death occurring

[31–38,40,43,47,50,51,64,66,68]
## Table 2a
Mortality and clinical course - comparative studies.

| Type of study | Study population/type of SOT | Mortality parameter | Mortality rates | Hospital admission | ICU Admission | Need for mechanical ventilation | Development AKI | Outcome |
|---------------|-------------------------------|---------------------|-----------------|-------------------|---------------|---------------------------------|-----------------|---------|
| Mixed type of SOT | Avery et al. [21] | Retrospective multicentre cohort study | 2472 patients: 45 SOT, 2427 non-transplant patients | In-hospital mortality | 4.6% SOT, 11.1% non-SOT | Only hospitalized patients | NR | 16.3% non-SOT, 6.7% SOT | NR | Risk of in-hospital mortality SOT vs non-SOT: HR 0.4 [95% CI 0.1–1.6], p = 0.19 |
| Retrospective single-centre cohort study | Chaudhry et al. [22] | 147 patients: 47 SOT, 100 non-transplant recipients | Overall mortality after 35 days | 22.8% SOT, 25% non-SOT | Only hospitalized patients | 37.1% SOT, 43% non-SOT | 34.3% SOT, 36% non-SOT | 46.8% SOT, 43% non-SOT | Outcomes SOT vs non-SOT: Death: OR 0.88 [95% CI 0.36–2.21], p = 0.80 |
| Retrospective matched cohort study | Fisher et al. [23] | 4035 patients: 128 SOT (106 KTR (82.8%), 9 LTR (7.0%), 6 HTR, 4 combined kidney/pancreas (3.1%), and 3 combined kidney/liver (2.3%)), 3907 matched non-transplant patients | Overall mortality | 21.9% SOT, 14.9% non-SOT | Only hospitalized patients | 39.1% SOT vs 33.7% non-SOT | 29.7% SOT vs 20.3% non-SOT | 33.6% SOT vs 20.2% non-SOT | Outcomes SOT vs non-SOT: Risk of mortality: OR 1.93 [95% CI, 1.18–3.15]; P < 0.01 |
| Retrospective matched cohort study | Hadi et al. [24] | 4596 patients: 2307 SOT (1740 KTR (75.4%), 418 LTR (18.1%), 262 HTR (11.4%), 180 Lung (7.8%)), 2289 matched non-transplant patients | 30-day mortality rate; 60-day mortality rate | Before matching: 30-day: 4.8% SOT, 1.9% non-SOT Before matching: 60-day: 6.0% SOT, 2.2% non-SOT After matching: 30-day: 6.5% versus 5.3%; After matching: 60-day: 6.0% SOT, 5.8% non-SOT | Before matching: 30.9% SOT, 9.2% non-SOT After matching: 31.0% vs 25.5% | Before matching: 11.0% SOT, 3.2% non-SOT After matching: 11.0% SOT, 9.5% non-SOT | Before matching: 6.7% SOT, 2.1% non-SOT After matching: 6.7% SOT, 2.1% non-SOT | Before matching: 24.7% SOT, 4.0% non-SOT | Outcomes SOT vs non-SOT after matching: Hospitalization rate: RR 1.22 [95% CI 1.11–1.34]; AKI: RR 1.73 [95% CI 1.53–1.96]; ICU admission: RR 1.16 [95% CI 0.98–1.38]; Need for mechanical ventilation after 30 days: RR 1.04 [95% CI 0.86–1.26]; Need for mechanical ventilation after 60 days: RR 1.03 |

(continued on next page)
| Study Type                          | Study Design                        | Population/Type of SOT                                                                 | Mortality Parameter | Mortality Rates | Hospital Admission | ICU Admission | Need for Mechanical Ventilation | AKI | Development | Outcome       |
|------------------------------------|-------------------------------------|----------------------------------------------------------------------------------------|---------------------|----------------|--------------------|---------------|---------------------------------|-----|-------------|---------------|
| Table 2a (continued)               |                                     |                                                                                        |                     |                |                    |               |                                 |     |             |               |
| Linares et al. [25]                | Prospective single-centre matched cohort study | 261 patients: 41 SOT (32 KTR (79%), 4 LTR (9.7%), 3 HTR (7.3%) and 2 combined liver-kidney (4.9%), 220 non-transplant patients | Mortality during hospitalization | 12.2% SOT, 15% non-SOT | Only hospitalized patients | 34% SOT, 41% non-SOT | 17% SOT, 19% non-SOT | 49% SOT, 16% non-SOT | [95% CI 0.86–1.24] Mortality after 30 days: RR 1.22 [95% CI, 0.88–1.68] Mortality after 60 days: RR 1.05 [95% CI, 0.83–1.32] Mortality: 15% SOT vs 12% non-SOT, p = 0.64 Mechanical ventilation: 17% SOT vs 19% non-SOT, p = 0.325 AKI: 49% SOT vs 16% non-SOT, p < 0.001 Risk factors of mortality: SOT: OR 0.79 [0.29–2.15], p = 0.640 |
| Miarons et al. [26]                | Retrospective single-centre matched cohort study | 212 patients: 46 SOT (30 KTR (65.2%), 13 Lung (28.3%), 3 LTR (6.5%), 166 Matched non-transplant recipients | 28-day mortality | 37% SOT, 22.9% non-SOT | Only hospitalized patients | 22.2% SOT vs 18.4% non-SOT | NR | 23.9% SOT vs 13.3% non-SOT | Mortality rate: 2.49/100 person-day SOT vs 1.39/100 person-day non-SOT, p = 0.51 ICU admission: 22.2% SOT vs 18.4% non-SOT, p = 0.16 AKI: OR 1.81 [0.76–4.29], p = 0.179 |
| Molnar et al. [52]                 | Retrospective multicentre matched cohort study | 386 patients: 98 SOT (67 KTR (68.4%), 13 LTR (13.3%), 13 HTR (13.3%), 4 Lung (4.1%), 1 pancreas (1.0%), 288 non-transplant patients | Death within 28 days of ICU admission | 40% SOT, 43% non-SOT | Only hospitalized patients | All ICU admitted | 56% SOT, 59% non-SOT | AKI requiring RRT: 37% SOT, 27% non-SOT | Outcomes SOT vs non-SOT: Death within 28d of ICU admission: RR 0.92 [95% CI 0.70–1.22], p = 0.58 AKI requiring RRT: RR 1.34 [95% CI 0.97–1.85], p = 0.07 Mechanical ventilation: RR 1.03 [95% CI 0.91–1.16], p = 0.65 |
| Ringer et al. [53]                 | Retrospective single-centre matched cohort study | 93 patients: 33 SOT (87% KTR, 10% LTR, 3% HTR), 60 non-transplant patients | 28-day mortality | 13% SOT, 13% non-SOT | Only hospitalized patients | NR | 27% SOT, 20% non-SOT | NR | Mortality: 13% SOT vs 13% non-SOT, p = 1.0 Mechanical ventilation: 27% SOT vs 20% non-SOT, p = 0.473 |
| Kidney Caillard et al. [27]        | Retrospective multicentre matched cohort study | 1101 patients: 306 KTR, 795 non-transplant patients | 30-day mortality | 17.9% KTR, 11.4% non-SOT | Only hospitalized patients | ICU or death: 43.8% KTR, 41.2% non-SOT | 28.1% KTR, 33.8% non-SOT | 45.8% KTR, 13.2% non-SOT | 30-day mortality: 17.9% KTR vs 11.4% Controls, p = 0.038 30-day cumulative incidence of severe COVID-19 or death: 43.8% vs 41.2%, p = 0.21 (continued on next page) |
| Type of study | Study population/type of SOT | Mortality parameter | Mortality rates | Hospital admission | ICU Admission | Need for mechanical ventilation | Development AKI | Outcome |
|---------------|-----------------------------|---------------------|----------------|-------------------|--------------|---------------------------------|----------------|---------|
| Chavarot et al. [28] | Retrospective multicentre matched cohort study | 2117 patients: 100 KTR, 2017 matched non-transplant patients | 30-day mortality | 26% KTR before matching | Only hospitalized patients | 34% KTR before matching | 29% KTR before matching | NR | After matching: 30-day survival: 62.9% KTR vs 71.0% non-SOT, p = 0.38 30-day severe disease-free survival: 50.6% KTR vs 47.5% non-SOT, p = 0.91 Overall survival: HR 1.38 [95% CI 0.67–2.83], p = 0.388 28-day probability of death in KTR vs DP: HR 1.23 [95% CI 0.95–1.63], P = 0.14 28-day probability of death in hospitalized patients: HR 1.56 [95% CI 1.17–2.07], P = 0.002 Adjusted 28-day probability of death in hospitalized patients: HR 0.81 [95% CI 0.59–1.10], P = 0.18 |
| Hilbrands et al. [29] | Retrospective multicentre cohort study | 1073 patients: 305 KTR, 768 DP | 28-day mortality | 21% KTR, 25% DP; 23.6% KTR, 33.5% DP; 45% KTR, 53% DP; 53% KTR, 59% DP | 89% KTR, 70% DP | 21% KTR, 12% DP | 18% KTR, 10% DP | NR | |
| Jager et al. [30] | Retrospective multicentre cohort study | 4298 patients: 1013 KTR, 3285 DP | 28-day mortality | 20.2% KTR, 21.2% DP | NR | NR | NR | NR | |
| Ozturk et al. [31] | Retrospective multicentre study | 1210 patients: 81 KTR, 289 CKD, 390 DP, 450 control | In-hospital mortality | 11.1% KTR, 4% control, 16.2% HD, 28.4% CKD | Only hospitalized patients | 21% KTR, 8% control, 25.4% HD, 39.4% CKD | 82.4% KTR, 58.8% control, 77.7% HD, 81.3% CKD | NR | |
| Liver Webb et al. [32] | Retrospective multicentre cohort study | 778 patients: 151 LTR, 627 non-transplant patients | Overall mortality | 19% LTR, 27% non-SOT | 82% LTR, 76% non-SOT | 28% LTR, 8% non-SOT | 20% LTR, 5% non-SOT | NR | ICU Admission: 28% LTR vs 8% non-SOT, p < 0.0001 Mechanical ventilation: 20% LTR vs 5% non-SOT, p < 0.001 Mortality: 19% LTR vs 27% non-SOT, p = 0.046 |

a Type of SOT not reported
b P-value not reported
Table 2b
Mortality and clinical course – non-comparative studies.

| Type of study | Study population/ type of SOT | Mortality parameter | Mortality rates | Hospital admission | ICU Admission | Need for mechanical ventilation | Development AKI |
|---------------|-------------------------------|---------------------|----------------|-------------------|--------------|-------------------------------|----------------|
| Mixed type of SOT |                               |                     |                |                   |              |                               |                |
| Ali et al. [54] | Prospective single-centre cohort study | 67 SOT: 44 KTR (65.7%), 15 LTR (22.4%), 8 Lung (11.9%) | Overall mortality | 4.3% | 70.1% | 14.9% | 4.3% | 19.1% |
| Heldman et al. [34] | Prospective multicentre cohort study | 1081 SOT: 11.1% Lung, 13.6% HTR, 16.0% LTR, 70.0% KTR, 6.3% Other | 28-day mortality | 24% Lung, 16% non-lung SOT | 66% hospitalized: 75% lung, 66% non-lung SOT | 44% lung, 37% non-lung SOT | NR |
| Kates et al. [35] | Retrospective multicentre cohort study | 482 SOT: 318 KTR or kidney/pancreas (66%), 73 LTR (15.1%), 57 HTR (11.8%), 30 lung (6.2%) | 28-day mortality | 18.7% non-hospitalized, 20.5% hospitalized | 78% 39.1% of hospitalized | 31.1% of hospitalized | 44.4% of hospitalized |
| Pereira MR, Mohan S. et al. [36] | Retrospective multicentre cohort study | 90 SOT: 46 KTR (51%), 17 lung (19%), 13 LTR (14%), 9 HTR (10%), 3 heart-kidney (3%), 1 liver-kidney (1%), 1 kidney-pancreas (1%) | Overall mortality | 28-day mortality | ICU-mortality | 16%; 36% | 77.7% | 35% | 35% of hospitalized | NR |
| Roberts et al. [55] | Retrospective multicentre cohort study | 210 SOT: 108 KTR (51.4%), 50 LTR (23.8%), 33 HTR (15.7%), 15 Lung (7.1%), 4 kidney-pancreas (1.9%) | Overall mortality after 20-days | 28-day mortality ICU-mortality | 16%; 36% | 77.7% | 35% | 35% of hospitalized | NR |
| Salto-alejandre et al. [37] | Prospective single-centre cohort study | 53 KTR | Mortality rate hospital; overall fatality rate | 33%; 28% | 84.9% | 22% of hospitalized | 90% of ICU | 33% |
| Cravedi et al. [41] | Retrospective multicentre cohort study | 144 KTR | Overall mortality during 52 days | 32% | Only hospitalized patients | 17.6% | 0% favourable outcome, 38.1% unfavourable outcome | NR |
| Cristelli et al. [42] | Prospective single-centre cohort study | 491 KTR | Overall mortality rate; 28-day mortality; hospital mortality; mortality mechanical ventilation | 28.5%; 22%; 41%; 85% | 63.9% | 15.7% total, 24.7% hospitalized | 10.5% total, 16.6% hospitalized | 24.1% hospitalized |
| Elias et al. [56] | Prospective multicentre cohort study | 1216 KTR, 66 COVID+ | Mortality in COVID+ patients; Mortality mechanical ventilation | 24%; 73% | 91% of hospitalized | 22% | 22% | 42% |
| Fava et al. [43] | Retrospective multicentre cohort study | 104 KTR | Overall mortality | 26.9% | Only hospitalized patients | 23.1% | 16.3% | 47% |
| Kute et al. [44] | Retrospective multicentre cohort study | 251 KTR | Overall mortality; hospital mortality; mortality mechanical ventilation | 11.6%; 14.5%; 96.7% | 80% | 21% | 12% | 48.4% |
| Requiao-Moura et al. [46] | Retrospective multicentre cohort study | 1680 KTR | 90-day cumulative incidence of death; Hospital mortality; | 21%; 31.6%; 58.2%; 75.5% | 65.1% | 34.6% | 24.9% | 23.2% |

(continued on next page)
3.11. COVID-19 vaccine immunogenicity studies reported lower CD8 non-SOT, and no difference for CD 8 detectable cell-mediated immunity after 6 months. [111] Besides, the two months onset were seen in both SOT patients and immunocompetent controls, and not in 15 SOT patients in the study of Zervou et al. [105] Specific T-cell responses after vaccination, which are summarized in Tables 5a and 5b. [69–85]

3.11.1. Vaccine response

SOT recipients developed a low vaccine response rate [70–77,80,83,84]. Compared to healthy controls, SOT recipients had lower numbers of serological response and lower antibody titers [69,71–74,76,77,84]. Even in seropositive recipients, mean antibody levels were significantly lower [72,76]. Additionally, KTR had reduced humoral responses compared to DP [70,71,73].

