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Systematic review

Clinical outcome in solid organ transplant recipients affected by COVID-19 compared to general population: a systematic review and meta-analysis

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Background: A significant increased risk of complications and mortality in immunocompromised patients affected by COVID-19 has been described. However, the impact of COVID-19 in solid organ transplant (SOT) recipients is an issue still under debate, due to conflicting evidence that has emerged from different observational studies.

Objectives: We performed a systematic review with a meta-analysis to assess the clinical outcome in SOT recipients compared with the general population.

Data sources: PubMed-MEDLINE and Scopus were independently searched until 13 October 2021.

Study eligibility criteria: Prospective or retrospective observational studies comparing clinical outcome in SOT recipients versus general populations affected by COVID-19 were included. The primary endpoint was 30-day mortality.

Participants: Participants were patients with confirmed COVID-19.

Interventions: Interventions reviewed were SOTs.

Methods: The quality of the included studies was independently assessed with the Risk of Bias in Non-randomized Studies of Interventions tool for observational studies. The meta-analysis was performed by pooling ORs retrieved from studies providing adjustment for confounders using a random-effects model with the inverse variance method. Multiple subgroups and sensitivity analyses were conducted to investigate the source of heterogeneity.

Results: A total of 3501 articles were screened, and 31 observational studies (N = 590,375; 5759 SOT recipients vs. 584,616 general population) were included in the meta-analyses. No difference in 30-day mortality rate was found in the primary analysis, including studies providing adjustment for confounders (N = 17; 3752 SOT recipients vs. 159,745 general population; OR: 1.13; 95% CI, 0.94–1.35; I² = 33.9%). No evidence of publication bias was reported. A higher risk of intensive care unit admission (OR: 1.56; 95% CI, 1.03–2.63) and occurrence of acute kidney injury (OR: 2.50; 95% CI, 1.81–3.45) was found in SOT recipients.

Conclusions: No increased risk in mortality was found in SOT recipients affected by COVID-19 compared with the general population when adjusted for demographic and clinical features and COVID-19 severity.

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Introduction

The significant increased risk of complications and mortality in immunocompromised patients affected by COVID-19 has been widely described [1,2], but the impact of COVID-19 on solid organ transplant (SOT) recipients remains an issue under debate. Particularly, although SOT recipients commonly exhibit a relevant burden of comorbidities affecting COVID outcome, the role of immunosuppressant therapy in reducing hyperinflammatory status may counterbalance this issue [3]. Furthermore, the majority of data are derived from small cohorts of patients or large registries without appropriate control groups. The first retrospective studies reported higher mortality rates among SOT recipients compared with the general population [4,5].

However, the results from an international registry study conducted during the first wave of COVID-19 suggest that transplantation was not independently associated with an increased risk of death, but SOT recipients had a rapidly evolving course in terms of intensive care unit (ICU) admission and invasive ventilation rates [6]. These findings have been further confirmed in a propensity-score analysis [7]. Nevertheless, subsequent studies involving SOT recipients from different waves yielded conflicting results [8,9]. With these assumptions, we conducted a systematic review and meta-analysis to assess the clinical outcome in SOT recipients affected by COVID-19 compared with the general population.

Methods

A systematic review and meta-analysis investigating the clinical outcome in SOT recipients affected by COVID-19 compared with the general population was performed. The meta-analysis was registered in the PROSPERO database (number CRD42021269372) and was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines [10].

Population, exposure, comparator, and outcome question

The population of interest was patients affected by COVID-19, and exposure of interest was SOTs. The comparator was the general population. The outcome analyzed was mortality rate.

Data source

Two authors (MiGa and MR) independently searched the PubMed-MEDLINE and Scopus databases from inception to 13 October 2021. The following search string was developed: (“solid organ transplant” OR “solid organ transplantation” OR “kidney transplant” OR “kidney transplantation” OR “liver transplant” OR “liver transplantation” OR “heart transplant” OR “heart transplantation” OR “lung transplant” OR “lung transplantation”) AND (“COVID” OR “COVID-19” OR “COVID disease” OR “SARS-CoV-2 infection”). Identified records were divided into three equal groups, and three pairs of authors (MiGa and MR, CB and ZP, LB and RP) independently screened titles and abstracts of each predefined group of records for potential relevance and assessed the eligibility of relevant full texts. Any disagreement was resolved by means of discussion or consultation with a third reviewer (MaGi).

