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

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Review article

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

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ABSTRACT

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.
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.
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.
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.
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.

1. Introduction

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 [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

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 SOT 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
  - o Age
  - o Gender
  - o Comorbidities

- Time after transplantation
- Mortality and clinical course
  - Mortality parameters
  - Hospital admission
  - Intensive care unit (ICU) admission
  - Need for mechanical ventilation
  - Acute kidney injury
- Waiting list patients comparison
  - Incidence
  - Mortality
- Immunosuppression
  - Maintenance immunosuppression
  - RAAS-inhibitor use
  - Management of immunosuppression
  - Treatment for COVID-19-disease
- Natural immunity after COVID-19
  - Humoral immunity
  - Cellular immunity
- Vaccination response after 2 doses
  - Type of vaccination
  - Type of assay
  - Humoral response
  - Cellular response
  - Adverse events (local or systemic)
  - Graft loss
  - Disease after vaccination

The entire data selection process was conducted by one reviewer only. No meta-analysis was performed because of the lack of sufficient data and the heterogeneity between the different studies.

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.

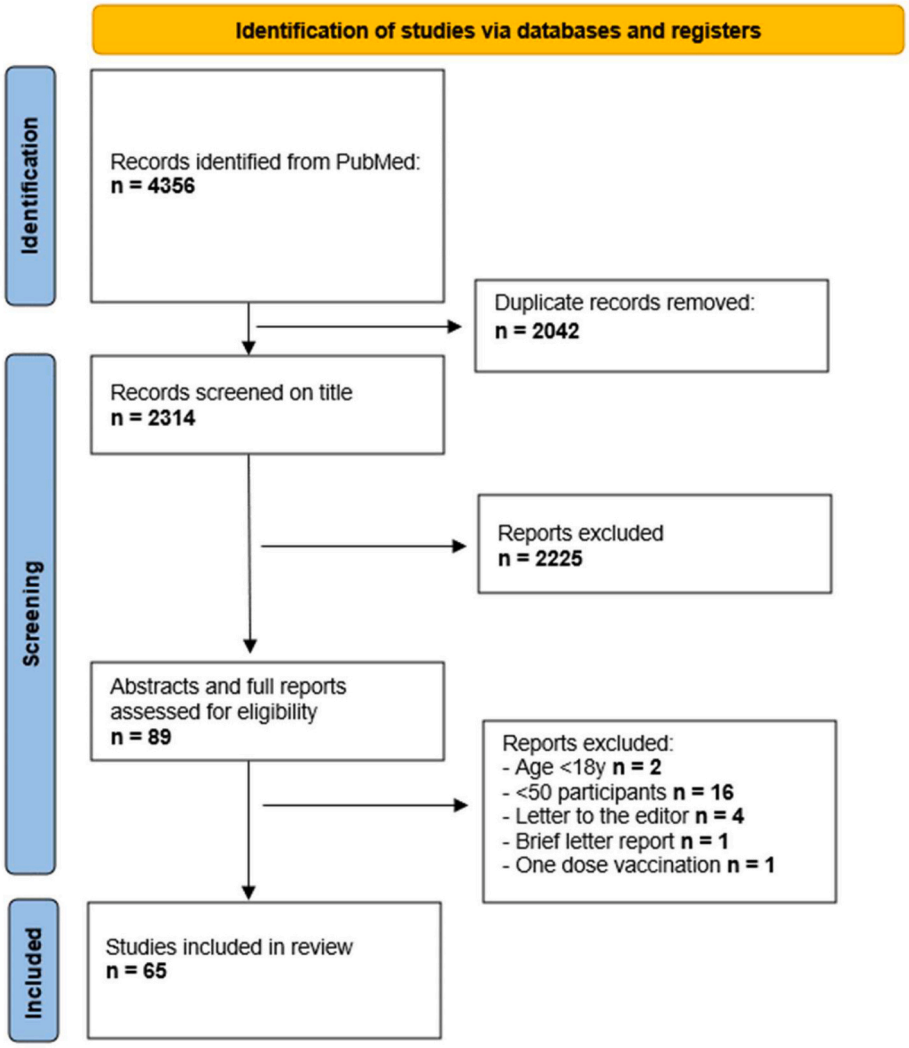

Fig. 1. PRISMA flow diagram.

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. [27,29,32,34,35,38,41,42,46] 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] Søfteland 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-score 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. [36–38]

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 3907 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
Risk factors – comparative studies.

	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[b], 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	NR	**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 History of malignancy: 23.3% vs. 10.9%, *p* = 0.023 Renal failure: 83.7% vs. 19.4%, *p* < 0.001 Liver disease: 34.9% vs. 8.5%, p < 0.001
Chaudhry et al. [22]	Retrospective single-centre cohort study	147 patients: 47 SOT[b], 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	NR	**Comorbidities SOT vs non-SOT:** Median BMI: 27.2 vs 32.3, p = 0.02 CKD: 89% vs 57% *P* = 0.0007 Diabetes: 66% vs 33% P = 0.0007 Hypertension: 94% vs 72%, *P* = 0.006 **Risk factors for mortality in hospitalized patients:** Age > 60y: OR 5.0 [95% CI 11.7–14.7], *P* = 0.003 **Risk factors for composite outcomes in hospitalized patients:** Age > 60y: OR 1.06 [95% CI 1.03–1.09], *p* = 0.0007 Diabetes: OR 4.07 [95% CI 1.52–10.89], *p* = 0.005
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%	NR	**Risk factors for mortality**: 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 0.78 [95% CI 0.64–0.96], *p* = 0.02
						NR	

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Table 1a (*continued*)

	Type of study	Study population/type of SOT	Median age	Gender	Comorbidities[a]	Time after transplantation	Outcome
Hadi et al. [24]	Retrospective multicentre matched cohort study	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	Mean age: 54.3 SOT, 45.9 non-SOT before matching	Male: 59.4% SOT, 44.5% non-SOT	Before matching: Hypertension: 92.1% SOT, 25.9% non-SOT Diabetes: 60.9% SOT, 13.5% non-SOT 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		**Demographics before matching SOT vs non-SOT:** Male gender: 59.4% vs 44.5% $P < 0.01$ Mean age: 54.3 vs 45.9;$P < 0.01$ Obesity: 34.46% vs 14.16%; P < 0.01 Hypertension: 92.11% vs 25.85%; P < 0.01 Chronic lower respiratory disease:29.56% vs 14.26%; P < 0.01 Diabetes: 60.86% vs 13.45%; P < 0.01 Ischemic heart disease: 43.91% vs 7.52%; P < 0.01
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%) and 2 combined liver-kidney (4.9%)), 220 non-transplant patients	Median age: 58 SOT, 63 non-SOT	Male: 66% SOT, 66% non-SOT	Before matching: Hypertension: 81% SOT, 45% non-SOT CKD: 34% SOT, 5% non-SOT Cardiovascular disease: 24% SOT, 13% non-SOT COPD: 20% SOT, 17% non-SOT Diabetes: 16% SOT, 32% non-SOT	Median years: 6y	**Comorbidities SOT vs non-SOT:** Hypertension: 81% vs 45%, $p < 0.001$ Diabetes mellitus: 16% vs 32%, $p = 0.013$ CKD: 34% vs 5%, $p < 0.001$ **Risk factors for mortality[c]:** Age > 63y: OR 1.14 [95% CI 1.08–1.197]
Miarons et al.	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	Mean age: 62.7 SOT, 66 non-SOT	Male: 71.7% SOT, 73.5% non-SOT	Before matching: Hypertension: 78.3% SOT, 56.5% non-SOT Chronic renal failure: 78.3% SOT, 18.1% non-SOT Diabetes: 44.4% SOT, 35.2% non-SOT 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[d]: 5 SOT, 4 non-SOT	Median years: 4.8y	**Comorbidities SOT vs non-SOT:** Hypertension: OR 2.72 [95% CI 1.25–5.92], $p = 0.012$ Chronic renal failure: OR 83.39 [95% CI 11.3–614.9], $p < 0.001$ **Risk factors for mortality in SOT:** Age: HR 1.08 [95% CI 1.02–1.14], $p = 0.016$ CCI: HR 1.22 [95% CI 1.03–1.44]; $p = 0.037$
Kidney Caillard et al. [27]	Retrospective multicentre matched cohort study	1101 patients: 306 KTR, 795 non-transplant patients	Median age: 62 KTR, 69 non-SOT	Male: 67.6% KTR, 58.6% non-SOT	Before matching: Hypertension: 91.3% KTR, 49.8% non-SOT BMI > 25 kg/m^2: 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 12% first year post-transplantation	**Risk factors for severe disease:** Cardiovascular disease: HR 1.35 [95% CI 1.03–1.76], $p = 0.028$ **Risk factors for mortality:** Age > 60y: HR 3.47 [95% CI 1.86–6.47], $p < 0.001$