Only eight studies analyzed cellular immune response [69,70,74,75,78,79,81,84]. These documented that SOT recipients have significantly lower frequencies of reactive T-cells compared to healthy controls [69,74,75]. Furthermore, SOT patients develop an impaired interferon response and other effector cytokine production. [69,74,75]

3.11.2. Factors affecting vaccine response

Stumpf et al. reported age and immunosuppressive drug number as major risk factors for seroconversion failure (Age: OR 1.03 [95% CI 1.01–1.047], p = 0.006; Number of IS drugs: OR 2.06 [95% CI 1.34–3.16], p = 0.001) [75]. Smaller studies confirmed the finding of older age as an independent risk factor [72,76,83]. When considering immunosuppression, other studies documented triple therapy immunosuppression as a risk factor for negative humoral response [72,76,77]. Additionally, immunosuppressive regimens containing mycophenolate were independently associated with lower odds of a positive humoral response [72,75,76,81,83,85]. Belatacept use was a strong risk factor for humoral failure after vaccination. (7.085 [95% CI 1.97; 25.45], p = 0.003) [75] This was also suggested by Bertrand and Osmanodja et al. including only a small number of belatacept patients, but no significance was found [70,86]. In contrast, only three studies analyzed the factors affecting a positive humoral response [70,81,83]. Belatacept and other immunosuppressives as a risk factor for negative humoral response [72,76,83].

In addition, the humoral response to SARS-COV-2 is comparable to immunocompetent patients [102–106]. In the study of Zervou et al., 83.6% of the 61 SOT patients had seropositive IgG results after two months. [107] Besides, the study of Magicova reported higher IgG levels in 1073 KTR compared to healthcare workers. [102] Considering the different subtypes of IgG, no difference was found in prevalence of anti-S antibody response and anti-S IgG levels comparing SOT patients to immunocompetent controls. [108,109] In contrast, SOT patients developed lower levels of anti-nucleocapsid antibodies compared to immunocompetent controls at different points in time. [103,105,108–110] The study of Burack et al. indicated that after 7 days of diagnosis only 51% of 70 SOT patients had positive anti-nucleocapsid antibodies. [112] Two other studies confirmed this, showing delayed antibody response and anti-S IgG levels comparing SOT patients to immunocompetent controls. [108,109] In summary, despite initial delay, later levels of IgG did not significantly differ between SOT patients and immunocompetent controls [103,104,106].

Moderate to severe symptoms were the only factor affecting IgG levels, indicating lower antibody levels in patients with mild disease [102,109]. This finding could only be observed in a group of 57 immunocompetent controls, and not in 15 SOT patients in the study of Zavaglio et al. [105]

3.10.2. Cellular response

In comparison to non-immunosuppressed patients, no difference in cellular immunity was found. [104,111] Specific T-cell responses after two months onset were seen in both SOT patients and immunocompetent controls [105]. A substantial proportion of KT recipients exhibited detectable cell-mediated immunity after 6 months. [111] Besides, the prevalence of reactive CD4+ T-cells was similar among SOT patients and non-SOT, and no difference for CD 8+ T-cells was found. [101,104] Two studies reported lower CD8+ T-cell levels in SOT patients, although this did not reach significance. [104,105]

3.11. COVID-19 vaccine immunogenicity

Seventeen studies described vaccine responses after two doses of SARS-COV-2-mRNA-vaccines, adverse events and disease after
suggested that SOT recipients vaccinated with the mRNA-1273-Pfizer vaccine received higher rates of seropositive response compared to the BNT126b2-Moderna vaccine [75,77].

3.11.3. Adverse events
Nine studies reported adverse events after vaccination [72,76–81,83,85]. Pain at the injection site was the most commonly reported local reaction [72,76–81]. Considering systemic reactions, mild reactions including fatigue, fever, chills, nausea, diarrhea, myalgia, arthralgia or headache, were most prevalent. In contrast, no severe systemic reactions such as acute rejection, anaphylaxis or new neurological illness occurred during the follow-up periods [72,74,76,77,79–81,83,85]. Besides, two studies reported that the rates of adverse events were similar between SOT recipients and healthy controls [72,76].

| Type of study                  | Type of SOT                      | Incidence of COVID-19-infection | Mortality | ICU admission | Need for mechanical ventilation | Outcomes                                      |
|--------------------------------|----------------------------------|---------------------------------|-----------|---------------|----------------------------------|-----------------------------------------------|
| Mixed type of SOT              | Arias-murillo et al. [57]        | Retrospective multicentre cohort study | 11,034 patients: 8108 SOT, 2926 WL COVID-: 84 SOT (83.3% kidney, 8.3% liver, 6.0% heart, 2.4% lung), 74 WL | 1% SOT, 2.5% WL | 13.3% overall mortality: 14.3% SOT 12.2% WL | NR | NR | Mortality rates: 14.3% SOT vs 12.2% WL, P = 0.90 Incidence: 1% SOT vs 2.5% WL, p < 0.0001 |
|                                | Ravan et al. [58]                | Retrospective multicentre cohort study | 51,973 patients: 46789 SOT (69.5% kidney, 18.7% liver, 4.7% heart, 2.8% lung), 5184 WL | 1.3% SOT, 3.8% WL | 25.8% SOT, 10.2% WL | NR | NR | |
| Kidney                         | Craig-shapiro et al. [59]        | Prospective single-centre cohort study | 136 patients: 80 KTR, 56 WL | NR | Mortality of hospitalized: 25% SOT, 41% WL | NR | 31% SOT, 29% WL | Multivariate analysis risk of mortality: Waitlist status: OR 3.60 [95% CI 1.38–9.39], P = 0.009 |
|                                | Mamode et al. [63]               | Retrospective multicentre cohort study | 173 patients: 121 KTR, 52 WL | NR | Mortality of hospitalized: 30% KTR, 27% WL | 29.7% KTR, 32.7% WL | 20.2% KTR, 15.6% WL | |
|                                | Mohamed et al. [60]              | Prospective single-centre cohort study | 1755 patients: 1434 KTR, 321 WL 60 COVID-: 28 KTR, 32 WL | Incidence of symptomatic covid: 1.9% KTR, 9.9% WL | COVID-mortality in positive patients: 32% KTR, 15% WL | Overall mortality: 0.6% KTR, 1.5% WL | NR | NR | |
|                                | Thaunat et al. [61]              | Nationwide prospective registry study | 59,022 patients: 42812 KTR, 16210 WL | 1.42% KTR, 2.95% WL | COVID-19-attributable mortality: 44% KTR, 42% WL | NR | NR | |
| Liver                          | Polak et al. [62]                | Multicentre survey study         | 76,956 patients: 71516 LTR, 5440 WL 329 COVID-: 272 LTR, 57 WL | Overall crude incidence of covid-19: 0.34% LTR, 1.05% WL, 0.33% general population | Mortality after covid-19 infection: 15 LTR, 17% WL, 8% general population | Incidence of ICU admission: 14% LTR, 14% WL | NR | NR | Overall crude incidence of covid-19: 1.05% WL vs 0.34% LTR, p < 0.001 1.05% WL vs 0.33% general population, p < 0.01 Mortality: 15% LTR vs 8% general population, P < 0.001 |
### Table 4a
Treatment and immunosuppressive management – comparative studies.

| Study Type                          | Study Design          | Study Population/Type of SOT | Baseline Immunosuppression + Use of RAAS Inhibition | Immunosuppressive Modifications | Treatment | Mortality | Graft Loss | Outcome |
|------------------------------------|-----------------------|-----------------------------|----------------------------------------------------|---------------------------------|-----------|-----------|------------|---------|
| **Mixed Type of SOT**               |                       |                             |                                                    |                                 |           |           |            |         |
| Avery et al. [21]                  | Retrospective multicentre cohort study | 2472 patients: 45 SOT*, 2427 non-transplant patients | Steroids: prednisone 60% CI: Tacrolimus 84.4% AM: Mycophenolate mofetil 13.3% | NR                              | Antiviral: Hydroxychloroquine 28.9% SOT, 16.0% non-SOT Remdesivir 17.8% SOT, 14.2% non-SOT Anti-inflammator: Tacrolimus 13.3% SOT, 3.6% non-SOT Hydrocortisone 4.8% SOT, 2.7% non-SOT Dexamethasone 13.3% SOT, 11.7% non-SOT Methylprednisolone 6.7% SOT, 4.6% non-SOT | In-hospital mortality: 4.4% SOT, 11.1% non-SOT | NR | Treatment SOT vs non-SOT: Tacrolimus: 13.3% SOT vs 3.6% non-SOT, \( p = 0.006 \) Steroids: NS difference |
| Chaudhry et al. [22]               | Retrospective single-centre cohort study | 147 patients: 47 SOT*, 100 non-transplant recipients | NR | Changes in immunosuppression 69.5% CI: decrease or stop 15% AM: decrease or stop 84% mTOR-i: decrease or stop 3% Belatacept: decrease or stop 3% | Antiviral: Hydroxychloroquine 91.4% SOT, 79% non-SOT Anti-inflammator: Tacrolimus 8.6% SOT, 18% non-SOT Corticosteroids 65.7% SOT, 65% non-SOT | Overall mortality after 35-d: 22.8% SOT, 25% non-SOT | NR | Treatment SOT vs non-SOT: NS difference Changes IS: 82.4% hospitalized SOT vs 33% non-hospitalized SOT, \( p = 0.006 \) |
| Fisher et al. [23]                 | Retrospective multicentre cohort study | 4035 patients: 128 SOT (106 KTR (82.8%), 9 LTR (7.0%), 6 HTR, 4 combined KT/pancreas (3.1%), and 3 combined KT/LT (2.3%)), 3907 matched non-transplant patients | Steroids: prednisone 48.4% CI: tacrolimus 74.2%, cyclosporine 3.9% AM: mycophenolate mofetil 45.3% mTOR-i: sirolimus 4.7% | NR | Antiviral: Remdesivir 16.4% SOT, 24.7% non-SOT Anti-inflammator: Tacrolimus 6.2% SOT, 7% non-SOT Prednisone 60.2% SOT, 19.8% non-SOT Dexamethasone 28.1% SOT, 44.5% non-SOT Methylprednisolone 10.2% SOT, 15.6% non-SOT | Overall mortality: 21.9% SOT, 14.9% non-SOT | NR | Treatment SOT vs non-SOT: Remdesivir: 24.7% SOT vs 16.4% non-SOT, \( p = 0.04 \) Prednisone: 60.2% SOT vs 19.8% non-SOT, \( p < 0.01 \) Convalescent plasma: NS difference Tacrolimus: NS difference |
| Hadi et al. [24]                   | Retrospective multicentre matched cohort study | 4596 patients: 2307 SOT (1740 KTR (75.4%), 418 LTR (18.1%), 262 HTR (11.3%), 180 Lung (7.8%), 2289 matched non-transplant patients | CI: Tacrolimus 70%, Cyclosporine 6% AM: Mycophenolate mofetil 47% | NR | Antiviral: Hydroxychloroquine 6.1% SOT Remdesivir 6.6% SOT Anti-inflammator: Glucocorticoids 45.4% SOT Tacrolimus 1.4% SOT Azithromycin 15.2% SOT | Overall mortality: 30-day mortality: 6.45% SOT, 5.29% non-SOT | NR | Treatment SOT vs non-SOT: Remdesivir: 6.6% SOT vs 3.2% non-SOT, \( p < 0.01 \) Convalescent plasma: NS difference Tacrolimus: NS difference |
| Linares et al. [25]                | Prospective single-centre matched cohort study | 261 patients: 41 SOT (32 KTR (78%), 4 LTR (9.7%), 3 HTR (7.3%), 2 combined LT/ KT (4.9%), 220 non-transplant patients | CI based therapy 63% (Tacrolimus or Cyclosporine + cell inhibitor + prednisone) mTOR-i based therapy 37% (Everolimus or sirolimus + cell cycle inhibitor + prednisone) Steroids: prednisone increase 100% AM: mycophenolate stop 100% mTOR-i: stop 100% | NR | Antiviral: Hydroxychloroquine 98% SOT, 98% non-SOT Remdesivir/ritonavir 76% SOT, 93% non-SOT Remdesivir 0% SOT, 13% non-SOT Interferon 7% SOT Anti-inflammator: Tacrolimus 46% SOT, 57% non-SOT Anakinra 17% SOT, 2% non-SOT | 14% SOT, 17% non-SOT | NR | Treatment SOT vs non-SOT: Lopinavir/ritonavir: 76% SOT vs 93% non-SOT, \( p = 0.001 \) Anakinra: 17% SOT vs 2% non-SOT, \( p < 0.001 \) Remdesivir: 0% SOT vs 13% non-SOT, \( p = 0.005 \) Other: difference NS |