Study eligibility criteria

Prospective or retrospective observational studies, published in all languages, comparing clinical outcomes in SOT recipients affected by COVID-19 versus the general population were included. Studies were excluded if no comparator group was provided or quantitative target outcome results were lacking. For studies using the same SOT registry as the data source, the report with the largest number of patients was considered. Additionally, conference abstracts or case reports/series were also not eligible.

The primary outcome was the 30-day mortality rate in each of the two groups (SOT recipients and general population), assessed after hospital admission or COVID-19 diagnosis according to the criteria used in different studies. Secondary outcomes included the requirement for hospital and/or ICU admission, occurrence of severe respiratory failure, requirement for mechanical ventilation, vasopressors administration, development of acute kidney injury (AKI), occurrence of superinfections (including both bacterial and invasive fungal infections), and cytomegalovirus reactivation. Severe respiratory failure was defined according to the WHO criteria as oxygen saturation <93% with 100% fraction of inspired oxygen (reservoir mask or continuous positive airway pressure ventilation or other noninvasive ventilation), respiratory rate >30 breath/min, or respiratory distress (http://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-ncov-infection-is-suspected, accessed 13 October 2021). Additionally, requirements for noninvasive pressure-positive ventilation, mechanical ventilation, or ICU admission were also considered as criteria for severe COVID-19.

Three pairs of authors (MiGa and MR, CB and ZP, LB and RP) independently screened titles and abstracts of each predefined group of records for potential relevance and assessed the eligibility of relevant full texts. Any disagreement was resolved by means of discussion or consultation with a third reviewer (MaGi).

Data extraction

Three pairs of authors (MiGa and MR, CB and ZP, LB and RP) independently extracted data from each included study retrieved in the assigned group in a prespecified form. The following data were extracted: (a) study author and year of publication, as well as the country in which the study was conducted; (b) study characteristics (including study design, time period, sample size, exclusion criteria, and funding); (c) features of the patients (including age, sex, type of SOT, time from transplant to COVID-19 occurrence, graft function at COVID-19 diagnosis, immunosuppressive treatment at baseline, adjustments in immunosuppressive treatment, and severity of COVID-19 at the time of enrolment), specific COVID-19 treatment (including administration of monoclonal antibodies, corticosteroids, tocilizumab, remdesivir, or other drugs), and preventive strategies (including vaccination and implementation of telemedicine); and (d) types of outcome measurements.

Corresponding authors of publications that reported unclear data that may lead to misinterpretations were contacted by email for clarification and/or to request supplemental information of the included studies.

Assessment of risk of bias

Two authors (MiGa and CB) independently assessed the risk of bias of the included studies with regard to the primary outcome. The Risk of Bias in Non-randomized Studies of Interventions tool [11] was used to assess the risk of bias in observational studies. Any disagreement was resolved by means of discussion or consultation with a third reviewer (MaGi).

Methods of data synthesis

A primary meta-analysis investigating primary and secondary outcomes was performed by pooling ORs retrieved from studies providing adjustment for confounders in the comparison between SOT recipients and the general population (adjusted OR) through the implementation of matched cohorts, regression, or
propensity score analyses. Treatment effects were calculated as OR with 95% CI for dichotomous data by using a random-effect model with the inverse variance method. Significance was assessed using a Z-test, where \( p < 0.05 \) is considered significant. Statistical heterogeneity among the studies was assessed with a \( \chi^2 \) test (\( p < 0.10 \) indicated significant heterogeneity) and \( I^2 \) (degree of heterogeneity). An \( I^2 \) of >50% was considered indicative of substantial heterogeneity.

Subgroup analysis was prespecified according to the comparator group (SOT waitlisted patients), type of SOT, type of immunosuppressive agents at baseline, or change in immunosuppressant management after COVID-19 infection. At least three studies providing available adjusted data for the primary outcome were required to progress to subgroup analyses. Sensitivity analyses were also conducted by pooling included studies without adjustment for confounding factors, by excluding each study (leave-one-out approach), and according to the risk of bias to investigate the confidence of the outcomes. Publication bias was assessed by visual inspection of the funnel plot and Egger’s test [12].

Statistical analysis was performed using MedCalc statistical software, version 19.6.1, MedCalc Software Ltd, Ostend, Belgium.