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Table 1a (*continued*)

	Type of study	Study population/type of SOT	Median age	Gender	Comorbidities[a]	Time after transplantation	Outcome
					Smoking: 12.7% KTR, 4.4% non-SOT		
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	Before matching: Hypertension: 85% KTR, 50% non-SOT Diabetes: 48% SOT, 29.4% non-SOT Cardiopathy: 35% KTR, 21.3% non-SOT Atrial fibrillation: 20% 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%, $p < 0.001$ Cardiopathy: 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	Hypertension: 27.2% KTR, 10.7% DP Diabetes mellitus: 10.5% KTR, 5.5% 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% 1-5y: 10.2% >5y: 19.7%	**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	NR	NR	Median age 71.7 vs 60.9 dialysis, $p < 0.001$ **Risk factors for mortality in KTR**[c]: Age 65–74: HR 2.72 [95% CI: 1.95–3.80] Age > 75: HR 5.10 [95% CI: 3.55–7.34]
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	**Comorbidities:** Diabetes mellitus: 15.5% control vs 25.3% KTR, $p < 0.05$ Hypertension: 30% control vs 72.2% KTR, $p < 0.05$ **Risk factors for in-hospital mortality:** Age: HR 1.019 [95% CI 1.003–1.03], $p = 0.017$ HD: HR 2.33 [95% CI 1.21–4.47], $p = 0.011$ CKD: HR 2.88 [95% CI 1.524–5.442], $p = 0.001$ KTR group: HR 1.90 [95% CI 0.76–4.73], $p = 0.169$, NS **Risk factors for mortality or ICU admission**: Age: HR 1.02 [95% CI 1.003–1.032], $p = 0.016$ HD-group: HR 2.26 [95% CI 1.24–4.12], $p = 0.008$ CKD group: HR 2.44 [95% CI 1.35–4.41], $p = 0.003$

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Table 1a (*continued*)

	Type of study	Study population/type of SOT	Median age	Gender	Comorbidities[a]	Time after transplantation	Outcome
Liver							
Webb et al. [32]	Retrospective multicentre cohort study	778 patients: 151 LTR, 627 non-transplant patients	Median age: 60y LTR, 73y non-SOT	Male: 68% LTR, 52% non-SOT	Diabetes: 43% LTR, 23% non-SOT Hypertension: 42% LTR, 38% non-SOT Obesity: 29% LTR, 25% non-SOT Cardiovascular disease: 15% LTR, 32% non-SOT Non-liver cancer: 5% KTR, 15% non-SOT COPD: 3% LTR, 9% non-SOT	Median years: 5y	**Risk for ICU admission in total cohort:** Age: OR 1.04 [95% CI 1.00–1.09] per 1 year increase, p = 0.035 Non-liver cancer: OR 18.30 [95% CI 1.96–170.75], *p* = 0.001

[a] Ranked by highest prevalence.
[b] Type of SOT not reported.
[c] *P*-value not reported.

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 found 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], $p < 0.01$). [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.

Table 1b
Risk factors – non-comparative studies

	Type of study	Study population/type of SOT	Median age	Gender	Comorbidities	Time after transplantation	Outcome
Mixed type of SOT							
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%)	Median age: 61	Male: 66%	NR	Median months: 59	**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], $p < 0.001$
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 Lung, NR non-lung SOT	Male: 51.7% Lung, 63.5% non-lung SOT	CKD: 51.7% Lung, 35.0% non-lung SOT Hypertension: 50.0% lung, 80.8% non-lung Diabetes mellitus: 46.7% lung, 50.9% non-lung Obesity: 24.8% lung, 37.2% non-lung Heart failure: 6.7% lung, 6.0% non-lung Chronic lung disease: 5% in non-lung	NR	**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 1.5–3.0], $p < 0.001$ 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
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%)	Mean age: 58	Male: 61%	Hypertension: 77.4% Diabetes: 51% CKD: 37.3% Obesitas: 35.1% Coronary artery disease: 21.8% Chronic lung disease: 10.4% Congestive heart failure: 8.3%	Median time: 5y	**Risk factors for mortality:** 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], ≥2 vs. 0: OR 11.0 [95% CI 5.0–24.0]
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%)	Median 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	**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
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%)	Median age: 63 61 favourable outcome (FO)[a], 65 unfavourable outcome (UO)[b]	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 7.1y FO vs 5.5y UO	**Comorbidities FO vs UO:** Age > 70y: 21.8% FO vs 46.6% UO, p = 0.001 Time after transplantation: 7.1y vs 5.5y, $p = 0.048$

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Table 1b (*continued*)

	Type of study	Study population/type of SOT	Median age	Gender	Comorbidities	Time after transplantation	Outcome
					Chronic liver disease: 12.2% FO, 17.5% UO Cancer: 10.2% FO, 15.9% UO Morbid obesity: 6.1% FO, 1.6% UO		Diabetes mellitus: 28.6% FO vs 44.4% UO, $p = 0.03$ Chronic cardiopathy: 21.1% FO vs 36.5% UO, $p = 0.02$ **Risk factors for UO:**[c] Age > 70y: OR 3.01 [95% CI 1.30–7.00]
Søfteland 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%	Hypertension: 75.1% Diabetes: 30% BMI >30: 23.9% Renal impairment: 16.1% Cardiovascular disease: 8.7% Malignancy: 2.6% CCI: CCO 0 (15.2%), CCI 1–2 (56.5%), CCI ≥3 (28.3%)	Median time: 78 months 12.6% within 1y of transplantation, 5.2% within 3 months	**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], $p = 0.026$ **Predictors of hospitalization:** Age 70+:OR 7.32 [95% CI 1.10–65.23], $p = 0.047$ Age 60–69: OR 7.55 [95% CI 2.42–25.77], $p < 0.001$ Age 50–59: OR 3.54 [95% CI 1.36–9.68], $p = 0.011$ CCI score 1–2: OR 8.30 [95% CI 2.36–40.11]; $p = 0.003$ Sex female: OR 0.33 [95% CI 0.13–0.79]; $p = 0.015$
Kidney							
AlOtaibi et al. [39]	Retrospective single-centre cohort study	104 KTR	Median age: 51 Mean age: 49.3	Male: 75%	Hypertension: 64.4% Diabetes: 51% Ischemic heart disease: 20.2% Pulmonary disease: 8.7% Obesity: 5.7%	Median time: 72 months	**Comorbidities ICU vs non-ICU:** Diabetes mellitus: 42.5% non-ICU vs 64.5% ICU, p = 0.04 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
Bossini et al. [40]	Prospective single-centre cohort study	53 KTR	Median age: 60	Male: 79%	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]; $P = 0.01$
Cravedi et al. [41]	Retrospective multicentre cohort study	144 KTR	Median age: 62	Male: 66%	Hypertension: 95% Diabetes: 52% Obesity: 49% Heart disease: 28% Lung disease: 19%	Mean time: 5y 16% Diagnosis in first year	Age: 66 non-survivors vs 60 survivors; P < 0.001
Cristelli et al. [42]		491 KTR	Median age: 53	Male: 60%	Hypertension: 68% Diabetes: 32%	Median time: 6.6y <3 m: 3%	**Comorbidities survivors vs non-**