(continued on next page)
Table 4a (continued)

| Type of study | Study population/ type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|---------------|--------------------------------|----------------------------------------------------|---------------------------------|------------|-----------|-----------|---------|
| Retrospective single-centre matched cohort study | 212 patients: 46 SOT (30 KTR (65.2%), 13 Lung (28.3%), 3 LTR (6.5%)), 166 matched non-transplant recipients | Steroids: Prednisone 84.4% CI: Tacrolimus 89%, Cyclosporine 2.2% AM: Mycophenolate mofetil 60.9% mTOR-i: Everolimus 15.2%, Sirolimus 15.2% | CI: Tacrolimus 61.1% stop, 50% decrease, 11.2% increase mTOR-i: Everolimus or sirolimus stop 100% | Steroids pulse 41% SOT Biologicals: Baricitinib 2% SOT, 0% non-SOT Other: Azithromycin 100% SOT, 100% non-SOT | 28-day mortality: 37% SOT, 22.9% non-SOT | | |
| Retrospective multicentre matched cohort study | 386 patients: 98 SOT (67 KTR (68.4%), 13 LTR (13.3%), 13 HTR (13.3%), 4 lung (4.1%), 1 pancreas (1.0%)), 288 non-transplant patients – all ICU admitted | Steroids: 15% CI: 83% AM: Mycophenolate mofetil 68%, Azathioprine 0% Other 13% RAAS-I: ACE-I 11.9%, ARB 21% | | | | | |
| Retrospective single-centre matched cohort study | 93 patients: 33 SOT (87% KTR, 10% LTR, 3% HTR), 60 non-transplant patients | Steroids: Prednisone 83% CI: Tacrolimus 70%, Cyclosporine 3% AM: MMF 63%, Azathioprine 7% Belatacept 20% | Overall continuation of immunosuppression 45% Steroids: prednisone continuation 100% CI: tacrolimus continuation 100% AM: stop MMF 89% | | | | |
| Retrospective multicentre matched cohort study | 1101 patients: 306 KTR, 795 non-transplant patients | Steroids 75.2% CI 82.7% AM: Mycophenolate 77.1%, Azathioprine 3.9% mTOR-i: 11.1% Belatacept 6.5% | CI stop 26% AM stop 75.3% mTOR-i stop 41.2% Belatacept stop 35.0% | | | | |
| | | | Antiviral: Hydroxychloroquine 23.1% KTR, 20.1% non-SOT Remdesivir 0.7% KTR, 0% non-SOT Lopinavir/ritonavir | | 30-day mortality: 17.9% KTR, 11.4% non-SOT | | |
| | | | | Treatment KTR vs non-SOT: Azithromycin: 24.2% vs 45.1%, p < 0.01 Antibiotics: 65.6% vs 74.7%, p < 0.01 Lopinavir/ritonavir: | | | |

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| R. Opsomer and D. Kuypers |
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Table 4a (continued)

| Type of study | Study population/ type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|---------------|--------------------------------|-----------------------------------------------------|---------------------------------|-----------|-----------|-----------|---------|
| RAAS-I: 48.8% KTR, 34.4% non-transplant | | | | 5.5% KTR, 26% non-SOT | Oselatamivir 22.2% KTR, Anti-inflammatory: Tocilizumab 5.5% KTR, 1.1% non-SOT | Other: Azithromycin 24.2% KTR, 45.1% non-SOT | Other antibiotics 65.6% KTR, 74.7% non-SOT | 5.2% vs 21.8%, p < 0.01 |

Chavarat et al. [38]
Multicentre retrospective matched cohort study
2117 patients: 100 KTR, 2017 non-transplant patients

| Steroids: 96.8% CI: 83% AM: Mycophenolic acid 73.4%, Azathioprine 7.4% mTOR-I: 8.5% Belatacept 10.6% RAAS-I: ARB 20%, ACE-I 21% | CI: stop 40% AM: stop 78.9% Belatacept stop 80% | Antiviral: Hydroxychloroquine 12.9% Anti-inflammatory: Tocilizumab 15.9% Other: Azithromycin 45.2% | | 26% KTR | NR |

Hilbrands et al. [50,29]
Retrospective multicentre cohort study
1073 patients: 305 KTR, 768 DP

| Steroids: Prednisone 84% CI: tacrolimus 77%, cyclosporine 10% AM: mycophenolate 66%, azathioprine 5% mTOR-I: 1% RAAS-I: ARB 20%, ACE-I 21% | Steroids: Prednisone: 58% no change, 1% decrease, 41% increase CI: Tacrolimus: 47% no change, 26% decrease, 27% stop Cyclosporin: 95% no change, 3% decrease, 2% stop AM: Mycophenolate: 39% no change, 7% decrease, 54% stop Azathioprine: 96% no change, 1% decrease, 3% stop mTOR-I: 86% no change, 3% decrease, 11% stop | Antiviral: Hydroxychloroquine 73% KTR, 67% DP Lopinavir/ritonavir 18% KTR, 26% DP Remdesivir 1% KTR, 1% DP Interferon 2% KTR, 3% DP Anti-inflammatory: Tocilizumab 9% KTR, 3% DP Anakinra 2% KTR, 2% DP High dose steroids 18% KTR, 11% DP | | 28-day probability of death: 21.3% KTR, 25% DP | Multivariate analysis risk factors associated 28-day case fatality rate: Use of prednisone in KTR: HR 2.8 [95% CI 1.03–8.03], p = 0.04 |

Ozturk et al. [31]
Retrospective multicentre cohort study
1210 patients: 81 KTR, 289 CKD, 390 DP, 450 control

| Steroids: 97.4% CI: Tacrolimus 80.8%, Cyclosporine 9% AM: MME/MFA 83.3%, azathioprine 7.7% mTOR-I: 10.3% RAAS-I: ARB 9% control, 9.4% DP, 15.6% KTR, 35.3% CKD ACE-I 10% control, 21.6% DP, 17.9% KTR, 29.3% CKD | NR | Antiviral: Hydroxychloroquine (95.1% control, 96.3% DP, 100% KTR, 97.2% CKD), Oselatamivir (71.8% control, 63.7% DP, 61.3% KTR, 74.8% CKD) Lopinavir-ritonavir (2.1% control, 1.9% DP, 14.1% KTR, 12.7% CKD), Favipavir (26.2% control, 31.7% DP, 49.3% KTR, 50.2% CKD) Anti-inflammatory: Glucocorticoids (4.1% control, 3.8% DP, 55.3% KTR, 12.3% CKD), Tocilizumab (2.4% control, 1.9% DP, 12.2% KTR, 2.1% CKD), Canakinumab/anakinra (0% control, 0.6% DP, 4% KTR, 0.5% CKD) Other: Convalescent plasma (0.3% control, 0.3% DP, 4% KTR, 0% CKD) Macrolides (87.3%) | In-hospital mortality: Control 4%, HD 16.2%, KTR 11.1%, CKD 28.4% | NR | Baseline IS: NS difference survivors vs non-survivors |

Treatment non-survivors vs survivors:
Oselatamivir: 80.1% vs 67.8%, p = 0.002
Macrolides: 90% vs 81.5%, p = 0.008
Lopinavir/ritonavir: 16.5% vs 3.7%, p < 0.001
Favipiravir: 75.2% vs 27.2%, p < 0.001
Glucocorticoids: 30.6% vs 6.7%, p < 0.001
Tocilizumab: 103% vs 1.7%, p < 0.001
Convalescent plasma: 2.6% vs 0.3%, p = 0.019
ACE-I: 24.5% vs 16.9%, p = 0.028
ARB: 19.1% vs 13.9%, p = 0.101
Anticoagulants/ (continued on next page)
| Type of study | Study population/ type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|---------------|--------------------------------|------------------------------------------------------|---------------------------------|------------|-----------|------------|---------|
| Mohamed et al. [60] | Prospective single-centre cohort study | 1434 KTR, 321 WL | Ciclosporin/ prednisolone 7% Tacrolimus/ prednisolone 4% Tacrolimus/MMF/ prednisolone 59% Ciclosporin/MMF/ prednisolone 19% Tacrolimus/AZA/ prednisolone 11% | **Steroids**: increase 48% AM: MMF stop 70.4%, MMF decrease 3.7%, A2A stop 11%, no change AM 11% | control, 75.7% DP, 66.3% KTR, 87.8% CKD | NR | 15% WL, 32% SOT | NR |
| Liver Webb et al. [32] | Retrospective multicentre cohort study | 778 patients: 151 LTR, 627 non-transplant patients | Steroids: Prednisone 44% CI: Tacrolimus 84%, ciclosporin 5% AM: mycophenolate mofetil 51%, azathioprine 9% mTOR-i: Sirolimus 5% | NR | 19% SOT, 27% non-SOT | NR | Risk for mortality: Baseline IS: NS difference survivors vs non-survivors Treatment: NS difference survivors vs non-survivors |
| Rabiee et al. [64] | Retrospective multicentre cohort study | 487 patients: 112 LTR, 375 matched non-transplant patients | Steroids: Prednisone, low dose 24.1% Prednisone, high dose 6.3% CI: Tacrolimus 91.2%, Cyclosporine 6.3% AM: MMF 50%, Azathioprine 0.9% mTOR-i: 3.6% Other 2.7% | Change in IS: 49.4% CI: 25.9% tacrolimus decrease, 4.9% stop AM: 33.3% stop MMF | 0% Overall mortality 22.3% | 0% | Risk for mortality: Reduction in immunosuppression: OR 2.51 (95% CI 0.90–6.95), P = 0.084 Baseline IS: NS |
| Lung Coiffard et al. [65] | Multicentre survey study | 78 transplant centres from 15 countries | NR | Estimated numbers:<sup>3</sup> Steroids: mild: 55% no change, 8% increase Moderate: 42% no change, 18% increase Severe: 30% no change, 28% increase CI: mild: 58% no change, 12% decrease Moderate: 52% no change, 14% decrease Severe: 38% no change, 21% decrease, 5% stop AM: Mild: 28% no change, 22% | NR | NR | NR |

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3.11.4. Disease after vaccination
Six studies reported disease after vaccination [70,72,75,79,82,83]. Aslam et al. stated that the incidence rate of COVID-19 disease was significantly lower in vaccinated SOT patients compared to non-vaccinated (IRR 0.065 [95% CI 0.024–0.17] vaccinated vs 0.34 [95% CI 0.26–0.44] non-vaccinated, p < 0.0001) [82].

4. Discussion
Studies investigating the impact of the COVID-19 pandemic on SOT recipients are currently limited. In this systematic review, we analyzed 77 studies to discuss the risk factors that make SOT patients with COVID-19 more vulnerable for severe disease or mortality and the impact of immunosuppressive therapy. Furthermore, their clinical outcomes, mortality risk, immunosuppression, natural immune response after COVID-19 infection and COVID-19 vaccination efficacy are discussed.

4.1. Risk factors for mortality and clinical course of COVID-19 in SOT recipients
Across the individual studies, gender, post-transplantation time or comorbidities such as hypertension, diabetes mellitus, coronary artery disease, heart failure, chronic kidney disease and chronic lung disease were variably identified as independent risk factors for mortality or severe disease. However, overall, no comorbidity was generally reported as a major risk factor. Despite the high prevalence of comorbidities in SOT recipients, this did not seem to negatively affect the mortality compared to non-transplanted patients. The hypothesis that SOT is a possible associated factor for a worse outcome of COVID-19 could thus not be confirmed. However, a more cautious interpretation is needed. Due to the higher hospitalization risk of SOT patients, higher mortality in SOT recipients, this did not seem to negatively affect the mortality compared to the general population [113].

However, a higher rate of AKI in SOT recipients compared to non-transplanted patients was observed. Although this might be reflecting a certain selection bias despite the high number of KTR included, an additional study analyzed that AKI risk in SOT patients was strongly influenced by independent risk factors, including comorbidities, age and male sex, possibly reflecting a reduced renal functional reserve or injury-repair capacity associated with the latter factors [87].

The role of comorbidities was strongly influenced by the important effect of age, as comorbidities increase with older age of the recipients. Age was commonly documented as a risk factor for mortality and composite outcomes. The role of advanced age in COVID-19 confirms what has been extensively observed in the general population [1,88,89].

Furthermore, only two studies suggested a higher mortality risk in lung transplant recipients concerning different types of SOT. However, no other distinctions among the different types of SOT were found. More studies are needed to address the direct effect of COVID-19 disease on the transplanted organ in lung transplant recipients as well as in other less included types of SOT. Comparing to dialysis patients, no difference in overall mortality was found. Besides, due to better health of SOT recipients, Hilbrands et al. highlighted a higher mortality in SOT recipients compared to dialysis patients, after adjusting for age and comorbidities [29].

Only three studies suggested an increased mortality in recently transplanted patients, with 64% higher mortality risk in KTR performed in <6 months compared to those >6 months, as reported by Villanego et al. [47] As most studies included recipients with a long median interval after transplantation and a low number of studies divided them in subgroups, there might be statistical power issues analyzing this effect of post-transplantation time.