Results

An electronic and manual search identified 3501 potential studies, and among these, 1300 were removed as duplicates. After an initial screening of titles and abstracts, 2164 studies were excluded. Overall, 37 full-text articles were assessed for eligibility, and finally 31 studies met the inclusion criteria. Six studies were excluded according to the following criteria: use of the same transplant registry in multiple included studies (four studies), and systematic review (two studies; Fig. 1).

Characteristics of included studies

Features of the 31 included studies are shown in Table 1 and Table S1. Overall, 590,375 enrolled patients were included (5759 SOT recipients vs. 584,616 in the general population). Six studies were prospective and 25 retrospective [4–7,9,13–38]. Sixteen studies were conducted in North America (15 in the United States and 1 in Canada), 14 in Europe, and 1 in Asia. Mean or median patient age ranged from 38 to 65.5 years, with a male predominance (up to 83.0%). Most studies (28 of 31) were conducted during the first wave of COVID-19, and in three cases, the analysis was prolonged up to January 2021. According to the study periods, no vaccinated patients were included among SOT recipients or general population due to a lack of COVID-19 vaccine availability.

Liver and kidney transplant recipients accounted for more than 85% of included transplant patients. Severe COVID-19 at diagnosis ranged from 1.1% to 78.0% in the transplant recipient group. Median timing of SOT in relationship with COVID-19 infection was provided in 18 studies, ranging from 3.4 to 9 years. Seven and three studies included only kidney or liver transplant recipients, respectively. In 17 studies, a match between SOT recipients and the control group was performed according to demographic and/or clinical features (Table 1). In six studies, the control group consisted of SOT waitlisted patients (kidney or kidney/pancreas in four studies, lung and all SOT in one study each).

Outcome assessment

A summary of the results of the meta-analysis for the primary and secondary outcomes is shown in Table 2.

30-day mortality rate

Thirty-day mortality was assessed after hospital admission, after COVID-19 diagnosis, and after ICU admission in 16, 14, and 1 study, respectively. A total of 17 studies (3752 SOT recipients vs. 159,745 patients in the general population) provided adjusted data for the 30-day mortality rate [5–7,9,14–16,20,21,23,25–28,30,31,33]. In 11 studies, adjustment for confounders was performed by using a propensity score analysis, and exact matched cohorts and a regression analysis were implemented in 5 and 1 study, respectively. Overall, no significant difference emerged between SOT recipients and the general population (OR: 1.13; 95% CI, 0.94–1.35; Fig. 2). A moderate degree of heterogeneity was observed (\( I^2 = 33.9\% \); \( p = 0.09 \)). The funnel plot and Egger’s test (\( p = 0.69 \); Table 2) showed no evidence of publication bias.

Secondary outcomes

SOT recipients were associated with a significant increased risk of AKI occurrence (\( n = 10 \); OR: 2.50; 95% CI, 1.81–3.45) and ICU admission (\( n = 9 \); OR: 1.56; 95% CI, 1.03–2.36) compared with the general population (Table 2). No association with a significant increased risk of hospitalization (\( n = 15 \); OR: 0.99; 95% CI, 0.57–1.70), mechanical ventilation (\( n = 12 \); OR: 1.38; 95% CI, 0.91–2.09), severe respiratory failure (\( n = 6 \); OR: 1.35; 95% CI, 0.89–2.04), superinfections (\( n = 6 \); OR: 1.12; 95% CI, 0.35–3.92), and requirement for vasopressors (\( n = 5 \); OR: 0.84; 95% CI, 0.43–1.63) was found in SOT recipients compared with the general population.

A substantial degree of heterogeneity was observed for each secondary outcome, except for hospitalization. The funnel plot and Egger’s test showed evidence of publication bias only for secondary outcomes investigating hospitalization and occurrence of superinfections (Table 2). No study assessed the occurrence of cytomegalovirus reactivation.

Subgroup analysis

Comparator group

Six studies compared SOT recipients with SOT waitlisted patients affected by COVID-19 (1197 vs. 1242 patients) [17,24,32,34,37,38]. Considering that none of these studies provided adjusted data for primary or secondary outcomes, meta-analysis was not performed.