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Table 1b (*continued*)

	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:**[c] 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 neoplasm: 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, $p < 0.0001$ $\geq$ 1 comorbidities: 39.3% survivors vs 96.5% non-survivors, $p < 0.0001$
Nahi et al. [45]	Retrospective single-centre cohort study	53 KTR	NR	NR	Hypertension: 100% Diabetes: 55% Obesity: 42% Heart disease: 26%	NR	**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, $p = 0.02$
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 $\geq$ 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 1.03 [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]; $p = 0.021$ **Risk factors for mortality:** Age: OR 1.05 [95% CI 1.04–1.07]; $p < 0.001$

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Table 1b (*continued*)

	Type of study	Study population/type of SOT	Median age	Gender	Comorbidities	Time after transplantation	Outcome
							Time after transplantation: OR 1.03 [95% CI 1.002–1.05], $p = 0.030$ Hypertension: OR 1.57 [95% CI 1.07–2.29], p = 0.021 Cardiovascular disease: OR 1.52; [95% CI 1.05–2.2]; $p = 0.028$
Villaneggo et al. [47]	Retrospective multicentre cohort study	1011 KTR	Median age: 60	Male: 62.8%	NR	Median months: 72 <6 m: 8.5% >6 m: 91.5%	**Risk factors for mortality:** Age: HR 1.06 [95% CI 1.05–1.08], $p < 0.0001$ KT <6 m: HR 1.64 [95% CI 1.07–2.5], p = 0.021
Liver							
Becchetti et al. [48]	Prospective multicentre cohort study	57 LTR	Median age: 65y	Male: 70%	Arterial hypertension: 56% Clinical history of neoplasia: 42% Cardiovascular disease: 37% Diabetes: 37% CKD: 28% Concomitant respiratory diseases: 23% Active or former smoker: 12%	Median time: 6y	**Comorbidities survivors vs non survivor:** Active cancer: 43% survivors vs 43% non-survivors, $p = 0.011$ **Comorbidities in ARDS vs non-ARDS:** History of cancer: 82% ARDS vs 33% non-ARDS, $p = 0.005$ Active cancer: 36% ARDS vs 2% non-ARDS, $p = 0.004$
Belli et al. [49]	Retrospective multicentre cohort study	243 LTR	Median age: 63	Male: 70.4%	Hypertension: 45.7% Diabetes mellitus: 38.7% CKD: 20.2% BMI >30: 18.9% Chronic lung disease: 10.3% Chronic artery disease: 7.0%	Median time: 8y	**Risk factors for mortality:**[c] Advanced age (>70 vs <60 years): HR 4.16 [95% CI 1.78–9.73]
Colmenero et al. [50]	Prospective multicentre cohort study	111 LTR	Median age: 65.3	Male: 71.2%	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[d]: 3 non-severe, 5 severe	Median months: 105 15% first year post-transplantation	**Risk factors for severe disease[d] in hospitalized patients:** CCI: RR 1.28 [95% CI 1.05–1.56], p = 0.015 Male gender: RR 2.49 [95% CI 1.14–5.41], p = 0.021
Heart							
Genuardi et al. [51]	Prospective multicentre cohort study	99 HTR	Median age: 60	Male: 75%	Hypertension: 79% non-severe, 100% severe[e] Diabetes: 49% non-severe, 75% severe Obstructive sleep apnea: 16% non-severe, 42% severe Ischemic cardiomyopathy:13% non-severe, 29% severe COPD: 9% non-severe, 29% severe BMI: 28.5 not-severe, 30.2 severe	Median time post-transplant: 5.6y	**Risk factors for mortality:**[c] 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

[c] *P*-value not reported
[d] Severe disease: requirement of respiratory support, admission in intensive care unit and/or death
[e] 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]

3.5.3. 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. [28,31–38,40,43,47,49,55,64] 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. [27,29,31,41,43,44,47–50,52,55,68] At the time of diagnosis, 21% received angiotensin-converting enzyme inhibitors (ACE—I) and 20% angiotensin II receptor antagonists (ARB), as described by Hilbrands 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, antimetabolites (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 antimetabolites 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]

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[a], 2427 non-transplant patients	In-hospital mortality	4.4% 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], $p = 0.19$ Need for mechanical ventilation: 16.3% SOT vs 6.7% non-SOT, p = 0.1
Chaudhry et al. [22]	Retrospective single-centre cohort study	147 patients: 47 SOT[a], 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], $p = 0.80$ ICU Admission: OR 0.78, [0.35–1.73], $p = 0.55$ Mechanical ventilation: OR 0.93, [0.41–2.08], $p = 0.86$ AKI: OR 2.24, [95% CI 1.02–4.95], $p = 0.05$
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	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 Need for invasive mechanical ventilation: OR 2.34 [95% CI 1.51–3.65], p < 0.01 AKI: OR 2.41 [95% CI 1.59–3.65], $p <$ 0.01 ICU admission: OR 1.46 [95% CI 0.99–2.16], $p = 0.06$
Hadi et al. [24]	Retrospective multicentre matched cohort study	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: 30.99% 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, 5.6% non-SOT	Before matching: 24.7% SOT, 4.0% non-SOT After matching: 24.7% SOT, 14.3% non-SOT	**Outcomes SOT vs non-SOT after matching:**[b] 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

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Table 2a (*continued*)

	Type of study	Study population/type of SOT	Mortality parameter	Mortality rates	Hospital admission	ICU Admission	Need for mechanical ventilation	Development AKI	Outcome
									[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]
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%) 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	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: 2.49/100person-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-d 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%, $p = 0.21$

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Table 2a (*continued*)