4.2. Higher incidence in candidates
The incidence of COVID-19 infection in waiting list patients is higher than in SOT recipients. Considering the high amount of included kidney transplantation candidates, this might be due to difficulties in social distancing in patients relying on hemodialysis. Because of the small number of waiting list studies included, no consensus was found for mortality between candidates and recipients.

4.3. Immunosuppression and treatment for COVID-19
In general, the largest part of the studies could not find an independent association between type of baseline immunosuppression and mortality or severe disease. Besides, modification of immunosuppressive therapy reflected individualized adjustment based on the severity of the disease. However, a complete discontinuation of immunosuppressive therapy was rare and occurred in ICU-admitted patients. Interestingly, the included studies suggest that the current practice of immunosuppressive management is an appropriate measure without causing significant short-term adverse effect on graft function. However, the short follow-up time in most of the studies might confound this, clarifying that long follow-up studies are needed to evaluate the modifications on graft function. Additionally, studies investigating the reintroduction or increase of maintenance immunosuppression after COVID-19 disease are needed.

Furthermore, concerning the potential hypercoagulative response after binding of SARS-COV-2 to vascular ACE-2 receptors, more studies are necessary to address the role of prophylactic or therapeutic anticoagulation and RAAS-I use in SOT recipients with severe disease.
| Type of study                  | Study population/type of SOT                                                                 | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications                                                                 | Treatment                                                                 | Mortality          | Graft loss | Outcome |
|-------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------|------------|---------|
| Mixed type of SOT             | Ali et al. [54] Prospective single-centre cohort study                                         | 67 SOT: 44 KTR (65.7%), 15 LTR (22.4%), 8 Lung (11.9%) | Steroids: Predisone 85% CI: Tacrolimus 97% AM: Antimetabolites 87%                                | Steroids: 100% prednisone no change or increase                          | Overall mortality 4.3% | 4.3% graft loss |         |
|                               | Coll et al. [33] Retrospective multicentre cohort study                                         | 778 SOT and HSCT: 423 KTR (54%), 113 HSCT (15%), 110 LTR (14%), 69 HTR (9%), 54 lung (7%), 8 pancreas (1%), 1 multivisceral (0.1%) | Steroids: 68% CI: 78% AM: 59% mTOR-i: 21%                                                  | IS change: 85% Steroids: 1.7% stop, 55% start/ increase, 0.4% decrease, 42.8% no change | Case-fatality rate 27% | NR         |         |
|                               | Heldman et al. [34] Prospective multicentre cohort study                                        | 1081 SOT: 11.1% Lung, 13.6% HTR, 16.0% LTR, 70.0% KTR, 0.3% Other | CI, AM and steroids (70% lung, 50.5% non-lung) Any steroid containing regimen (97.5%, 70.2%) Any CI containing regimen (97.5%, 1.4%) Any AM containing regimen (71.7%, 75.7%) Any mTOR-i containing regimen (7.5%, 5.4%) | Reduction in IS 56.6% lung, 74.1% non-lung CI: change 10.8% lung, 23.1% non-lung AM: stop 45% lung vs 54% non-lung, decrease 3.3% lung vs 8.9% non-lung mTOR-i: decrease or stop 1.67% lung vs 1.14% non-lung | 24% lung, 16% non-lung SOT | NR         |         |
|                               | Kates et al. [35] Retrospective multicentre cohort study                                        | 482 SOT: 318 KTR or kidney/pancreas (66%), 73 LTR (15.1%), 57 HTR (11.8%), 30 lung (6.2%) | CNI, AM and steroids 49.6% CNI and steroids 14.9% CNI and AM 14.7% mTOR-i: 6.6% Other 22.2% Modification of IS: 70% Discontinuation of all IS: <1% AM: stop 56%, decrease 10% | Antifungal: Hydroxychloroquine 61% Remdesivir 2.9% Antifungal: Or alisatamab 13% Corticosteroids 10% Other: Convalescent plasma | 28-day mortality: 20.5% | NR         |         |

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Table 4b (continued)  

| Type of study | Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|---------------|-------------------------------|-----------------------------------------------------|--------------------------------|-----------|----------|-----------|---------|
| Pereira MR, Aversa MM et al. [66] | Retrospective matched cohort study | 58 SOT: 26 KTR (44.8%), 15 Lung (25.9%), 2 LTR (3.4%), 10 HTR (17.2%), 3 heart-kidney (5.2%), 2 kidney-pancreas (3.4%) | Steroids 71% CI 91% AM: Mycophenolate 78% Belatacept 5% | 3.1%, Azithromycin 31%, IV IG 1.9% Other 3.7% | Antiviral: Hydroxychloroquine 81% Remdesivir 9% Anti-inflammatory: Tocilizumab 50% High dose corticosteroids 72% Other: Azithromycin 55% | 41% tocilizumab SOT, 26% non-tocilizumab SOT before matching, 41% vs 28% after matching | Overall 90-day mortality before matching: 41% tocilizumab vs 26% no tocilizumab, P = 0.03 Overall 90-day mortality after matching: 41% tocilizumab vs 28% no tocilizumab, P = 0.27 ICU-admission: 62% tocilizumab vs 28% no tocilizumab, P = 0.008 Mechanical ventilation: 62% tocilizumab vs 21% no tocilizumab, P = 0.003 Steroid treatment: 76% tocilizumab vs 24% no tocilizumab, P < 0.01 |
| Pereira MR, Mohan S. et al. [36] | Retrospective multicentre cohort study | 90 SOT: 46 KTR (51%), 17 lung (19%), 13 LTR (14%), 9 HTR (10%), 3 heart-kidney (3%), 1 liver-kidney (1%), 1 kidney-pancreas (1%) | Steroids: 59% CN: 86% AM: Mycophenolate 72%, Azathioprine 4% mTOR-i: 7% Belatacept 6% | Steroids: Decrease or stop 7% (4% mild, 13% severe) CI: Decrease or stop 18% (14% mild, 23% severe) AM: Decrease or stop 88% (84% mild, 94% severe) | Antiviral: Hydroxychloroquine 91%, remdesivir 3% Anti-inflammatory: Tocilizumab 21%, High dose steroids 24% Other: Azithromycin 66% | 24% 0% | Overall mortality 16% 6% suspected episode of rejection Baseline IS: NS difference hospitalized vs non-hospitalized Change IS: NS difference ICU vs non ICU Treatment: Antibiotics: 100% ICU vs 43% non-ICU patients, p = 0.0021 Other: NS difference |
| Roberts et al. [55] | Retrospective multicentre cohort study | 52 SOT: 29 KTR (55.8%), 9 LTR (17.3%), 6 HTR (11.5%), 6 Lung (11.5%), 2 Multi-organ (3.8%) | Steroids: prednisone 71%, High dose prednisone 8% CI: 85% AM: Mycophenolate/azathioprine 73% mTOR-i: Sirolimus/everolimus 10% Belatacept 10% | IS change 69% Steroids: stop 0%, increase 16% CI: no change 4%, start 3% AM: no change 50%, decrease 29% mTOR-i: no change 100% Belatacept no change 67% | Antiviral: Hydroxychloroquine 34% Remdesivir 3% Anti-inflammatory: Tocilizumab 3% Other: Antibiotics 63% | 24% 0% | Overall mortality 16% 6% suspected episode of rejection Baseline IS: NS difference hospitalized vs non-hospitalized Change IS: NS difference ICU vs non ICU Treatment: Antibiotics: 100% ICU vs 43% non-ICU patients, p = 0.0021 Other: NS difference |
| Salto-alejandro et al. [37] | Prospective multicentre cohort study | 210 SOT: 108 KTR (51.4%), 50 LTR (23.8%), 33 HTR (15.7%), 15 Lung (7.1%), 4 kidney-pancreas (1.9%) | RAAS-I: 13% Steroids: Prednisone (66% FO vs 77.8% UO) CI: Ciclosporin (6.1% FO vs 14.6% UO) Tacrolimus (74.8% FO vs 73.0% UO) AM: Mofetil mycophenolate (68.7% FO vs 69.8% UO), Azathioprine (2.7% FO vs 1.6% UO) mTOR-i: Sirolimus/everolimus (25.9% FO vs 17.5% UO) NR | Modification of IS 82.4% Steroids: Decrease or stop 8.9% total, 7.2% FO, 12.2% UO CI: Decrease or stop 70.0% total, 69.5% FO, 71.2% UO AM: Decrease or stop 73.3% total, 73.3% FO, 73.3% UO mTOR-i: Decrease or stop 71.4% total, 68.4% FO, 81.8% UO NR | Antiviral: Hydroxychloroquine 96.5% total, 95.7% FO, 98.3% UO Lopinavir/ritonavir 45.5% total, 38.6% FO, 61.7% UO Darunavir/cobicistat 3.5% total, 2.9% FO, 5.0% UO Interferon 3.0% total, 1.4% FO, 6.7% UO Anti-inflammatory: Tocilizumab 24.5% total, 16.4% FO, 43.3% UO Methylprednisolone 10.0% total, 10.0% FO, 10.0% UO Other: Azithromycin 17.0% total, 20.0% FO, 10.0% UO NR | Mortality rate 21.4% 5.7% graft dysfunction, 2.4% graft loss 147 FO, 63 UO | Treatment FO vs UO: Tocilizumab: 16.4% FO vs 43.3% UO, p < 0.001 Lopinavir/ritonavir 38.6% FO vs 61.7% UO, p = 0.003 Other: NS Baseline IS: NS difference FO vs UO Changes in IS: NS difference FO vs UO |

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| Type of study          | Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment                                      | Mortality | Graft loss | Outcome                          |
|-----------------------|-------------------------------|------------------------------------------------------|--------------------------------|------------------------------------------------|-----------|-----------|----------------------------------|
| Sandal et al. [67]    | Retrospective survey study    | 71 countries: 55.5% KTR, 19.9% LTR, 8.6% HTR, 8.2% Lung, 6.2% multiple, 1.6% pancreas | Steroids: no change 95.3%, decrease or stop 1.8% CI: no change 94.1%, decrease or stop 4.1% AM: no change 86.7%, decrease or stop 10.3% mTOR-i: no change 85.4%, decrease or stop 5.5% | Decrease or stop in mild, moderate or severe covid-19: AM: 59.7% mild, 76.0% moderate, 79.5% severe CI: 23.2% mild, 45.4% moderate, 68.2% severe mTOR-i: 25.7% mild, 43.9% moderate, 57.7% severe Increase steroids: 2.1% mild, 30.6% moderate, 46.0% severe |          |           | Decrease or stop in mild, moderate or severe covid-19: AM: 59.7% mild, 76.0% moderate, 79.5% severe CI: 23.2% mild, 45.4% moderate, 68.2% severe mTOR-i: 25.7% mild, 43.9% moderate, 57.7% severe Increase steroids: 2.1% mild, 30.6% moderate, 46.0% severe |
| Østlund et al. [38]   | Retrospective multicentre cohort study | 230 SOT: 162 KTR (70.4%), 35 LTR (15.2%), 17 HTR (7.4%), 16 lung (7%) | Steroids: 84.7% CI: Tacrolimus 82.5%, Cyclosporin 13.1% AM: Mycophenolate 73.2%, Azathioprine 5.2% mTOR-i: 6.1% belatacept 0.9% | No change in immunosuppression 51.7% Steroids: decrease or stop 2.6%, increase 24.7% CI: decrease or stop 19.2% AM: reduction or stop 13.9% mTOR-i reduction or stop 14.3% | Antiviral: Hydroxychloroquine 0% Remdesivir 4.3% Lopinavir/ritonavir 0% Anti-inflammatory: Dexamethasone/betamethasone 10.0% Other: Antibiotics 35.4% | 0.4% graft loss | 0% non-hospitalized | Baseline IS: NS difference hospitalized vs non-hospitalized Baseline IS: NS difference mortality |
| Kidney Aloabi et al. [39] | Retrospective single-centre cohort study | 104 KTR | Steroids: 99% CI: Cyclosporine based 27.9%, Tacrolimus based 59.6% AM: Mycophenolate 86.5%, Azathioprine 4.8% mTOR-i: Sirolimus 3.8% | No change 45.2% Steroids: increase 54.8% CI: stop 33.7% AM: stop 54.8% Stop AM and CI 10.6% Stop AM, CI and increased steroid 23.1% | Steroids: Antiviral: Hydroxychloroquine 0% Oseltamivir 8.6% no-oseltamivir agents 7.7% Anti-inflammatory: tocilizumab 8.7% steroid 31.7% Other: Antibiotics 57.7% | 14.9% hospitalized, 0% non-hospitalized | Overall mortality 10.3% | 3.8% failed graft, 11.5% impaired graft |
| Bossini et al. [40]   | Prospective single-centre cohort study | 53 KTR | Steroids: 57% CI: Cyclosporine 32%, Tacrolimus 58% AM: MMF 60% mTOR-i: 11% | Antiviral: Hydroxychloroquine 75.6%, Lopinavir/ritonavir 40%, Darunavir + ritonavir 31.1% Anti-inflammatory: Start steroid 33.3% Other: Antibiotics 67.3% | Antiviral: Hydroxychloroquine | Overall fatality rate 28% | NR | Risk for mortality: Baseline IS: NS association Hydroxychloroquine treatment: NS association Antiviral therapy: NS association |