Type of solid organ transplant

Four studies provided adjusted outcome data comparing only kidney transplant recipients and the general population affected by COVID-19 (448 vs. 850 patients; Table S2) [15,16,28,31]. No significant difference in 30-day mortality rate was found between kidney transplant recipients and the general population (\( n = 4 \); OR: 1.44; 95% CI, 0.85–2.44; Fig. S1). A moderate degree of heterogeneity was observed (\( I^2 = 46.3\% \); \( p = 0.13 \), and no evidence of publication bias was reported. With regard to secondary outcomes, no significant difference was found between kidney transplant recipients and the general population (Table S2).

Three studies provided adjusted outcome data comparing only liver transplant recipients and the general population affected by COVID-19 (387 vs. 147,442 patients; Table S2) [6,20,33]. No significant difference in 30-day mortality rate was found between liver transplant recipients and the general population (\( n = 3 \); OR: 0.90; 95% CI, 0.55–1.47; Fig. S2). A substantial degree of heterogeneity was observed (\( I^2 = 53.8\% \); \( p = 0.11 \), but no evidence of publication bias was reported. With regard to secondary outcomes, liver transplant recipients were associated with an increased risk of
hospitalization compared with the general population (n = 2; OR: 1.75; 95% CI, 1.19–2.57; Table S2). Subgroup analyses for other types of SOTs (namely lung and heart transplant recipients) according to different number and type of immunosuppressive agents at baseline or according to change in immunosuppressant management after COVID-19 infection were not allowed due to lack of outcome data.

**Sensitivity analysis**

After inclusion of studies providing unadjusted outcome data, SOT recipients showed a significant higher risk of 30-day mortality rate compared with the general population (n = 30; OR: 1.37; 95% CI, 1.05–1.78; Fig. S3). Similarly, an increased risk of severe respiratory failure (n = 9; OR: 1.49; 95% CI, 1.04–2.13), mechanical ventilation (n = 21; OR: 1.74; 95% CI, 1.21–2.50), ICU admission (n = 17; OR: 2.22; 95% CI, 1.51–3.27), and AKI occurrence (n = 13; OR: 2.66; 95% CI, 1.96–3.59) were reported in SOT recipients (Table S3).

After exclusion of studies with serious/critical risk of bias, no significant difference in 30-day mortality rate emerged between SOT recipients and the general population (n = 13; OR: 1.06; 95% CI, 0.88–1.28). Compared with the primary analysis, SOT recipients were not associated with an increased risk of ICU admission (n = 8; OR: 1.42; 95% CI, 0.93–2.19).

In the leave-one-out analysis, SOT recipients were associated with a slightly higher risk of 30-day mortality rate after excluding the study by Webb et al. [6] (OR: 1.18; 95% CI, 1.01–1.39). SOT recipients were not associated with a higher risk of ICU admission after excluding the study performed by Fisher et al. [9] (OR: 1.60; 95% CI, 0.95–2.70), Hadi et al. [25] (OR: 1.62; 95% CI, 0.96–2.74), Miorons et al. [5] (OR: 1.56; 95% CI, 0.99–2.45), and Ozturk et al. [16] (OR: 1.42; 95% CI, 0.93–2.19). A lower risk of requirement for vasopressors was found in SOT recipients after excluding the study by Fisher et al. [9] (OR: 0.62; 95% CI, 0.41–0.95).

**Quality of included studies**

Eighteen of 31 included studies showed serious or critical risk of bias in at least one domain. Bias due to confounding was the most frequently reported, considering that in 14 studies no adjustment for confounders was performed, and the adjustment was performed only for age and sex in three cases. All studies were classified as low risk of bias for measurement of primary outcome (i.e. mortality rate) and bias due to missing data. Thirteen studies were classified as being at moderate risk of bias, and none exhibited a low risk of bias (Table S4).

**Discussion**

Our meta-analysis found that SOT recipients affected by COVID-19 were not associated with an increased risk of mortality compared with the general population when appropriate adjustment for demographic and clinical features, including comorbidities and COVID-19 severity, were made at baseline. Although SOT recipients affected by COVID-19 showed a higher risk of mortality compared with the general population in different studies [4,13,22], the remarkable diversity in the comparator group, coupled with no adjustment for confounding factors, could have strongly affected the findings. Indeed, the presence of comorbidities (i.e. hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease) coupled with old age has been largely found to be associated with a higher risk of developing severe or fatal COVID-19 [39,40]. Pre-existing comorbidities were frequently reported in SOT recipients affected by COVID-19, thus potentially affecting clinical outcomes [3]. Consequently, the selection of appropriate comparators and the implementation of adequate study designs or analyses allowing for the adjustment for confounders may be crucial to provide an accurate interpretation of results.