	Type of study	Study population/type of SOT	Mortality parameter	Mortality rates	Hospital admission	ICU Admission	Need for mechanical ventilation	Development AKI	Outcome
									AKI: 46.1% KTR vs 11.2%, Controls, $p < 0.001$
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], $p = 0.388$
Hilbrands et al. [29]	Retrospective multicentre cohort study	1073 patients: 305 KTR, 768 DP	28-day probability of death; 28-day probability in hospitalized patients; 28-day probability of death after ICU admission; 28-day probability of death after mechanical ventilation	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	28-day probability of death in DP vs KTR: HR 1.23 [95% CI 0.93–1.63], $P = 0.14$ 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
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	Mortality risk KTR vs DP: HR 1.28 [95% CI 1.02–1.60][b]
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	Mortality KTR vs control: HR 1.89 [0.76–4.72], P = 0.169 Combined outcomes KTR vs control: HR 1.87 [0.81–4.28], $P = 0.138$
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, 0.3% Other	28-day mortality	24% Lung, 16% non-lung SOT	66% hospitalized: 75% lung, 66% non-lung SOT	44% lung, 37% non-lung SOT	28% lung, 27% 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 after 20-days	24%	76%	26%	35%	NR
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%)	28-day mortality ICU-mortality	16%; 36%	77.7%	35%	35% of hospitalized	NR
Salto-alejandre 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%)	Favourable outcome[a] unfavourable outcome[b] after 30 days	70% favourable outcome, 30% unfavourable outcome: 21.4% mortality rate, 17.6% ICU admission	Only hospitalized patients	17.6%	0% favourable outcome, 38.1% unfavourable outcome	NR
Søfteland et al. [38]	Retrospective multicentre cohort study	230 SOT: 162 KTR (70.4%), 35 LTR (15.2%), 17 HTR (7.4%), 16 lung (7%)	30-day mortality	14.9% hospitalized, 0% non-hospitalized Total: 9.6%	63.9%	15.7% total, 24.7% hospitalized	10.5% total, 16.6% hospitalized	24.1% hospitalized
Kidney								
Bossini et al. [40]	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	NR	29%	51%
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%	69%	61%	75% of ICU	47%
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%

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Table 2b (*continued*)

	Type of study	Study population/ type of SOT	Mortality parameter	Mortality rates	Hospital admission	ICU Admission	Need for mechanical ventilation	Development AKI
			ICU mortality; Mortality mechanical ventilation					
Villanego et al. [47]	Retrospective multicentre cohort study	1011 KTR	Overall mortality rate	21.7%	78.2%	13.8%	NR	NR
Liver								
Becchetti et al. [48]	Prospective multicentre cohort study	57 LTR	Overall case fatality rate; fatality rate among hospitalized patients	12%; 17%	72%	10% of hospitalized	10%	NR
Colmenero et al. [50]	Prospective multicentre cohort study	111 LTR	Overall mortality	18%	86.5%	10.8%	NR	NR
Heart								
Genuardi et al. [51]	Prospective multicentre cohort study	99 HTR	Overall case fatality rate; Hospital mortality	15% all, 16% symptomatic patients, 24% hospital mortality	64%	NR	32% hospitalized, 22% symptomatic patients	NR

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

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 IgG responses compared to immunocompetent individuals. [103,106] 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 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 [72,75,76,79–81,83,85]. 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 cellular response [70,78,81]. The risk factors mentioned above (age, number of immunosuppression, mycophenolate) were not found associative to cellular response [70,78,81].

Other risk factors affecting humoral response, including individual immunosuppressive therapies, post-transplantation time, type of SOT or decreasing eGFR, were reported in a smaller number of studies [70,72,75,76,78,80,81,83].

Lastly, only five studies used different vaccine types. Two studies

Table 3
Incidence, mortality and clinical course compared to waiting list patients.

	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, $p < 0.0001$
Ravanan 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	**Mortality rates:** 30% KTR vs 27% WL, $p = 0.71$ ICU admission: 29.7% KTR vs 32.7% WL, $p = 0.7$ Mechanical ventilation: 20.2% KTR vs 15.6% WL, p = 0.5
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	**Incidence of symptomatic COVID-19:** 9.9% WL vs 1.9% KTR, $P < 0.001$ **Mortality in COVID+ patients:** 15% WL vs 32% KTR, $P = 0.726$ **Overall mortality:** 1.5% WL vs 0.6% KTR, $P < 0.001$
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	**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, $P < 0.001$

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].

Table 4a
Treatment and immunosuppressive management – comparative studies.

	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								
Avery et al. [21]	Retrospective multicentre cohort study	2472 patients: 45 SOT[a], 2427 non-transplant patients	**Steroids**: prednisone 60% **CI**: Tacrolimus 84.4% **AM**: Mycophenolate mofetil 13.3%	NR	**Antiviral**: Hydroxychloroquine 28.9% SOT, 16,0.3% non-SOT Remdesivir 17.8% SOT, 14.2% non-SOT **Anti-inflammatory**: Tocilizumab 13.3% SOT, 3.6% non-SOT Hydrocortisone 4.4% 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:** Tocilizumab: 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[a], 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-inflammatory**: Tocilizumab 8.6% SOT, 18% non-SOT Corticosteroids 65.7% SOT, 65% non-SOT **Other**: Empiric antibiotic 74.3% SOT, 72% 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 matched 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 **Ant-inflammatory:** Tocilizumab 6.2% SOT, 7% non-SOT Prednisone 60.2% SOT, 19.8% non-SOT Dexamethasone28.1% SOT, 44.5% non-SOT Methylprednisolone 10.2% SOT, 15.6% non-SOT **Other:** convalescent plasma 11.7% SOT, 16.2% 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 Tocilizumab: 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 (11.36%), 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-inflammatory:** Glucocorticoids 45.4% SOT Tocilizumab 1.4% SOT Azithromycin 15.2% SOT	30-day mortality: 6.45% SOT, 5.29% non-SOT	NR	
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 + cycle cell inhibitor + prednisone) **mTOR-i** based therapy 37% (Everolimus or sirolimus + cycle cell inhibitor + prednisone)	**Steroids**: prednisone increase 100% **AM**: mycophenolate stop 100% **mTOR-i**: stop 100%	**Antiviral**: Hydroxychloroquine 98% SOT, 98% non-SOT Lopinavir/ritonavir 76% SOT, 93% non-SOT Remdesivir 0% SOT, 13% non-SOT Interferon 7% SOT **Anti-inflammatory**: Tocilizumab 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