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| Table 4b (continued) | Type of study | Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|-----------------------|---------------|-----------------------------|-----------------------------------------------------|---------------------------------|-----------|-----------|-----------|---------|
| Cravedi et al. [41]   | Retrospective multicentre cohort study | 144 KTR | Steroids: 86%<br> Cic: tacrolimus 91.0%<br> MMF: mycophenolate 77.1%<br> mTOR-i: everolimus 7.6%<br> RAAS-I: ARB 16.7%, ACE-I 13.9% | Steroids: increase 66%<br> Cic: tacrolimus stop 22.9%<br> MMF or everolimus stop 67.9% | Antiviral: hydroxychloroquine 70.6%<br> Remdesivir 6.3%<br> Lopinavir-ritonavir 4.9%<br> Darunavir-ritonavir 2.1%<br> Darunavir-cobicistat 0.7%<br> Anti-inflammatory: tocilizumab 13.4%<br> Other: antibiotics 74% | Overall mortality 32%<br> NR | | |
| Cristelli et al. [42] | Prospective single-centre cohort study | 491 KTR | Tacrolimus + prednisone + MMF 46%,<br> Cyclosporine + prednisone + MMF 3%<br> Cic: tacrolimus + prednisone + AZA 18%<br> Cic: tacrolimus + prednisone + AZA 7%<br> Cic: tacrolimus + prednisone + mTOR-i 8%,<br> Cic: cyclosporine + prednisone + mTOR-i 0.4% | No IS discontinuation 48%<br> All IS discontinued, except steroids 36%<br> AM stop 12%<br> Cic stop 1% | Azithromycin 27%<br> Azithromycin + chloroquine 11%<br> Azithromycin + steroids 7%<br> Ivermectin 1%<br> Other antibiotics 14% | Overall mortality 28.5%<br> 4% graft loss | | |
| Elias et al. [56]     | Prospective multicentre cohort study | 1216 KTR, 66 covid+ | Steroids: 83%<br> Cic: 86%<br> MMF/MPA/AZA 92%<br> Belatacept 9% | Only AM stopped 62%<br> Only Cic stopped 4%<br> Stopped all IS 2%<br> Belatacept hold 17%<br> No change 36% | Hydroxychloroquine 11%<br> Tocilizumab 2%<br> Eculizumab 3% | COVID related mortality 24%<br> NR | | |
| Fava et al. [43]      | Retrospective multicentre cohort study | 104 KTR | Steroids: Prednisone 92.3%,<br> Cic: Tacrolimus 85.5%,<br> Cyclosporine 2.88%<br> MMF/MPA 83.6%<br> mTOR-i: 19.3%<br> RAAS-I: 35.6% | Overall IS stop: 89.5% survivors, 96.4% non-survivors<br> Steroids: stop 1.4% survivors, 3.7% non-survivors<br> Cic: stop 69% survivors, 68% non-survivors<br> AM: stop 73.1% survivors, 84.6% non-survivors<br> mTOR-i: stop 52.9% survivors, 100% non-survivors | Antiviral: Hydroxychloroquine 97.4% survivors, 96.4% non-survivors<br> Lopinavir-ritonavir 48.7% survivors, 46.4% non-survivors<br> Darunavir-ritonavir 4.2% survivors, 0% non-survivors<br> Darunavir-cobicistat 5.4% survivors, 3.6% non-survivors<br> Remdesivir 2.6% survivors, 0% non-survivors<br> Interferon beta-1a 6.6% survivors, 14.3% non-survivors<br> Anti-inflammatory: Tocilizumab 32.9% survivors, 35.7% non-survivors<br> Other: Azithromycin 60.5% survivors, 71.4% non-survivors | Overall mortality 26.9%<br> 0%<br> | | |
| Kute et al. [44]      | Retrospective multicentre cohort study | 251 KTR | Steroids: prednisolone 100% | Steroids: increase (32%) survivors, 100% non-survivors | Antiviral: Hydroxychloroquine (61.5% survivors, 65% non-survivors) | Overall mortality 11.6%<br> 4.5% survivors,<br> | | |

(continued on next page)
Table 4b (continued)

| Type of study                        | Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|--------------------------------------|-----------------------------|------------------------------------------------------|---------------------------------|-----------|-----------|-----------|---------|
| Retrospective multicentre cohort study |                             | CI: 94.4% AM: 100% mTOR-i: Sirolimus/everolimus 5.6% RAAS-I: 30% | survivors), no change (67% survivors, 0% non-survivors) CI: no change (74.6% survivors, 0% non-survivors), decrease (19% survivors, 27.5%), stop (0% survivors, 72.4% non-survivors) AM: stop (71.9% survivors, 100% non-survivors), decrease (28% survivors, 0% non-survivors) | survivors), favipiravir (22.1% survivors, 17.2% non-survivors), remdesivir (12.6% survivors, 24% non-survivors) Anti-inflammatories: tocilizumab (2.7% survivors, 68.9% non-survivors), Other: azithromycin (79.1% survivors, 86% non-survivors, convalescent plasma (2.3% survivors, 34.4% non-survivors), IV immunoglobulins (4.5% survivors, 0% non-survivors) | 6.8% non-survivors | 6.8% non-survivors | 6.8% non-survivors |
| Perez-Saez et al. [66] | Retrospective multicentre cohort study | 80 KTR Steroids: prednisone 91.3% AM: mycophenolate 80% mTOR-i: 17.5% | Only CI stop: 5.2% Only MMF or mTOR-i stop 33.8% Both CNI and MMF or mTOR-i stop 5.8% | Antiviral: hydroxychloroquine 98.8%, antivirals 48.8%, Interferon 6.3% Anti-inflammatories: Tocilizumab 100% Steroids 80% Anakinra 7.5% Other: antibiotics 76.3%, azithromycin 73.8%, immunoglobulins 15% RAAS-I: 32.5% | Fatality rate 32.5% | 3.8% non-survivors | 3.8% non-survivors |
| | | | | Treatment: Tocilizumab >1 dose: 13% survivors vs. 34.6% non-survivors, p = 0.02 Steroids: 72.2% survivors vs 96.2% non-survivors, p = 0.01 Interferon: 0% survivors vs 19.2% non-survivors, p = 0.001 Anakinra: 3.7% survivors vs 15.4% non-survivors, p = 0.08 RAAS-I treatment: 29.6% survivors vs 34.3% non-survivors, p = 0.48 IS management: NS difference survivors vs non-survivors | Risk for mortality within 90-days: (continued on next page) |
| | | | | | | | | |
| 1680 KTR CI: azathioprine 15% CI: MPA 59.4% | CI: decrease or stop 4.4% hospitalized, 0.2% non- | Antiviral: Hydroxychloroquine 16% hospitalized, 2.7% non- | NR | | | | |

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Table 4b (continued)

| Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|-----------------------------|-----------------------------------------------------|--------------------------------|-----------|-----------|-----------|---------|
| Requiao-Moura et al. [46] | Retrospective multicentre cohort study               | CI - mTOR-i 9.3% No CI 9.8% Other 5.9% | hospitalized AM: decrease or stop 37.2% hospitalized, 14.8% non-hospitalized Stop all IS 36.4% hospitalized, 0.2% non-hospitalized No change 25.6% hospitalized, 84% non-hospitalized | hospitalized Oseltamivir 16.6% hospitalized, 2.7% non-hospitalized Anti-inflammatory: High-dose steroids 43.6% hospitalized, 12.5% non-hospitalized Other: Azithromycin 56.5% hospitalized, 32.9% non-hospitalized Antibiotics 70.7% hospitalized, 15.7% non-hospitalized Ivermectin 9.3% hospitalized, 14.2% non-hospitalized | Fatality rate: 31.6% Hospitalized patients | CI-MPA: OR 1.197; 95% CI 1.02–1.40, p = 0.026 Recent high dose of steroids: OR 1.53 [95% CI 1.06–2.21], p = 0.022 |
| Villanego et al. [47]     | Retrospective multicentre cohort study               | 1011 KTR Steroids: prednisone 76.9% CI: Tacrolimus 82% AM: Mycophenolate 72.5% mTOR-i: 17.2% | NR | Overall mortality 21.7% | NR | Treatment non-survivors vs survivors: Glucocorticoids: 65% non-survivors vs 44.4% survivors, p < 0.001 Hydroxychloroquine: 57.3% non-survivors vs 44.8% survivors, p = 0.001 Lopinavir-ritonavir: 31.4% non-survivors vs 14.5% survivors, p = 0.001 Tocilizumab: 22.7% non-survivors vs 11.5% survivors, p = 0.001 RAAS-I treatment: ACE–I: 14.2%, ARB: 27.1% RAAS-I treatment: AE–I: 14.1% non-survivors vs 14.3% survivors, p = 0.94 ARB: 24.5% non-survivors vs 27.8% survivors, p = 0.33 Baseline IS survivors vs non-survivors: NS difference |
| Liver Becchetti et al. [48] | Prospective multicentre cohort study                | 57 LTR Single agent: Steroid 2% CNI 28% MMF 3% mTORi 4% Combination: mTORi + MMF 3% CNI’s + AZA 2% CNI + steroids 16% CNI + mTORi 5% CNI + MMF 37% RAAS-I: ACE-I or ARB 23% | IS decrease: 39% IS complete stop: 7% Steroid: 100% no change CI: 12.5% decrease, 12.5% stop, 75% no change AM: MMF 100% stop mTOR-i: 50% stop, 50% no change CNI’s + MMF: 29% decrease, 38% stop, 33% no change CNI + mTORi: 33.3% decrease, 33.3% stop, 33.3% no change RAAS-I: ACE-I or ARB 23% | Antiviral: Hydroxychloroquine 44%, Other antivirals 9% (lopinavir/ritonavir 5%, darunavir/ cobicistat 2% and remdesivir 2%) Anti-inflammatory: Tocilizumab 2%, Rituximab 2%, Ruxolitinib 2% Steroids 35% Other: Antibiotics 63% (Azithromycin 27%) | Case fatality rate hospitalized 17% | NR | Treatment non-survivors vs survivors: Antibiotics: 100% non-survivors vs 57% survivors, p = 0.038 RAAS-I: 50% vs 20%, p = 0.136 Other treatment: NS |

(continued on next page)
| Type of study | Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|---------------|----------------------------|--------------------------------------------------|--------------------------------|------------|-----------|-----------|---------|
| **Steroids:** 23.1% | 243 LTR | IS change: 10.3% home, 42.5% ward, 59.5% ICU, 93.9% total | None: 84.6% home, 27.5% ward, 40.5% ICU, 38.7% total | 0% home, 17.4% ward, 54.0% ICU, 20.2% total | NR | | |
| CI: Tacrolimus 66.7%, Cyclosporine 11.9% | | | | | | | |
| AM: Mycophenolate mofetil 49.0% | | | | | | | |
| mTOR-i: 15.2% | | | | | | | |
| RAAS-I: 2.56% home, 28.1% ward, 29.7% ICU, 24.3% total | | | | | | | |
| Bell et al. [49] | Retrospective multicentre cohort study | | | | | | |
| Colmenero et al. [50] | Prospective multicentre cohort study | 111 LTR | | | | | |
| Steroids: 24% | NR | | | | | | |
| CI: Tacrolimus 66%, Cyclosporine 6% | | | | | | | |
| AM: Mycophenolate 57% | | | | | | | |
| mTOR-i: Everolimus 23% | | | | | | | |
| RAAS-I: ACE-I 33% | | | | | | | |
| Antivirals: Hydroxychloroquine 88% | Overall mortality 18% | 2.7% graft dysfunction, 0% graft loss | | | | | |
| Lopinavir/ritonavir 40% | | | | | | | |
| Remdesivir 1% | | | | | | | |
| Interferon 3% | | | | | | | |
| Anti-inflammatory: | | | | | | | |
| Tocilizumab 15% | | | | | | | |
| High dose corticosteroids 12% | | | | | | | |
| Other: | Azithromycin 60% | | | | | | |
| | | | | | | | |
| | Treatment in hospitalized vs non-hospitalized: | | | | | | |
| | Steroids: 45% hospitalized vs 7% non-hospitalized, p = 0.01 | | | | | | |
| | Hydroxychloroquine: 55% hospitalized vs 13% non-hospitalized, p = 0.006 | | | | | | |
| | RAAS-I: 25% hospitalized vs 20% non-hospitalized, p = 1 | | | | | | |

(continued on next page)
Table 4b (continued)

| Type of study | Study population/type of SOT | Baseline immunosuppression + use of RAAS inhibition | Immunosuppressive modifications | Treatment | Mortality | Graft loss | Outcome |
|---------------|------------------------------|----------------------------------------------------|--------------------------------|-----------|-----------|-----------|---------|
| Heart         | Genuardi et al. [51]         | Prospective multicentre cohort study               | 99 HTR                         | Steroids: prednisone 47% CI + AM 37% CI + AM + prednisone 21% CI + steroid 16% CI + mTORi 13% Other 13% | IS decrease: 14% home, 76% hospitalized, 57% all patients | Antiviral: Remdesivir 17% hospitalized, 12% overall Anti-inflammatory: Tocilizumab 10% hospitalized, 7% overall Dexamethasone or other pulsed steroid 21% overall, 30% hospitalized Other: Convalescent plasma 17% hospitalized, 12% overall | 15% overall case fatality rate | / |
|               |                              |                                                    |                                | Baseline IS: Use of tacrolimus: 88% non-severe vs 67% severe disease, $p = 0.03$ Risk factors for severe COVID-19: use of mTOR-i: OR 6.8 [95% CI 1.3–41], $p = 0.026$ Triple therapy: OR 7.3 [95% CI 1.8–36], $p = 0.009$ Multivariate analysis risk of mortality: Triple therapy: OR 17.8 [95% CI 2.1–24.5], $p$ not reported |

FO = favourable outcome = full recovery and discharged or stable clinical condition
UO = unfavourable outcome = admission to ICU or death