The attributable risk of immunosuppression versus other comorbidities on COVID-19 severity and outcomes in SOT recipients is a matter of debate. SOT recipients usually receive combined immunosuppressive regimens, which may increase their susceptibility to viral infections and subsequent complications [3,41]. However, the association between severe COVID-19 manifestations and excessive cytokine release raises the possibility that immunosuppression could modulate the exuberant inflammatory response, thus possibly promoting the prevention of severe complications in SOT recipients [42,43]. It is possible that both sides of the coin are counterbalanced: thus, comorbidities may play a crucial role in the outcomes of SOT recipients with COVID-19. Unfortunately, our analysis was not able to assess the impact of...
| Study reference | Stud design | Country | Time period | No. of enrolled patients (SOT vs. general population) | Age (y), Sex (male), % | Intervention group (SOT) | Comparator group (general population) |
|-----------------|-------------|---------|-------------|-----------------------------------------------------|------------------------|--------------------------|----------------------------------------|
| Chavarot et al. [31] | Retrospective case-control study | France | 26/02/2020–22/05/2020 | 83 vs. 83 | 64.7 vs. 64.0 vs. 0.0 | 83 | 0 | 0 | 0 |
| Hilbrands et al. [32] | Prospective multicentre cohort study | The Netherlands | 01/02/2020–01/05/2020 | 305 vs. 768 | 60 vs. 60.0 | 305 | 0 | 0 | 0 |
| Colmenero et al. [33] | Prospective nation-wide study | Spain | 28/02/2020–07/04/2020 | 111 vs. 146,690 | N/A vs. N/A | 0 | 0 | 0 | 0 |
| McLennaghan et al. [34] | Retrospective cohort study | Worldwide | Beginning pandemic–13/06/2020 | 32 vs. 149 | 38 vs. 24 | 0 | 0 | 28 | 2 |
| Monreal et al. [35] | Retrospective case-control study | Spain | Beginning pandemic–15/04/2020 | 9 vs. 687 | 65.5 vs. 66.7 vs. 2 | 7 | 0 | 0 | 0 |
| Najafi et al. [36] | Retrospective cohort study | Iran | 21/02/2020–02/08/2020 | 35 vs. 451 | N/A vs. N/A | 35 | 0 | 0 | 0 |
| Ravanam et al. [37] | Retrospective cohort study | UK | 01/02/2020–02/05/2020 | 597 vs. 197 | 56 vs. 53 | 470 | 23 | 13 | 3 |
| Craig-Schapiro et al. [38] | Retrospective case-control study | United States | 13/03/2020–20/05/2020 | 80 vs. 56 | 57 vs. 60 | 80 | 0 | 0 | 0 |
| Webb et al. [6] | Prospective multicentre cohort study | United Kingdom/United States | 25/03/2020–26/06/2020 | 151 vs. 627 | 60 vs. 73 | 151 | 0 | 0 | 0 |
| Fisher et al. [9] | Prospective cohort study | United States | 10/03/2020–01/09/2020 | 128 vs. 3907 | 60 vs. 61.7 | 113 | 6 | 0 | 3 |
| Hadi et al. [25] | Retrospective cohort study | United States | 20/01/2020–30/09/2020 | 2289 vs. 2289 | 54.5 vs. 59.3 vs. 418 | 1740 | 262 | 180 | 0 |
| Molnár et al. [26] | Retrospective multicentric cohort study | United States | 04/03/2020–05/06/2020 | 98 vs. 288 | 58 vs. 61 | 67 | 17 | 4 | 4 |
| Pereira et al. [27] | Retrospective case-control study | United States | 10/03/2020–30/05/2020 | 117 vs. 350 | 61 vs. N/A | 92 | 22 | 25 | 34 |
| Hardesty et al. [28] | Retrospective case-control study | United States | 01/03/2020–18/05/2020 | 11 vs. 44 | 55 vs. 53 | 11 | 0 | 0 | 0 |
| Tripiani et al. [13] | Retrospective cohort study | Italy | 21/02/2020–22/06/2020 | 450 vs. 238,895 | 59.1 vs. 75.6 vs. 89 | 285 | 53 | 15 | 8 |
| Avery et al. [14] | Retrospective case-control study | United States | 01/03/2020–21/08/2020 | 45 vs. 2427 | 59 vs. 59 | N/A vs. N/A | N/A | N/A | N/A |