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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
					Steroids pulse 41% SOT **Biologicals**: Baricitimib 2% SOT, 0% non-SOT **Other**: Azithromycin 100% SOT, 100% non-SOT			
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	**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%	**Antiviral**: Hydroxychloroquine 95.7% Lopinavir/ritonavir 50% Darunavir/cobicistat 13% Interferon b 6.5% **Anti-inflammatory**: Tocilizumab 45.7% **Other**: azithromycine 89.1%	28-day mortality: 37% SOT, 22.9% non-SOT	0%	
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 – all ICU admitted	**Steroids**: 15% **CI**: 83% **AM**: Mycophenolate mofetil 68%, Azathioprine 0% Other 13% **RAAS-I**: ACE-I 19%, ARB 21%	NR	**Antiviral:** Hydroxychloroquine 63% SOT, 68% non-SOT Hydroxychloroquine + azithromycin 76% SOT, 81% non-SOT Remdesivir 6% SOT, 7% non-SOT Ribavirin 0% SOT, 0% non-SOT Lopinavir/ritonavir 3% SOT, 4% non-SOT **Anti-inflammatory**: Tocilizumab 23% SOT vs 16% non-SOT Corticosteroids 65% SOT, 38% non-SOT Other IL-6-inh 1% SOT, 0% non-SOT **Other**: Convalescent plasma 5% SOT, 2% non-SOT Azithromycin 50% SOT, 52% non-SOT **Start of ACE—I**: 3% SOT, 2% non-SOT **Start of ARB**: 4% SOT, 3% non-SOT	Death within 28-d of ICU admission: 40% SOT, 43% non-SOT	NR	**Treatment SOT vs non-SOT:** Corticosteroids: 65% SOT vs 38% non-SOT, $p < 0.01$ Other: NS difference
Ringer et al. [53]	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%	**Antiviral**: Hydroxychloroquine 93% SOT, 78% non-SOT Atazanavir 23% SOT, 33% non-SOT Remdesivir 0% SOT, 5% non-SOT **Anti-inflammatory**: Tocilizumab 63% SOT, 48% non-SOT Steroids 37% SOT, 20% non-SOT **Other**: Convalescent plasma 3% SOT, 0% non-SOT Azithromycin 10% SOT, 10% non-SOT	28-day mortality: 13% SOT, 13% non-SOT	NR	Treatment SOT vs non-SOT: NS difference
Kidney Caillard et al. [27]	Retrospective multicentre matched cohort study	1101 patients: 306 KTR, 795 non-transplant patients	**Steroids** 75.2% **CI** 82.7% **AM**: Mycophenolate 77.1%, Azathioprin 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	NR	**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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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 Oseltamivir 2.2% 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 Tocilizumab: 5.6% vs 1% p < 0.001 Other: NS Risk factors for severe covid: RAAS-I: HR 0.92 [0.70–1.20], *p* = 0.534 Risk factors for mortality: RAAS-I: HR 1.16 [0.76–1.78], *p* = 0.492
Chavarot et al. [28]	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%	**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 69%, azathioprine 5% **mTOR-i**: 14% **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 **RAAS-I change**: ARB continued 8%, discontinued 12% ACE-I continued 11%, discontinued 9%	28-day probability of death: 21.3% KTR, 25% DP	NR	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**: MMF/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 (99.1% control, 96.3% DP, 100% KTR, 97.2% CKD), Oseltamivir (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:** Oseltamivir: 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/

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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
					control, 75.7% DP, 66.3% KTR, 87.8% CKD)			antiaggregant: 54.7% vs 37.9%, $p < 0.0001$
Mohamed et al. [60]	Prospective single-centre cohort study	1434 KTR, 321 WL 60 COVID+ patients: 28 KTR, 32 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%, AZA stop 11%, no change AM 11%	NR	15% WL, 32% SOT	NR	**Mortality risk:** Steroid increase: p = 0.035
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	**Antiviral**: (hydroxy) chloroquine 25% LT, 1% non-SOT Lopinavir or ritonavir 6% LT, 1% non-SOT Remdesivir 4% SOT, <1% non-SOT Oseltamivir 2% SOT, 0% non-SOT Sofosbuvir 1% SOT, 0% non-SOT Interferon 0% SOT, <1% non-SOT **Anti-inflammatory**: Tocilizumab 1% SOT, 0% non-SOT Anakinra 1% SOT, 0% non-SOT **Other**: IV immunoglobulin 0% SOT, <1% non-SOT Convalescent plasma 1% SOT, 0% non-SOT Azithromycin 1% SOT, 0% non-SOT	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 91.9%, 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	**Antiviral**: Hydroxychloroquine 37.5% Hydroxychloroquine + azithromycin 23.2% Remdesivir 2.7% **Anti-inflammatory**: Steroids 3.6% **Other**: Azithromycin alone 27.7%	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:[b] **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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Table 4a (*continued*)

Type of study	Study population/ type of SOT	Baseline immunosuppression + use of RAAS inhibition	Immunosuppressive modifications	Treatment	Mortality	Graft loss	Outcome
			decrease, 20% stop Moderate: 12% no change, 26% decrease, 28% stop Severe: 12% no change, 12% decrease, 42% stop **mTOR-i:** mild: 42% no change, 15% decrease, 12% stop moderate: 32% no change, 18% decrease, 18% stop severe: 25% no change, 12% decrease, 28% stop				

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, in-hospital mortality risk would falsely appear equal in SOT 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 beter 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 re-introduction 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.

Table 4b
Treatment and immunosuppressive management – non-comparative studies.

	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**: Prednisone 85% **CI**: Tacrolimus 97% **AM**: Antimetabolites 87%	**Steroids**: 100% prednisone no change or increase **CI**: 100% Tacrolimus no change **AM**: 100% stop	**Antivirals**: Hydroxychloroquine 82.9% **Anti-inflammatory**: Tocilizumab 23.4% Dexamethasone 19.1% **Other**: Azithromycin 89.4%	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 **CI**: tacrolimus: 36.4% stop, 28.2% decrease, 1.1% start/increase, 34.1% no change Ciclosporin: 36.8% stop, 13.2% decrease, 0% start/increase, 50% no change **AM**: mycophenolate: 70.7% stop, 6.3% decrease, 0% start/increase, 23% no change Azathioprine: 50% stop, 50% no change **mTOR -i**: 51.9% stop, 9.2% decrease, 2.3% start/increase, 36.6% no change	**Antiviral**: Hydroxychloroquine 84% Lopinavir/ritonavir % Interferon 5% Other antiviral 1% **Anti-inflammatory**: Tocilizumab 21% Corticosteroids 41% Anakinra 14% **Other**: Azithromycin 53%	Case-fatality rate 27%	NR	**Mortality ARDS patients:** Hydroxychloroquine alone or with azythromycin: 51% vs 92% none, p = 0.003 AM adjustment: 83% no adjustment vs 58% stop, p = 0.033 **Baseline IS:** NS difference survivors vs non-survivor
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 regiment (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	**Anti-inflammatory**: Corticosteroids 55.8% lung, 31.6% non-lung Remdesivir 54.2% lung, 26.3% non-lung **Other**: Convalescent plasma 28.3% lung, 16.4% non-lung	24% lung, 16% non-lung SOT	NR	Reduction in IS: 56.6% lung vs 74.1% non-lung, p < 0.001 Treatment: Corticosteroids: 55.8% lung vs 31.6% non-lung, p < 0.001 Remdesivir 54.2% lung vs 26.3% non-lung, p < 0.001 Convalescent plasma: 28.3% lung vs 16.4% non-lung, p = 0.001 **All hospitalized SOT's risk factors for mortality:** Baseline mTOR-i: OR 0.3. [95% CI 0.1–0.8. p = 0.03] Other baseline IS: NS association
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%	**Antiviral**: Hydroxychloroquine 61% Remdesivir 2.9% **Anti-inflammatory**: Tocilizumab or sarilumab 13% Corticosteroids 10% **Other**: Convalescent plasma	28-day mortality: 20.5%	NR	**Mortality:** Type of IS: NS association Number of IS: 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
					3.1%, Azithromycin 31%, IV IG 1.9% Other 3.7%			
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%	NR	**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% **CNI**: 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%	
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% **RAAS-I**: 13%	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%	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-alejandre 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%)	**Steroids**: Prednisone (66% FO[a] vs 77.8% UO[b]) **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	**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% 147 FO[a], 63 UO[b] NR	5.7% graft dysfunction, 2.4% graft loss NR	**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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Table 4b (*continued*)