Age: patients with mild COVID-19 symptoms: more likely to be treated as an outpatient; patients with moderate COVID-19 symptoms: more likely to be treated as an inpatient but not ICU; patients with severe COVID-19 symptoms: needing care in the ICU

Impaired graft = impairment >25% of baseline value

need for mechanical ventilation, admission to the intensive care unit and/or death
Table 5a
COVID-19 vaccine efficacy and safety – comparative studies.

| Type of study | Study population/ type of SOT | Type of vaccine | Type of Assay | Humoral response | Cellular response | Adverse events | Disease after vaccination | Outcome |
|---------------|-------------------------------|-----------------|---------------|------------------|-------------------|---------------|---------------------------|---------|
| **Mixed type of SOT** | | | | | | | | |
| Schramm et al. [69] | Prospective single-centre cohort study | 100 patients: 50 SOT (42 HTR (84%), 7 Lung (14%), 1 Heart-lung (2%)), 50 controls | 100% BNT162b2 | Humoral response: Anti-S: IgG II Quant assay Abbott, Euroimmun, Roche Elecsys Neutralizing Ab's: sVNT Genscript | IgG titres: Non-SOT: 98% after first dose, 100% after second dose SOT: 4% after first dose, 10% after second dose | IFN-γ release: | NR | NR | Humoral or T-cell response: 10% Median IFN-γ response: 0.031 SOT vs 0.512 non-SOT, p < 0.0001 |
| **Kidney** | | | | | | | | |
| Bertrand et al. [70] | Retrospective single-centre cohort study | 50 patients: 45 KTR, 10 DP | 100% BNT162b2 | Anti-S: IgG II Quant test (Abbott) T-cell: Elispot | Anti-S Abs: DP: 11.1% after 1st dose, 88.9% after 2nd dose KTR: 2.2% after 1st dose, 17.8% after 2nd dose | Spike-specific T-cell response: After 1st dose: 55.6% DP, 24.4% KTR After 2nd dose: 100% DP, 57.8% KTR | NR | No cases after 1 month | Anti-spike Abs after 2nd dose: 88.9% DP vs 17.8% KTR, p < 0.001 Spike-reactive T-cell response after 2nd dose: 100% PD vs 57.8% KTR, p = 0.06 Univariate analysis predictors of a positive antibody response: Duration of KT: p = 0.003 Cyclosporin-based IS: p < 0.001 |
| Danthu et al. [71] | Prospective single-centre cohort study | 159 patients: 74 KTR, 78 DP, 7 healthy controls | 100% BNT162b2 | Anti-S: LIAISON SARS-CoV-2 Trimeric S IgG (DiaSorin) | Anti-S IgG response: 100% control, 81% DP, 4.1% KTR | NR | NR | NR | Seropositive responders at 36d: 4.1% KTR vs 85.5% DP, p < 0.001 4.1% KTR vs 100% Controls, p < 0.001 85.5% DP vs 100% Controls, p = 0.38 Median IgG anti-spike level: 5.9 AU/ml KTR vs 189.0 AU/ml non-SOT, p < 0.001 |
| Grupper et al. [72] | Prospective single-centre cohort study | 161 patients: 136 KTR, 25 healthy non-transplant patients | 100% BNT162b2 | Anti-S1/S2: LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin S.p.A) | Anti-S1/S2 IgG after 2nd dose: KTR: 37.5% Non-SOT: 100% | NR | Local reaction: Pain at injection site: 52.2% 2 cases, both seronegative | Systemic reaction: Mild systemic reaction: 19.2% Acute rejection: 0% Anaphylaxis: 0% New neurological illness: 0% | Multivariate analysis of risk factors for negative serology in KTR: Older age: OR 1.66 [95% CI 1.17–2.69], p = 0.026 |

(continued on next page)
| Study population/ type of SOT | Type of vaccine | Type of Assay | Humoral response | Cellular response | Adverse events | Disease after vaccination | Outcome |
|-------------------------------|----------------|---------------|------------------|-------------------|---------------|--------------------------|---------|
| 119 patients: 40 KTR, 44 DP, 35 controls | 100% BNT162b2 | Anti-S1: Euroimmun ELISA | Anti-S1 Abs after 2nd dose: Controls: 100% Anti-S1 IgG, 100% Anti-S1 IgA | NR | NR | NR | High dose steroids in the last 12 months: OR 1.3 [95% CI 1.09–1.86], p = 0.048 Triple IS: OR 1.43 [95% CI 1.06–2.15], p = 0.038 Regimen that includes mycophenolate: OR 1.47 [95% CI 1.26–2.27], p = 0.049 |
| 104 patients: 39 KTR, 26 DP, 39 matched healthy controls | 100% BNT126b2 | Humoral response: Anti-S1 IgG: Euroimmun ELISA Anti-S1 IgA: Euroimmun ELISA Neutralizing Abs: sVNT GenScript | Anti-S1 IgG response: 2.6% KTR, 84.6% DP, 100% controls | Spike specific CD4+ responders: 92.3% KTR, 100% DP, 100% controls | Acute rejection: 0% | NR | Anti-S1 IgG response: 100% controls vs 70.5% DP, p < 0.0001 100% controls vs 2.5% KTR, p < 0.0001 70.5% DP vs 2.5% KTR, p < 0.0001 Anti-S1 IgA response: 100% controls vs 68.2% DP, p < 0.0001 100% controls vs 10% KTR, p < 0.0001 68.2% DP vs 10% KTR, p < 0.0001 |
| 1768 patients: 368 KTR, 1256 DP, 144 controls | BNT162b2: 28% KTR, 17% DP, 27.8% controls mRNA-1273: 72.0% KTR, 83.0% DP, 72.2% controls | Humoral response: Anti-S1: Euroimmun ELISA Anti-NCP: Euroimmun ELISA Anti-RBD: Euroimmun ELISA | Anti-S1 Abs: KTR: 8% after 1st dose, 42% after 2nd dose DP: 62% after 1st dose, 95% after 2nd dose Controls: 96% after 1st dose, 99% after 2nd dose | IGRA: KTR: 8% after 1st dose, 30% after 2nd dose DP: 44% after 1st dose, 78% after 2nd dose Controls: 81% after 1st dose, 86% after 2nd dose | Symptomatic: 0.45% (8 cases) Asymptomatic: 0.8% KTR, 2.8% DP, 2.1% controls | NR | Serocconversion rates depending on vaccine type: KTR: 49% mRNA-1273 vs 26% BNT162b2, p < 0.001 DP: 97% mRNA-1273 vs 88% BNT162b2, p < 0.001 Multiple logistic regression seronegative vs seropositive response in KTR: Age: OR 1.03 [95% CI 1.01–1.05], p = 0.006 Time on transplantation: OR 0.95, [95% CI 0.91–0.98], p = 0.004 Number of IS drugs: OR |
Table 5a (continued)

| Type of study | Study population/ type of SOT | Type of vaccine | Type of Assay | Humoral response | Cellular response | Adverse events | Disease after vaccination | Outcome |
|---------------|-------------------------------|-----------------|---------------|------------------|-------------------|-----------------|----------------------------|----------|
| Rabinowich et al. [76] | Prospective single-centre cohort study | 105 patients: 80 LTR, 25 healthy non-transplant patients | 100% BNT162b2 | Anti-S1/S2: LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin S.p.A) | Anti-S1/S2 after 2nd dose: LTR: 47.5% Controls: 100% | NR | Local reaction: Pain at injection site: After 1st dose: 60.5% LTR, 71% controls After 2nd dose: 53.5% LTR, 71% controls Systemic reaction: Mild systemic reaction: After 1st dose: 19.7% LTR, 28% controls After 2nd dose: 25% LTR, 85.7% controls Acute rejection: 0% Anaphylaxis: 0% New neurological illness: 0% | NR |
| Thuluvath et al. [77] | Prospective single-centre cohort study | 233 patients: 62 LTR, 79 cirrhosis patients, 92 with chronic liver diseases without cirrhosis | 49% mRNA-1273, 45% BNT162b2, 8% Ad26.COV2S | Anti-S1: Roche Elecsys Undetectable Spike protein Ab levels: 17.8% LT, 3.8% cirrhosis, 4.3% chronic liver diseases without cirrhosis | NR | Local events: Pain at injection site: 53% after 1st dose, 49% after 2nd dose | NR |

Liver

Rabinowich et al. [76] | Prospective single-centre cohort study | 105 patients: 80 LTR, 25 healthy non-transplant patients | BNT162b2 | Anti-S1/S2: LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay (DiaSorin S.p.A) | Anti-S1/S2 after 2nd dose: LTR: 47.5% Controls: 100% | NR | Local reaction: Pain at injection site: After 1st dose: 60.5% LTR, 71% controls After 2nd dose: 53.5% LTR, 71% controls Systemic reaction: Mild systemic reaction: After 1st dose: 19.7% LTR, 28% controls After 2nd dose: 25% LTR, 85.7% controls Acute rejection: 0% Anaphylaxis: 0% New neurological illness: 0% | NR |

Thuluvath et al. [77] | Prospective single-centre cohort study | 233 patients: 62 LTR, 79 cirrhosis patients, 92 with chronic liver diseases without cirrhosis | BNT162b2 | Anti-S1: Roche Elecsys Undetectable Spike protein Ab levels: 17.8% LT, 3.8% cirrhosis, 4.3% chronic liver diseases without cirrhosis | NR | Local events: Pain at injection site: 53% after 1st dose, 49% after 2nd dose | NR |

Risk factor assessment of IS drugs regarding humoral failure:
- CI: OR 3.60 [95% CI 1.80–7.22], p < 0.001
- AM: OR 1.94 [95% CI 2.24–6.43], p < 0.001
- Belatacept: OR 7.09 [95% CI 1.97–25.45], p = 0.003

Mean antibody levels seropositive LTR vs non-SOT: 95.41 AU/ml LTR vs. 200.5 AU/ml non-SOT, p < 0.001

Factors associated (continued on next page)
## Table 5a (continued)

| Type of vaccine | Outcome | Suboptimal/undetectable Ab response | Optimal timing frames of serological assessment | Allergic or anaphylactic events | Disease after vaccination |
|-----------------|---------|-------------------------------------|-----------------------------------------------|----------------------------------|---------------------------|
| BNT162b2 Moderna vaccine | Optimal: 35.7% after 1st dose, 23.9% after 2nd dose | Fever, headache, fatigue, myalgia, arthralgia, nausea, vomiting, diarrhea | Optimal: 35.7% after 1st dose, 23.9% after 2nd dose | 1.6% after 1st dose, 1.6% after 2nd dose | Two doses of BNT162b2 Moderna vaccine |
| mRNA-1273 Pfizer vaccine | Suboptimal: 43.3% with dual or triple regimens and by the use of antimebollites on humoral response was confirmed by other studies [97–99]. Other studies confirmed our finding of age-dependent vaccination response. [94,100] Furthermore, this review gives evidence for the safety of COVID-19 vaccination in SOT recipients. Due to the low rate of severe adverse events, other larger studies are needed to clarify whether younger organ transplant recipients under adjusted maintenance immunosuppression may confer to better humoral response. Furthermore, the reports of cellular immunity in SOT recipients are scarce, although cellular immunity plays an important role in long-term immunological memory. [92] Studies concerning how serological response is joined by the cellular response and linked to clinical effectiveness in SOT patients are needed. |
| Ad26.COV2.S Johnson & Johnson vaccine | Optimal: 35.7% after 1st dose, 23.9% after 2nd dose | Fever, headache, fatigue, myalgia, arthralgia, nausea, vomiting, diarrhea | Optimal: 35.7% after 1st dose, 23.9% after 2nd dose | 1.6% after 1st dose, 1.6% after 2nd dose | Two doses of Ad26.COV2.S Johnson & Johnson vaccine |

### 4.4. COVID-19 natural immunity, vaccine immunogenicity and safety

Despite an initial delay in IgG response, SOT recipients show similar humoral and cellular immune responses after COVID-19 infection. In contrast, SOT recipients showed a low immune response after vaccination. This reduced immunogenicity in transplant recipients was showed for other common vaccines, including influenza, pneumococcus, hepatitis B and HPV. [94–97]

The influential role played by more sustained immunosuppression (with dual or triple regimens) and by the use of antimebollites on humoral response was confirmed by other studies [97–99]. Other studies confirmed our finding of age-dependent vaccination response. [94,100] Furthermore, this review gives evidence for the safety of COVID-19 vaccination in SOT recipients. Due to the low rate of severe adverse events, other larger studies are needed to clarify whether younger organ transplant recipients under adjusted maintenance immunosuppression may confer to better humoral response. Furthermore, the reports of cellular immunity in SOT recipients are scarce, although cellular immunity plays an important role in long-term immunological memory. [92] Studies concerning how serological response is joined by the cellular response and linked to clinical effectiveness in SOT patients are needed.

### 4.5. Strengths and limitations

This systematic review has an important value because it presents a clear overview of the different aspects about COVID-19 disease regarding different types of SOT. However, our findings must be interpreted while considering this study's limitations.

First, this systematic review covers a very broad topic, including a large amount of studies, consequently giving rise to heterogeneity. For this reason, executing a meta-analysis was not possible. Furthermore, this review needed to mostly rely on studies that were largely retrospective observational cohort studies. The study design did not include articles containing <50 SOT recipients or non-English articles, which can lead to selection bias by excluding more scarce types of SOT. Only one study analyzing the disease in lung transplant recipients only was included and only one study studied heart transplant recipients. A low number concerning only liver transplant recipients studies was included.