Cohort of patients with COVID-19 derived from retrospective multicentre study including 2878 patients hospitalized for COVID-19 in 24 French medical centres. Immunosuppressed were excluded. Cases and controls were matched 1:1 according to age, sex, BMI, diabetes, cardiopathy, hypertension, lung disease, and renal function

Patients undergoing scheduled intermittent haemodialysis

General population from national COVID-19 database balanced for age and sex

Patients affected by cystic fibrosis included in an international register and affected by COVID-19

Hospitalized patients affected by COVID-19 with no autoimmune disease or receiving immunosuppressant agents

Hospitalized patients affected by COVID-19 with no chronic kidney disease

Kidney transplant waitlisted patients affected by COVID-19

Contemporaneous cohort of consecutive patients affected by COVID-19 retrieved from the electronic patient records of the Oxford University Hospitals and adjusted for age, sex, renal function, obesity, hypertension, diabetes, and ethnicity

Patients hospitalized with COVID-19 matched for age, sex, race, ethnicity, BMI, hypertension, diabetes mellitus, congestive heart failure, and obesity

Patients with COVID-19 admitted to intensive care unit and matched for age, sex, race, ethnicity, comorbidities, active malignancies, HIV, smoking status, and medications used prior to hospital admission

Adults hospitalized with COVID-19 matched 3:1 for age categories, sex, BMI, race, ethnicity, hypertension, and diabetes

Adults hospitalized with COVID-19 matched for age and sex

All Italian patients affected by COVID-19 retrieved from national COVID-19 database up to 22/06/2020

Dataset of inpatient patients matched for age, sex, race, oxygen therapy requirement at admission, and severity score at admission

(continued on next page)
different immunsuppressive approaches implemented in SOT recipients affected by COVID-19 due to a lack of outcome data.

A higher risk of ICU admission in SOT recipients affected by COVID-19 compared with the general population emerged from our analysis. However, according to the lack of significant differences in mortality rate, higher ICU admission rates may not entirely reflect COVID-19 severity but rather a closer management strategy implemented by treating physicians and a massive use of health care resources in this fragile population [29,44]. Indeed, in SOT patients, the hospitalization rates ranged between 60% and 86.5%, and COVID-19 severity ranged from 23% to 35%. The prompt use of health care resources in SOT patients may also have contributed to a more favourable outcome.

Notably, our analysis found a 2.5-fold greater risk of AKI occurrence in SOT recipients affected by COVID-19 compared with the general population, as previously reported [3,45]. This probably reflects kidney function vulnerability in SOT recipients, mainly due to the chronic use of calcineurin inhibitors, which are known to cause nephrotoxicity and levels of which may increase during the acute phase of infection [46]. Furthermore, it is worth remarking that more than half of included cases consisted of kidney transplants.

The risk of bacterial and fungal superinfections in SOT recipients affected by COVID-19 represents a remarkable issue. Although reductions in immunosuppression (particularly involving antimetabolites and calcineurin inhibitors) are usually implemented in SOT recipients affected by COVID-19 [41], the increased...
susceptibility to bacterial or fungal superinfections is maintained. Our analysis found no significant higher risk of superinfections in SOT recipients affected by COVID-19. However, special care should be paid in this scenario. Notably, no study explored the impact of a reduction in immunosuppression on graft dysfunction and rejection. SOT waitlisted patients usually exhibit several comorbidities associated with poor COVID-19 prognosis [47]. Furthermore, the requirement for scheduled haemodialysis makes kidney transplant candidates more exposed to infected individuals [17]. Although several studies compared transplant candidates and SOT recipients in COVID-19 scenarios [17,24,32,34,37,38], none provided adjusted outcome data; thus, this issue has yet to be investigated.

To the best of our knowledge, only a previous meta-analysis comparing clinical outcomes between SOT recipients and the general population affected by COVID-19 currently exists [48]. Our findings are only partially consistent with those reported by Ao et al. [48], considering that a slightly higher risk of mortality was found in SOT recipients in their pooled analysis of adjusted results. However, it is important to highlight that our meta-analysis included more than double the number of studies and participants (of which the number of SOT recipients was almost four-fold greater) compared with the previous meta-analysis [48], thus providing an updated assessment of this issue.