	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**[c]: 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
Søfteland 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% Triple regimen 69% Double regimen 26.2% Mono regimen 4.8%	No change in immunosuppression 51.7% **Steroid**: decrease or stop 2.6%, increase 24.7% **CI**: decrease or stop 19.2% **AM**: reduction or stop 38.9% **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%	30-day mortality: 14.9% hospitalized, 0% non-hospitalized	0.4% graft loss	**Baseline IS:** NS difference hospitalized vs non-hospitalized **Baseline IS:** NS difference mortality **Treatment hospitalized vs non-hospitalized:** Reduction/stop AM: 52.7% vs 16.2%, $p < 0.001$ Reduction/stop CI: 27.1% vs 5.1%, $p < 0.001$ Increased prednisone: 33.9% vs 9.6%, $p < 0.001$ Dexamethasone/ betamethasone: 15.7% vs 0%, $p < 0.001$ Remdesivir: 6.8% vs 0%, $p = 0.015$
Kidney								
AlOtaibi 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 AM 54.8% Stop **AM** and **CI** 10.6% Stop **AM, CI** and increased **steroid** 23.1%	**Antiviral**: Antiviral 16.3% Oseltamivir 8.6% no-oseltamivir agents 7.7% **Anti-inflammatory**: tocilizumab 8.7% steroid 31.7% **Other**: antibiotics 57.7%	Overall mortality 10.3%	3.8% failed graft, 11.5% impaired graft[d]	
Bossini et al. [40]	Prospective single-centre cohort study	53 KTR	**Steroids**: 57% **CI**: Cyclosporine 32%, Tacrolimus 58% **AM**: MMF 60% **mTOR-i**: 11%	**Hospitalized**: Immunosuppression stop 93.3% **Steroids**: increase 42.2%, no change 24.4% stop MMF, decrease CI 6.7% **Non-hospitalized**: **Steroids**: increase or start 37.5%, no change 62.5% **CI**: decrease dose 12.5% **AM**: stop 12.5%, no change	**Hospitalized**: **Antiviral**: Hydroxychloroquine 75.6%, Lopinavir/ritonavir 40%, Darunavir + ritonavir 31.1% **Anti-inflammatory**: Start steroid 33.3% **Other**: Antibiotics 67.3% **Non-hospitalized**: **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
				12.5% Stop MMF, decrease CI 50% Stop mTORi, decrease CI 12.5%	100% **Other**: Azithromycin 100%			
Cravedi et al. [41]	Retrospective multicentre cohort study	144 KTR	**Steroids** 86% **CI**: tacrolimus 91.0% **AM**: mycophenolate 77.1% **mTOR-i**: everolimus 7.6% **RAAS-I**: ARB 16.7%, ACE-I 13.9%	**Steroids**: increase 66% **CI**: tacrolimus stop 22.9% **MMF** or **everolimus** stop 67.9%	**Antiviral:** hydroxychloroquine 70.6% Remdesivir 6.3% Lopinavir-ritonavir 4.9% Darunavir-ritonavir 2.1% Darunavir-cobicistat 0.7% **Anti-inflammatory**: tocilizumab 13.4% **Other**: antibiotics 74%	Overall mortality 32%	NR	**Treatment:** ACE—I: 14.3% survivors vs 13.0% non-survivors, p = 1 Antibiotics: 68% survivors vs 87% non-survivors, p = 0.023 Other treatment/ IS change: NS difference survivors vs non-survivors
Cristelli et al. [42]	Prospective single-centre cohort study	491 KTR	Tacrolimus + prednisone + MMF 46%, Cyclosporine + prednisone + MMF 3% tacrolimus + prednisone + AZA 18% cyclosporine + prednisone + AZA 7% tacrolimus + prednisone + mTOR-i 8%, cyclosporine + prednisone + mTOR-i 0.4% Other 14.6%	No IS discontinuation 48% All IS discontinued, except steroids 36% **AM** stop 12% **CI** stop 1%	**Antiviral**: Chloroquine 1% **Anti-inflammatory**: Steroids 2% **Other**: Azithromycin 27% Azithromycin + chloroquine 11% Azithromycin + steroids 7% Ivermectin 1% Other antibiotics 14%	Overall mortality 28.5%	4% graft loss	No IS drug discontinuation: 94% home, 52% ward, 13% ICU, p < 0.0001 All IS discontinued, except steroids: 0% home, 21% ward, 71% ICU, $p < 0.0001$ AM discontinued: 6% home, 23% ward, 10% ICU, p < 0.0001 CI discontinued: 0% home, 2% ward, 1% ICU, p < 0.0001
Elias et al. [56]	Prospective multicentre cohort study	1216 KTR, 66 covid+	**Steroids:** 83% **CI:** 86% **AM**: MMF/MPA/AZA 92% **Belatacept** 9%	Only **AM** stopped 62% Only **CI** stopped 4% Stopped **all IS** 2% **Belatacept** hold 17% No change 36%	Hydroxychloroquine 11% Tocilizumab 2% Eculizumab 3%	COVID related mortality 24%	NR	IS reduction: 87% invasive mechanical ventilation group vs 57% no invasive mechanical ventilation group, p not reported
Fava et al. [43]	Retrospective multicentre cohort study	104 KTR	**Steroids**: Prednisone 92.3% **CI**: Tacrolimus 85.5%, Cyclosporine 2.88% **AM**: MMF/MPA 83.6% **mTOR-i**: 19.3% **RAAS-I**: 35.6%	Overall IS stop: 89.5% survivors, 96.4% non-survivors **Steroids**: stop 1.4% survivors, 3.7% non-survivors **CI**: stop 69% survivors, 68% non-survivors **AM**: stop 73.1% survivors, 84.6% non-survivors **mTORi**: stop 52.9% survivors, 100% non-survivors	**Antiviral**: Hydroxychloroquine 97.4% survivors, 96.4% non-survivors Lopinavir/ritonavir 48.7% survivors, 46.4% non-survivors Darunavir/ritonavir 4.2% survivors, 0% non-survivors Darunavir/cobicistat 5.4% survivors, 3.6% non-survivors Remdesivir 2.6% survivors, 0% non-survivors Interferon beta-1a 6.6% survivors, 14.3% non-survivors **Anti-inflammatory**: Tocilizumab 32.9% survivors, 35.7% non-survivors **Other**: Azithromycin 60.5% survivors, 71.4% non-survivors	Overall mortality 26.9%	0%	**Change in IS:** IS stop: 83% no ARDS vs 98.2% ARDS, p = 0.01 CI stop: 48.6% no ARDS vs 74.4% ARDS, $p = 0.018$ mTORi stop: 36.4% no ARDS vs 88.9% ARDS, p = 0.028 **Treatment:** Interferon-β1a: 0% no ARDS vs 15.8% ARDS, p = 0.004 Tocilizumab: 12.8% no ARDS vs 50.9% ARDS, p < 0.001
Kute et al. [44]		251 KTR	**Steroids**: prednisolone 100%	**Steroids**: increase (32% survivors, 100% non-	**Antiviral**: Hydroxychloroquine (61.5% survivors, 65% non-	Overall mortality 11.6%	4.5% survivors,	**IS change:** Steroid increase: 32%