Additionally, the reporting method of mortality-rates highly varied. This diversity makes it difficult to compare outcome rates. Further, international standards during the different pandemic waves regarding baseline IS and treatment options may vary. Besides, some patients were still hospitalized after the short follow-up period in the studies. Also, the number of studies reporting non-hospitalized patients was low. Therefore, this study was restricted in its reporting of study outcomes, immunosuppressive modifications and treatment for non-hospitalized patients, with asymptomatic or mild disease. Similarly, our study does not address initial immunosuppression induction therapy due to the international differences for this therapy use.

Lastly, the included vaccination studies executed a short follow-up period. Nevertheless, long-term follow-up and cell-mediated responses to different vaccine types are needed in order to fully access the durability of antibody response and its implications for vaccine effectiveness can be fully assessed. Additionally, more studies are necessary to determine the validity of the different immunoassay types and the optimal timing frames of serological assessment.

### 5. Conclusion

In summary, we analyzed 65 studies in this systematic review to assess different aspects of the COVID-19 pandemic in SOT recipients.
Table 5b
COVID-19 vaccine efficacy and safety – non-comparative studies.

| Study population/ type of SOT | Type of study | Study type | Type of vaccine | Type of Assay | Humoral response | Cellular response | Adverse events | Disease after vaccination | Outcome |
|-------------------------------|---------------|------------|----------------|---------------|-----------------|------------------|---------------|----------------------------|---------|
| Mixed type of SOT             | Cucchiari et al. [78] | Prospective single-centre cohort study | 148 SOT: 133 KTR (89.9%), 15 Kidney-pancreas (10.1%) | 100% mRNA-1273 | Anti-S IgM/IgG: Luminex | Anti-S IgM/IgG after 2nd dose: 29.9% | Cellular response: 54.7% S-ELISPOT positivity 12.8% N-ELISPOT positivity | Local reaction: Pain at injection site: 86% after 1st dose, 75% after 2nd dose Redness: 6% after 1st, 14% after 2nd Swelling: 12% after 1st, 21% after 2nd Systemic reaction: Fatigue: 25% after 1st dose, 27% after 2nd dose Fever: 5% after 1st, 6% after 2nd Chills: 10% after 1st, 8% after 2nd Nausea: 1% after 1st, 1% after 2nd Diarrhea: 3% after 1st, 1% after 2nd Myalgia: 9% after 1st, 7% after 2nd Arthralgia: 6% after 1st, 4% after 2nd Headache: 6% after 1st, 6% after 2nd | NR | Development humoral + cellular response: 19.6% Vaccine response, Abs or ELISPOT: 65.0% |
| Hall et al. [79]              | Prospective single-centre cohort study | 127 SOT: 33 Lung (26%), 30 KTR (23.8%), 28 Kidney-pancreas (22.1%), 18 HTR (14.2%), 15 LTR (11.8%), 3 other (2.4%) | 100% mRNA-1273 | Humoral response: Anti-RBD: Roche Elecsys Neutralizing Abs: vVNT Genscript Cellar response: flow cytometry LSR II BGRV (BD biosciences) | Anti-RBD- Abs: 5% after first dose, 34.5% after 2nd dose Neutralizing Abs: 5.9% after 1st dose, 26.9% after 2nd dose | CD4+ T-cell response: 10% after 1st dose, 47.9% after 2nd dose | Local events: Pain, swelling: most reported Seronegative vs seropositive, p = 0.037 \( < 0.1\) \( < 0.1\) Acute rejection: 0% | 2 cases, both seronegative | Vaccine response, either humoral or cellular: 68.8% Factors associated with a positive anti-RBD response: Mycophenolate: 88.9% seronegative vs 47.4% seropositive, \( p < 0.001 \) Liver transplantation: 41.7% seronegative vs 21.1% |

(continued on next page)
| Type of study | Study population/ type of SOT | Type of vaccine | Type of Assay | Humoral response type | Cellular response | Adverse events | Disease after vaccination | Outcome |
|---------------|-------------------------------|----------------|---------------|-----------------------|-------------------|---------------|---------------------------|---------|
| Hallett et al. [80] | Prospective single-centre cohort study | 237 SOT: 134 HTR (56.4%), 103 Lung (43.4%) | Heart: 52% BNT162b2, 48% mRNA-1273 Lung: 54% BNT162b2, 46% mRNA-1273 | Anti-RBD: Roche Elecsys Anti-S1: Euroimmun ELISA | Anti-S1 or Anti-RBD Ab: Overall: 12% after 1st dose, 39% after 2nd dose, 49% non-responders Heart: 14% after 1st dose, 48% after 2nd dose, 38% non-responder Lung: 9% after 1st dose, 27% after 2nd dose, 64% non-responder | NR | NR | Local: Pain at injection site: 85% after 1st dose, 76% after 2nd dose Systemic: Fatigue: 32% after 1st dose, 56% after 2nd dose Headache: 24% after 1st dose, 39% after 2nd dose Acute rejection: 0% Anaphylaxis: 0% New neurological illness: 0% |
| Herrera et al. [81] | Prospective single-centre cohort study | 104 SOT: 58 LTR (55.8%), 46 HTR (44.2%) | 100% mRNA-1273 | Anti-S: IgM/IgG Siemens COV2T + COV2G T-cell response: Elispot | Anti-S Ab response: LTR: 37.9% after 1st dose, 71% after 2nd dose HTR: 11% after 1st dose, 57% after 2nd dose | S-ELISpot positivity after 2nd dose: 86% LTR, 70% HTR | NR | NR | Local events: Pain at injection site: 80% Swelling: 12% Systemic events: Fatigue: 15% Fever: 7% Acute rejection or graft dysfunction: 0% |
| Adam et al. [82] | Retrospective single-centre cohort study | 2151 SOT: 376 HTR (17.5%), 205 lung (9.5%), 603 LTR (28.0%), 967 KTR (44.9%) | 69.3% mRNA-1273, 41.1% BNT162b2, 1.9% Ad26. COV2-S | NR | NR | NR | NR | 65 cases: 4 fully vaccinated, 59 not vaccinated Deaths: 0% vaccinated, 3.9% not vaccinated |

(continued on next page)
Table 5b (continued)

| Kidney  | Rozen-Zvi et al. [83] | Prospective single-centre cohort study | 308 KTR | 100% BNT162b2 | Anti-S1: SARS-CoV-2 IgG II Quant (Abbott) | Anti-S1 Abs: 36.4% after 2nd dose | NR | Systemic reaction: Acute rejection 0% AKI 0% | Multivariate analysis of factors associated with seropositivity: Younger age: OR 1.04 [95% CI 1.02 – 1.06], p ≤ 0.001 eGFR: OR 1.03 [95% CI 1.02 – 1.05], p ≤ 0.001 Lower mycophenolic acid: OR 2.35 [95% CI 1.78 – 3.09], p < 0.001 No mTOR-i: OR 2.87 [95% CI 1.66 – 7.78], p = 0.038 Low Cl level: OR 1.99 [95% CI 1.15 – 3.44], p = 0.014

| Lung  | Narasimhan et al. [84] | Prospective single-centre cohort study | 73 Lung transplants | 66% BTN162b2, 34% mRNA1273 | Humoral response: Anti-CNP: IgG assay (Abbott) Anti-S: protein IgM assay (Abbott) Anti-S: IgG II Quant test (Abbott) | Anti-S IgG response: 25% Cylex ImmuKnow assay levels: 39.3% low, 46.4% moderate, 14.3% strong | NR | NR | Median anti-spike Ab response: 1.7 AU/mL LT vs 14.209 AU/mL non-transplanted, p < 0.0001

| Heart  | Peled et al. [85] | Prospective single-centre cohort study | 77 HTR | 100% BNT162b2 | Anti-RBD IgG: ‘in house’ enzyme-linked immunosorbent assay | IgG anti-RBD IgG after 2nd dose: 18% | NR | Local reaction: 56% after 1st dose, 49% after 2nd dose Systemic reaction: Mild systemic reaction: 37% after first dose, 49% after second dose Acute rejection: 0% Anaphylaxis: 0% | Multivariate analysis of predictors seropositive response: Mycophenolic acid: OR 0.12 [95% CI 0.01 – 0.82], p = 0.042

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* Exact numbers not reported.
* Pain at injection site, swelling, redness
Mortality was primarily associated with advanced age. Across the individual studies, post-transplantation time and comorbidities were variably identified as independent risk factors for mortality or severe disease. However, in general, no comorbidity was reported as a major risk factor. SOT recipients have a higher risk of AKI compared to non-transplanted patients. Interestingly, no highest rate of mortality was found. The largest part of the studies could not find an independent association between type of baseline immunosuppression and mortality or severe disease. Different modifications and treatment options were individually adjusted, without leading to high rates of short-term graft dysfunction. Despite an initial delay in IgG response, SOT recipients show similar humoral and cellular immune responses after COVID-19 infection. At last, SOT recipients experience a diminished immune response after two-dose vaccination with SARS-COV-2-mRNA-vaccines. More research is needed to address the direct effect of COVID-19 on the graft in lung transplant recipients, as well as the factors ameliorating the immune response after vaccination in SOT recipients.

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Submission declaration and verification

We confirm that it is an original work that has not been published elsewhere.

Declaration of Competing Interest

None.

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References

[1] Coronavirus disease (COVID-19) [Internet]. [cited 2022 Jan 8]. Available from, https://www.who.int/emergencies/diseases/novel-coronavirus-2019;
[2] Heldman MR, Kates OS. COVID-19 in solid organ transplant recipients: a review of the current literature. Garr Treat Options Infect Dis 2021 Jun;1(6);
[3] Moosavi SA, Mashhadigha A, Motazedian N, Hashemazar A, Hoveidi AH, Bollignano D. COVID-19 clinical manifestations and treatment strategies among solid-organ recipients: A systematic review of cases. In: Transplant infectious disease. vol. 22. Blackwell Publishing Inc.; 2020;
[4] Aziz F, Mandelbrot D, Singh T, Parajuli S, Garg N, Mohamed M, et al. Early report on published outcomes in kidney transplant recipients compared to nontransplant patients infected with coronavirus disease 2019. Transplant Proc 2020 Nov 1;52:2659–62;
[5] Angelico R, Blasi F, Manzia TM, Toti L, Tisone G, Cacciola R. The management of disease 2019: a systematic review and quantitative analysis. Transplant Proc 2020 Nov 1;52:2676–83;
[6] Singh SP, Pritum M, Panday R, Yadav TP. Microstructure, pathophysiology, and potential therapeutics of COVID-19: a comprehensive review. J Med Virol 2021 Jan 193:275–99;
[7] Mohamadani M, Chih I, Shoghi A, Bigliai S,Paramaneesh N, Esmailizadeh A. COVID-19: virology, biology and novel laboratory diagnosis. J Gene Med 2021 Feb 1:23:e3003;
[8] Anka AU, Tahir MI, Abubakar SD, Abubakhar M, Zian Z, Hemedifar H, et al. Coronavirus disease 2019 (COVID-19): an overview of the immunopathology, serological diagnosis and management. Scand J Immunol 2021 Apr 1;93: e12996;
Ravanan R, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, et al. [38]
Craig-Schapiro R, Salinas T, Lubetzky M, Abel BT, Sultan S, Lee JR, et al. COVID-19 in solid organ transplant recipients: a national cohort study. Transplantation 2021 Jun 1;2727:30-34.

Bouaziz N, Alberici F, Orsharba E, Valerio F, Manenti C, Posseint S, et al. Kidney transplant patients with SARS-CoV-2 infection: the Brescia renal COVID-19 task force experience. Am J Transplant 2020Nov 20;1;130:2919-29.

Cravedi P, Mothi SS, Azzy Y, Haverley M, Farokh SS, Perez-Saez MJ, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. Am J Transplant 2020 Nov 20;1;310:40.

Cristelli MP, Viana LA, Dantas MTC, Martins SB, Fernandes R, Nakamura MR, et al. The full spectrum of COVID-19 development and recovery among kidney transplant recipients. Transplantation 2021 Jul 1;110:1433-44.

Fava A, Cucchiara D, Montero N, Toapanta N, Centellas PJ, Vila-Santandreu E, et al. Clinical characteristics and risk factors for severe COVID-19 in hospitalized kidney transplant recipients: a multicentric cohort study. Am J Transplant 2020 Nov 20;1;320:40.

Kute VB, Bhalia AK, Guleria S, Ray DS, Bahadur MM, Shingare A, et al. Clinical profile and outcome of COVID-19 in 250 kidney transplant recipients: a multicenter cohort study from India. Transplantation 2021;105:851-60.

Nahin SL, Shetty AS, El-Sayed SD, Levinthal JR, et al. Allograft function in COVID-19 related acute kidney injury in solid organ transplant recipients infected with SARS-CoV-2 an academic single center experience. PLoS One 2021 Jun 1;16.

Requiao-Moursa LR, Sandoval-Graves TV, Viana LA, Cristelli MP, Andrade LGM, Garcia GD, et al. Impact of hospitalization among transplant recipients diagnosed with coronavirus disease 2019: results from the Brazilian multicenter cohort study. PLoS One 2021 Jul 1;16.

Villanueva F, Mazzucco A, Perez-Flores IM, Mostero F, Andreis A, Jimenez-Martin C, et al. Predictors of severe COVID-19 in kidney transplant recipients in the different epidemic waves: analysis of the Spanish registry. Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg 2021 Jun 1;2573-82.

Becchi C, Zambelli MF, Panalo L, Donato MF, Invernizzi F, Detry O, et al. COVID-19 in a European international liver transplant recipient cohort. Gut 2020 Oct 1;169:3830-40.