Limitations of our meta-analysis have to be addressed. First, none of the included observational studies exhibited a low risk of bias; thus, unmeasured confounders could affect our findings. However, we performed a sensitivity analysis including only studies showing no serious/critical risk of biases to minimize the relevance of potential unmeasured confounders. High statistical heterogeneity was found for most outcomes, possibly reflecting a certain degree of clinically meaningful heterogeneity between the comparator groups of the included studies. Additionally, no other subgroup analysis according to different clinical features (e.g. management of immunosuppressant therapy in SOT recipients) was performed due to a lack of available data. Most studies were retrospective with a limited follow-up. Thus, we were able to measure only some of the indicators of COVID-19 impact; for example, the burden of long COVID in SOT recipients versus the general population has yet to be investigated. Finally, the findings of our systematic review may not be applicable to emerging variants causing milder disease, such as the Omicron variant [49].

In conclusion, no increased risk in mortality was found in SOT recipients affected by COVID-19 compared with the general population. However, special care should be paid in this scenario. Notably, no study explored the impact of a reduction in immunosuppression on graft dysfunction and rejection.

**Table 2**

Results of meta-analysis for primary and secondary outcomes

| Outcome                        | Studies, n | No. of patients | No. of events in transplant group | No. of events in comparator group | Or (95% CI) | Heterogeneity ($I^2$, p-value) | Publication bias (p-value Egger's test) |
|-------------------------------|------------|-----------------|-----------------------------------|----------------------------------|-------------|-------------------------------|----------------------------------------|
| **Primary outcome**           |            |                 |                                   |                                  |             |                               |                                        |
| 30-d mortality rate           | 17         | 3752 vs. 159 745| 407/3752                          | 23 634/159 745                   | 1.13 (0.94–1.35); p = 0.20 | 33.9%; p = 0.09 | 0.69                      |
| Severe respiratory failure    | 6          | 667 vs. 5304    | 274/667                           | 1441/5304                        | 1.35 (0.89–2.04); p = 0.15 | 73.2%; p = 0.002 | 0.22                      |
| Mechanical ventilation        | 12         | 3376 vs. 12 637 | 452/3376                          | 2256/12 637                      | 1.38 (0.91–2.09); p = 0.13 | 85.8%; p < 0.001 | 0.14                      |
| Hospitalization admission     | 15         | 1352 vs. 10 766 | 1162/1352                         | 10 418/10 766                    | 0.99 (0.57–1.70); p = 0.96 | 25.7%; p = 0.17 | <0.001                    |
| Intensive care unit admission | 9          | 2989 vs. 8132   | 503/2989                          | 2050/8132                        | 1.56 (1.03–2.36); p = 0.03 | 79.1%; p < 0.001 | 0.69                      |
| Acute kidney injury occurrence| 10         | 3073 vs. 11 376 | 863/3073                          | 2064/11 376                      | 2.50 (1.81–3.45); p < 0.001 | 72.6%; p < 0.001 | 0.47                      |
| Vasopressor requirement       | 5          | 570 vs. 4748    | 141/570                           | 864/4748                         | 0.84 (0.43–1.63); p = 0.61 | 84.4%; p < 0.001 | 0.75                      |
| Superinfections               | 6          | 499 vs. 1051    | 109/499                           | 330/1051                         | 1.12 (0.35–3.52); p = 0.85 | 93.4%; p < 0.001 | 0.04                      |

**Fig. 2.** Forest plot of mortality rate in solid organ transplant recipients compared with the general population for the main analysis, including only studies providing adjusted outcome data.
population when appropriately matched for demographic features, comorbidities, and COVID-19 severity. Further studies are warranted to explore long-term clinical outcomes in SOT recipients compared with the general population.

Transparency declaration
No conflicts of interest to declare. This systematic review was developed as part of the ORCHESTRA project cohort (Connecting European Cohorts to increase common and effective SARS-CoV–2 Response), receiving funding from the European Union’s Horizon 2020 research and innovation program (Grant no. 101016167).

Author contributions
MiGa: conceptualization, data curation, formal analysis, and writing original draft; MR: data curation, and writing original draft; LB: data curation; CB: data curation; RP: data curation; ZP: data curation; FF: data curation; MNPG: data curation; AMM: data curation; HP: data curation; CB: data curation; RP: data curation; ZP: data curation; LB: data curation; Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Inci J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2020;360:4310.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.039.

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