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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
	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-inflammatory**: 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 immunoglobulin (4.5% survivors, 0% non-survivors)		6.8% non-survivors	survivors vs 100% non-survivors, $p < 0.0001$ Steroid no change: 67% survivors vs 0% non-survivors, $p < 0.0001$ AM stop: 71.9% survivors vs 100% non-survivors, $p = 0.0002$ AM decrease: 28% survivors vs 0% non-survivors, $p = 0.0002$ CI no change: 74.6% survivors vs 0% non-survivors, $p < 0.0001$ CI reduced: 19% survivors vs 27.5% non-survivors, $p < 0.0001$ CI stop: 0% survivors vs 72.4% non-survivors, $p < 0.0001$ **Treatment survivors vs non-survivors:** Tocilizumab: 2.6% survivors vs 68.9% non-survivors, $p < 0.0001$ Convalescent plasma: 2.3% survivors vs 34.4% non-survivors, $p < 0.0001$ Other: NS difference RAAS-I: 29.8% survivors vs 31% non-survivors, $p = 0.897$
Perez-Saez et al. [68]	Retrospective multicentre cohort study	80 KTR	**Steroids:** prednisone 91.3% **CI:** 82.5% **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-inflammatory**: 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, 0% 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 38.5% non-survivors, $p = 0.43$ **IS management:** NS difference survivors vs non-survivors
		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	**Risk for mortality within 90-days:**

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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
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	**Antiviral**: Hydroxychloroquine 47.5% Lopinavir/ritonavir 18.2% Remdesivir 2.6% **Anti-inflammatory**: Tocilizumab 13.9% Glucocorticoids 48.9% **Other**: Azithromycin 27.7% **RAAS-I**: ACE—I: 14.2%, ARB: 27.1%	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: 14.1% 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 CNI + steroids: 44.4% decrease, 44.4% stop, 11.2%	**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 **Treatment in ARDS vs non-ARDS:** Antibiotics: 91% ARDs vs 57% no-ARDS, $p = 0.039$ Other treatment: NS

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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
				no change CNI's + AZA: 100% no change MTORI+ MMF: 50% stop, 50% no change				**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
Belli et al. [49]	Retrospective multicentre cohort study	243 LTR	**Steroids**: 23.1% **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	IS change: 10.3% home, 42.5% ward, 59.5% ICU, 93.9% total **CI**: stop: 0% home, 6.6% ward, 13.5% ICU, 6.6% total 25–50% decrease: 5.1% home, 16.8% ward, 21.6% ICU, 15.6% total **AM**: stop: 2.6% home, 15.6% ward, 21.6% ICU, 14.4% total **mTOR-i**: stop: 0% home, 5.4% ward, 2.7% ICU, 4.1% total Other changes: 2.6% home, 3% ward, 0% ICU, 2.5% total	None: 84.6% home, 27.5% ward, 40.5% ICU, 38.7% total **Antiviral**: Hydroxychloroquine: 10.3% home, 59.3% ward, 35.1% ICU, 7.7% total Lopinavir/ritonavir:0% home, 21% ward, 16.2% ICU, 16.9% total Remdesivir: 0% home, 0% ward, 2.7% OCI, 0.4% total **Anti-inflammatory**: Tocilizumab: 0% home, 6.6% ward, 10.8%ICU, 6.2% total High-dose steroids 0% home, 15.6% ward, 21.6% ICU, 14% total Azithromycin: 5.1% home, 34.1% ward, 21.6% ICU, 27.6% total **Other** 2.6% home, 9% ward, 21.6% ICU, 9.9% total	0% home, 17.4% ward, 54.0% ICU, 20.2% total	NR	**IS change**: 10.3% home, 42.5% ward, 59.5% ICU, 93.9% total, p < 0.0001 **Treatment:** Lopinavir/ritonavir:0% home, 21% ward, 16.2% ICU, 16.9% total, p = 0.007 Hydroxychloroquine: 10.3% home, 59.3% ward, 35.1% ICU, 7.7% total, p < 0.001 High dose steroids: 0% home, 15.6% ward, 21.6% ICU, *p* = 0.0144 **Risk factors mortality univariate analysis:** Use of tacrolimus: HR 0.43 [95% CI 0.24–0.77], *p* = 0.0042 Treatment with RAAS-I: HR 1.92 [95% CI 1.06–3.49],p = 0.033 **Risk factors mortality multivariable analysis:** Use of tacrolimus: HR 0.55 [95% CI 0.31–0.99], *p* = 0.0472
Colmenero et al. [50]	Prospective multicentre cohort study	111 LTR	**Steroids**: 24% **CI**: Tacrolimus 66%, Cyclosporine 6% **AM**: Mycophenolate 57% **mTOR-i**: Everolimus 23% **RAAS-I**: ACE-I 33%	NR	**Antivirals**: Hydroxychloroquine 88% Lopinavir/ritonavir 40% Remdesivir 1% Interferon 3% **Anti-inflammatory**: Tocilizumab 15% High dose corticosteroids 12% **Other**: Azithromycin 60%	Overall mortality 18%	2.7% graft dysfunction, 0% graft loss	**Baseline IS non-severe vs severe[e] disease:** Mycophenolate: 43.4% non-severe vs 68.6% severe, p = 0.014 Other baseline IS: NS difference ACE—I: 24% non-severe vs 9% severe, *p* = 0.530 **Treatment non-severe vs severe disease**: Tocilizumab: 3% non-severe vs 12% severe, p < 0.001 High dose corticosteroids: 3% vs 9% severe, *p* = 0.007 **Risk factors of severe covid**

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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
								in hospitalized patients: Baseline IS with mycophenolate: RR 3.94 [95% CI 1.59–9.74], $p = 0.003$
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

[a] FO = favourable outcome = full recovery and discharged or stable clinical condition

[b] UO = unfavourable outcome = admission to ICU or death

[c] 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

[d] Impaired graft = impairment >25% of baseline value

[e] 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[a]	**Humoral response:** Anti-S: IgG II Quant assay Abott, Euroimmun, Roche Elecsys Neutralizing Ab's: sVNT Genscript **Cellular response:** IFN-γ release: QuantiFERON Monitor ELISA	**IgG titres:** Non-SOT: 98% after first dose, 100% after second dose SOT: 4% after first dose, 10% after second dose **Neutralizing Abs**: Non-SOT: 82% after 1st dose, 100% after 2nd dose SOT: 0% after 1st dose, 4% after 2nd dose	**IFN-g release:** 80% non-SOT, 16% SOT	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 TrimericS 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, $p = 0.38$
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% **Systemic reaction**: Mild systemic reaction[b]: 19.2% Acute rejection: 0% Anaphylaxis: 0% New neurological illness: 0%	2 cases, both seronegative	**Median IgG anti-spike level**: 5.9 AU/mL KTR vs 189.0 AU/mL non-SOT, $p < 0.001$ **Mean antibody levels seropositive KTR vs non-SOT**: 71.8 KTR vs. 189.0 AU/mL non-SOT, $p < 0.001$ **Multivariate analysis of risk factors for negative serology in KTR:** Older age: OR 1.66 [95% CI 1.17–2.69], $p = 0.026$