Belli LS, Fondevila C, Cortes PA, Mohan S, Cohen DJ, Husain SA, Dube GK, et al. COVID-19 transplant recipients. Am J Transplant 2021 Apr 1;21:1576-85.

Marinelli T, Shetty S, Sammartino C, Sivaprakasam R, Lindsey B, et al. Outcomes of renal transplant recipients with SARS-CoV-2 infection in the 2020 global pandemic storm: a comparative study with waitlisted patients. Transplantation 2021;105:115-20.

Thauan D, Legosi C, Glichiadiche D, Couzi L, Bianco H, Hazzan M, et al. Impact of the COVID-19 epidemic on the mortality of kidney transplant recipients and candidates in a French Nationwide registry study (IMPART). Kidney Int 2020 Dec 1;98:1568-77.

Polak WG, Fondevila C, Karam V, Adam R, Baumann U, Germani G, et al. Impact of COVID-19 on liver transplantation in Europe: alert from an early survey of 234 liver transplant centers in European liver transplant registry. Transplant Proc 2020 Oct 1;33:1244-52.

Mamode N, Ahmed Z, Jones G, Banga N, Motalebahzedeh R, Tolley H, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant registry. Transplant Proc 2021 Jan 1;110:212-5.

Rabiee A, Sadowski B, Adeni J, Perumalwami PV, Nguyen V, Moghe A, et al. Liver injury in liver transplant recipients with coronavirus disease 2019 (COVID-19): U.S. multicenter experience. Hepatology Dec 2020;1;72:1900-11.

Coiffard B, Lepper PM, Prudhomme D, Cavet D, Cassir N, Wilkens H, et al. Management of lung transplantation in the COVID-19 era—an international survey. Am J Transplant Apr 2021;1;21:1586-96.

Pereira MR, Averna MM, Far MA, Mikko BA, Azou-GJ, Mohan S, et al. Tollismub for severe COVID-19 in solid organ transplant recipients: a matched cohort study. Am J Transplant 2020 Nov 20;1;21:1989-205.

Sandel S, Boyarsky RJ, Masie A, Chiang TPY, Sugey DL, Cantarovich M. Immunosuppression practices during the COVID-19 pandemic: a multinational survey study of transplant programs. Clin Transplant 2021;35:14376. In press.

Perez-Saez MJ, Blasco M, Redondo-Pachon D, Ventura-Aguilar P, Bada-Tosh B, Perez-Flores J, et al. Use of tocilizumab in kidney transplant recipients with COVID-19. Am J Transplant 2020 Nov 20;1;21:2444-51.

Schramm R, Costard-Jacke A, Rivinino R, Fischer B, Muller B, Boeken U, et al. Poor humoral and T-cell response to two-dose SARS-CoV-2 mRNA vaccine candidate BNT162B2 in cardiothoracic transplant recipients. Clin Res Cardiol 2021 Aug 1;1122-9.

Bertrand D, Hanoy M, Edet S, Lemee V, Hamazou M, Laurent C, et al. Antibody response to SARS-CoV-2 mRNA BNT162B2 vaccine in kidney transplant recipients and in-Centre and satellite Centre haemodialysis patients. Kidney Int Jan 2021 Sep 1;112:217-28.

Danthu C, Hantz S, Dahlem A, Duval M, Ba G, Guibbert M, et al. Humoral response after SARS-CoV-2 mRNA vaccination in a cohort of haemodialysis patients and kidney transplant recipients. J Am Soc Nephrol 2021 Sep 32:2153-8.

Grupp A, Batcha TS, Mutter TG, Gaspers T, et al. SARS-CoV-2 mRNA vaccine response in kidney transplant recipients with COVID-19. N Engl J Med 2021 Apr 1;384:2272-9.

Rincón-Arevalo H, Choi M, Stefanisko A, Halleck F, Weber U, Széleski F, et al. Impaired humoral immunity to SARS-CoV-2 BNT162B2 vaccine in kidney transplant recipients and dialysis patients. Sci Immunol 2021 Jun 9.

Sattler A, Schrenzeimer E, Weber UA, Potekhin A, Buchfell, Schuhle-Hobenheilicher B, et al. Impaired humoral and cellular immunity after SARS-CoV-2 BNT162B2 (tozinameran) prime-boost vaccination in kidney transplant recipients. J Clin Invest 2021 Jul 1;131.

Mendes M, Karger C, Schwobel J, Anders L, et al. Humoral and cellular immunity to SARS-CoV-2 infection in renal transplant recipients and dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. Lancet Reg Heal Eur 2021 Jul 1;10:100178.

Babakirov B, Grupp A, Böhm Y, Vehovady M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021 Aug;75:435-8.

Thuluvath PJ, Roberts P, Chauhan M. Analysis of antibody responses after COVID-19 vaccination in liver transplant recipients and those with chronic liver diseases. J Hepatol 2021 Aug;75:1345-9.

Cucchiari E, Egri N, Bordo M, Herrera S, Del Rocio-Zeavallo J, Casals-Urcquia J, et al. Cellular and humoral response after mRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant 2021;21:2727-34.

Hall VG, Ferreira VH, Iervolo M, Tu K, Marinelli T, Majchrzak-Kita B, et al. Humoral and cellular immune response and safety of two-dose SARS-CoV-2 mRNA BNT162B2 vaccine in heart and liver transplant recipients. Am J Transplant 2021 Aug 1;21:3980-9.

Hallett AM, Greenberg RS, Boyarsky BJ, Shah PD, Ou MT, Teles AT, et al. SARS-CoV-2 messenger RNA vaccine antibody response and reactogenicity in heart and lung transplant recipients. J Heart Lung Transplant 2021 Aug;40:5579-88.

Herrera S, Colmenero M, Vecino JM, Del MA, Sole-Gonzalez E, et al. Cellular and humoral immune response after mRNA-1273 SARS-CoV-2 vaccine in heart and liver transplant recipients. Am J Transplant 2021 Aug;21:3971-9.

Aslam S, Adler E, Meekel K, Little SD. Clinical effectiveness of COVID-19 vaccination in solid organ transplant recipients. Transplant Infect Dis 2021 Jul;13:13705.

Rozen-Zvi B, Yahav D, Agur T, Zigerman B, Ben-Zvi H, Atamna A, et al. Antibody response to SARS-CoV-2 mRNA vaccine candidate BNT162b2: a multicenter prospective cohort study. Microbiol Infection 2021 Aug 27;1173:1-11.

Naraimishan M, Mahaimainathan L, Clark AE, Usmani A, Cao J, Araj E, et al. Serological response in lung transplant recipients after two doses of SARS-CoV-2 mRNA vaccines. Vaccines 2021 Jun;9.
[85] Peled Y, Ram E, Lavee J, Sternik I, Segev A, Wieder-Finoad A, et al. BNT162b2 vaccination in heart transplant recipients: clinical experience and antibody response. J Heart Lung Transplant 2021 Apr;40:759-62.

[86] Osmanbajda B, Ronicke S, Budke K, Jens A, Hammett C, Koch N, et al. Serological Response to Three, Four and Five Doses of SARS-CoV-2 Vaccine in Kidney Transplant Recipients. Clin J Med 2022 May 4;11. https://doi.org/10.3390/cjm1109256S. In press.

[87] Cai X, Wu G, Zhang J, Yang L. Risk factors for acute kidney injury in adult patients with COVID-19: a systematic review and meta-analysis. Front Med 2021 Dec 6:8.

[88] Damayanthi HDWT, Prabani KIP, Weerasekara I. Factors associated for mortality of older people with COVID-19: a systematic review and meta-analysis. Gerontol Geriatr Med 2021 Jan;7. 233372142110573.

[89] Romero Starke K, Reissig D, Petereit-Haack G, Schmauder S, Nienhaus A, et al. The immunology of SARS-CoV-2 infection and vaccines in solid organ transplant recipients. Viruses 2021 Sep 1-13.

[90] Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One 2013 Feb 22:e56974.

[91] Mirjalili M, Shafiekhani M, Vazin A. Coronavirus disease 2019 (COVID-19) and humoral immunity in transplant population is similar to the general population despite immunosuppression. Transplantation 2021 Mar;105:2156-64.

[92] Maggiore U, Aberamat W, Hameed S, Albert R, et al. Evidence of potent humoral immune activity in COVID-19-infected kidney transplant recipients. Am J Transplant 2020 Nov 1;20:3149-61.

[93] Sciutto A, Borello GB, D’Adda A, et al. Humoral response to SARS-CoV-2 is well preserved and symptom dependent in kidney transplant recipients. Am J Transplant 2021 Dec 1;21:3926-35.

[94] Fava A, Donadeu L, Sabet N, Pernin V, Gonzalez-Costello J, Lloido I, et al. SARS-CoV-2-specific serological and functional T cell immune responses during acute and early COVID-19 convalescence in solid organ transplant patients. Am J Transplant 2021 Aug 1;21:2749-61.

[95] Maggiore U, Ahearn P, Wang L, Yalamarti T, Hartzell S, Dzau V, et al. Delayed and persistent B- and T-cell responses after COVID-19 in immunocompetent and solid organ transplant recipients. Viruses 2021 Nov 1;13.

[96] Eckerle I, Rosenberger KD, Zwahlen M, Junghanss T. Serologic vaccination response after solid organ transplantation: a systematic review. PLoS One 2013 Feb 22:e56974.

[97] Hindriks MA, van der Hoven CJ, et al. Humoral response to SARS-CoV-2 infection among liver transplant recipients with prior COVID-19. Am J Transplant 2021 Aug 1;21:2785-86.

[98] Boey L, Curinckx A, Roelants M, Derdelinckx I, Van Wijngaerden E, De Munter P, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. Ther Drug Monit 2020 Jun 1;42:360-8.

[99] Becchetti C, Broekhoven AGC, Dahlqvist G, Fraga M, Zambelli MF, Ciccarelli O, et al. Longevity of anti-spike and anti-nucleocapsid antibodies after COVID-19 in solid organ transplant recipients compared to immunocompetent controls. Am J Transplant 2022 Apr 1;22:1245-52.

[100] Caballero-Marcos A, Salcedo M, Alonso-Fernández R, Rodríguez-Per álvez M, Olmedo M, Grau Morales J, et al. Changes in humoral immune response after SARS-CoV-2 infection in liver transplant recipients compared to immunocompetent patients. Am J Transplant 2021 Aug 1;21:2876-84.

[101] Fernandez-Ruiz M, Olea B, Almendro-Vazquez P, Gisbert E,玺arosco A, San Juan R, et al. T cell-mediated response to SARS-CoV-2 in liver transplant recipients with prior COVID-19. Am J Transplant 2019 Aug 1;19:2756-854.

[102] Boey L, Curinckx A, Roelants M, Derdelinckx I, Van Wijngaerden E, De Munter P, et al. Immunogenicity and safety of the 9-valent human papillomavirus vaccine in solid organ transplant recipients: a systematic review with meta-analysis. BMJ Glob Health 2021 Dec 16;6:e006434.

[103] Zavaglio F, Frangipane V, Morosini M, Gabanti E, Zelini P, Sammartino JC, et al. Robust and persistent B- and T-cell responses after COVID-19 in immunocompetent and solid organ transplant recipients. Viruses 2021 Nov 1;13.

[104] Zeros FS, Ali NM, Neumann HF, Madan RP, Mehta SA, SARS-CoV-2 antibody responses in solid organ transplant recipients. Transpl Infect Dis 2021 Oct 1;23.

[105] Becchetti C, Broekhoven AGC, Dahlqvist G, Fraga M, Zambelli MF, Ciccarelli O, et al. Humoral response to SARS-CoV-2 infection among liver transplant recipients. Gut 2022 Apr;71:746-56.

[106] Fava A, Donadeu L, Sabet N, Pernin V, Gonzalez-Costello J, Lloido I, et al. SARS-CoV-2-specific serological and functional T cell immune responses during acute and early COVID-19 convalescence in solid organ transplant patients. Am J Transplant 2021 Aug 1;21:2749-61.

[107] Zeros FS, Ali NM, Neumann HF, Madan RP, Mehta SA, SARS-CoV-2 antibody responses in solid organ transplant recipients. Transpl Infect Dis 2021 Oct 1;23.

[108] Zavaglio F, Frangipane V, Morosini M, Gabanti E, Zelini P, Sammartino JC, et al. Robust and persistent B- and T-cell responses after COVID-19 in immunocompetent and solid organ transplant recipients. Viruses 2021 Nov 1;13.

[109] Zeros FS, Ali NM, Neumann HF, Madan RP, Mehta SA, SARS-CoV-2 antibody responses in solid organ transplant recipients. Transpl Infect Dis 2021 Oct 1;23.

[110] Zavaglio F, Frangipane V, Morosini M, Gabanti E, Zelini P, Sammartino JC, et al. Robust and persistent B- and T-cell responses after COVID-19 in immunocompetent and solid organ transplant recipients. Viruses 2021 Nov 1;13.

[111] Zeros FS, Ali NM, Neumann HF, Madan RP, Mehta SA, SARS-CoV-2 antibody responses in solid organ transplant recipients. Transpl Infect Dis 2021 Oct 1;23.

[112] Zavaglio F, Frangipane V, Morosini M, Gabanti E, Zelini P, Sammartino JC, et al. Robust and persistent B- and T-cell responses after COVID-19 in immunocompetent and solid organ transplant recipients. Viruses 2021 Nov 1;13.

[113] Maggiore U, Riella LV, Ahearn P, Wang L, Yalamarti T, Hartzell S, Dzau V, et al. Delayed and persistent B- and T-cell responses after COVID-19 in immunocompetent and solid organ transplant recipients. Viruses 2021 Nov 1;13.