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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
									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], $p = 0.049$
Rincon-Arevalo et al. [73]	Prospective single-centre cohort study	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 DP: 70.5% IgG, 68.2% IgA KTR: 2.5% IgG, 10% IgA	NR	NR	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, $p < 0.0001$
Sattler et al. [74]	Prospective single-centre cohort study	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 Ab's: sVNT GenScript **Cellular response**: FACS	**Anti-S1 IgG response:** 2.6% KTR, 84.6% DP, 100% controls **Anti-S1 IgA response: 10**.3% KTR, 84.6% DP, 97.4% controls **Neutralizing Abs:** 0% KTR, 76.9% DP, 100% controls	**Spike specific CD4+ responders:** 92.3% KTR, 100% DP, 100% controls **Spike specific CD8+ responders**: 5.1% KTR, 30.8% DP, 46.2% controls	Acute rejection: 0%	NR	**Anti-S1 IgG response**: 100% controls vs 2.6% KTR, $p < 0.0001$ **Anti-S1 IgA response:** 97.44% controls vs 10.26% KTR, $p < 0.0001$ **Spike specific CD4+ responders**: 100% controls vs 92.3% KTR, $p = 0.240$ **Spike specific CD8+ responders:** 46.15% controls vs 5.13% KTR, $p < 0.0001$
Stumpf et al. [75]	Prospective multicentre cohort study	1768 patients: 368 KTR, 1256 DP, 144 controls	BNT162b2: 28% KTR, 17% DP, 27.8% controls mRNA-1273[c]: 72.0% KTR, 83.0% DP, 72.2% controls	**Humoral response:** Anti-S1: Euroimmun ELISA Anti-NCP: Euroimmun ELISA Anti-RBD: Euroimmun ELISA **Cellular response:** IGRA FACS	**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 **Anti-RBD Abs after 2nd dose:** KTR: 65% DP: 95% Controls: 100%	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	NR	**Symptomatic:** 0.45% (8 cases) **Asymptomatic:** 1.0% KTR, 2.8% DP, 2.1% controls	**Seroconversion 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

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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
									2.06, [95% CI 1.34–3.16],$p = 0.001$ Vaccine type mRNA1273: OR 0.36, [95% CI 0.21–0.62], $p < 0.001$ **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], $p = 0.003$
Liver									
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-NCP**: Architect i2000SR analyzer (Abbot)	**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	**Anti-S1/S2 positive serology:** 47.5% LT vs 100% non-SOT, p < 0.001 **Mean antibody levels seropositive LTR vs non-SOT**: 95.41 AU/ ml LT vs. 200.5 AU/ml non-SOT, p < 0.001 **Multivariate analysis risk for negative serology in LTR:** Age: OR 1.3 [95% CI 1.17–1.95], $p = 0.021$ Lower eGFR: OR 0.8 [95% CI 0.47–0.95], $p = 0.034$ High dose prednisone in the past 12 months: OR 1.8 [95% CI 1.58–4.61], $p = 0.041$ Triple therapy IS: OR 1.73 [95% CI 1.21–2.52], $p = 0.019$ Low dose steroids: OR 1.5 [95% CI 0.91–4.1], $p = 0.089$ AM: OR 1.8 [95% CI 1.15–3.47], $p = 0.037$
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[d]	**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	**Poor humoral response:** 84.2% Ad26.COV2S vs 23.6% mRNA-1273 vs 35.6% BNT162b2, $p < 0.001$ **Factors associated**

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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
						Systemic events:		**suboptimal/undetectable Ab response:**
				Suboptimal:		Fatigue: 16% after		Liver transplantation: OR
				43.5% LT, 9.0%		1st dose, 23% after		2.71 [95% CI 1.03–7.13]; p
				cirrhosis, 20.7%		2nd dose		= 0.04
				chronic liver diseases		Fever: 8% after 2nd		≤2–3 IS medications vs
				without cirrhosis		dose		none: OR 14.38 [95% CI
						Chills: 6% after 2nd		5.09–40.66], p < 0.0001
				Good response:		dose		mRNA-1273 vs Ad26.
				38.7% LT, 77.2%		Headache: 7% after		COV2S: OR 0.02 [95% CI
				cirrhosis, 75.0%		2nd dose		0.01–0.10], $p < 0.0001$
				chronic liver diseases		Myalgia: 6% after		BNT162b2 vs Ad26.COV2S:
				without cirrhosis		2nd dose		OR 0.06 [95% CI
						Acute rejection: 0%		0.02–0.24], $p = 0.03$
						Anaphylaxis: 0%		

[a] Two doses of BNT162b2 Moderna vaccine
[b] Fever, chills, headache, fatigue, myalgia, arthralgia, nausea, vomiting, diarrhea
[c] Two doses of the mRNA-1273 Pfizer vaccine
[d] One dose of Ad26.COV2.S Johnson&Johnson vaccine

Considering all the immunosuppressive modifications and the different therapy options, drug monitoring and potential drug interactions need to be taken into account in future studies [90–93].

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 antimetabolites 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.

	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									
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 **Cellular response:** EllSpot	**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% **Multivariable analysis factors associated seronegative response:** TAC + mTORi: OR 0.28 [95% CI 0.09–0.82], $p = 0.020$ **Multivariable analysis factors associated absence cellular immune response:** Diabetes: OR 5.65 [95% CI 1.67–19.04], $p = 0.005$ eGFR 45–60: OR 4.50 [95% CI 1.25–16.18], $p = 0.021$ eGFR 30–45: OR 3.67 [95% CI 1.13–11.97], $p = 0.030$ **Multivariable analysis vaccine no-response (no cellular + no humoral):** Diabetes: OR 4.65 [95% CI 1.41–15.31], $p = 0.037$ Antithymocyte globulin <1y: OR 7.23 [95% CI 1.12–46.51], p = 0.037
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: sVNT Genscript **Cellular 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[a] **Systemic events:** Fatigue, myalgia, headache: most reported[a] 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: 4.17% seronegative vs 21.1%

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Table 5b (*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
									seropositive $p = 0.002$
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's: **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	**Local reaction**: Pain at injection site: 85% after 1st dose, 76% after 2nd dose **Systemic reaction:** Fatigue: 32% after 1st dose, 56% after 2nd Headache: 24% after 1st dose, 39% after 2nd Acute rejection: 0% Anaphylaxis: 0% New neurological illness: 0%	NR	**Characteristics related to Ab response after 1st dose:** Age: IRR 0.61 [95% CI 0.41–0.92], $p = 0.02$ AM: IRR, 0.43 [95%CI 0.22–0.85], p = 0.02 **Characteristics related to Ab response after 2nd dose:** Type of transplant (heart vs lung): IRR 1.55 [95% CI 1.18–2.03], $p = 0.001$ AM: IRR 0.71, [95% CI 0.58–0.88], $p < 0.01$ Transplant-to-vaccination time $\geq$ 6 years: IRR 1.22 [95% CI 1.10–1.35], $p < 0.001$
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	**Local events:** Pain at injection site: 80% Swelling: 12% **Systemic events:** Fatigue: 15% Fever: 7% Acute rejection or graft dysfunction: 0%	NR	**Vaccine response, humoral or cellular:** 87% heart, 93% liver, 90% overall **Risk factors for seronegative response:** Vaccination in first posttransplant year: OR 30.7 [95% CI 3.1–307.2] High-dose mycophenolate acid use: OR 10.1 [95% CI 2.3–44.3] **Risk factors for negative cellular response**: NS
Aslam 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%) 912 fully vaccinated, 88 partially vaccinated,	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, 3.3% not vaccinated	**Incidence rate for COVID-19 per 1000/person days:** IR 0.065 [95% CI 0.024–0.17] vaccinated vs IR 0.34 [95% CI 0.26–0.44] not-vaccinated, p < 0.0001

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Table 5b (*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
		1151 not vaccinated							
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%	4 cases symptomatic, all seronegative	**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 1.06–7.78], p = 0.038 Low CI 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) **Cellular response:** CD4+ T-cell: Cylex ImmuKnow assay	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**[b]: 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%	NR	**Multivariate analysis of predictors seropositive response:** Mycophenolic acid: OR 0.12 [95% CI 0.01–0.82], $p = 0.042$

[a] Exact numbers not reported.
[b] 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 higher 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-vaccins.

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

Declaration of Competing Interest

None.

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