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.

Clinical Microbiology and Infection 28 (2022) 1057–1065

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Systematic review

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

Milo Gatti [1, 2], Matteo Rinaldi [1, 2], Linda Bussini [1, 2], Cecilia Bonazzetti [1, 2], Renato Pascale [1, 2], Zeno Pasquini [1, 2], Francesca Fani [1, 2], Mariana Nunes Pinho Guedes [3], Anna Maria Azzini [3], Elena Carrara [3], Zaira R. Palacios-Baena [4, 5], Giulia Caponcello [4], Eduardo Reyna-Villasmil [4], Evelina Tacconelli [3], Jesús Rodríguez-Baño [4, 5], Pierluigi Viale [1, 2], Maddalena Giannella [1, 2, *] on behalf of the ORCHESTRA study group

[1] Infectious Diseases Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
[2] Department of Medical and Surgical Sciences, University of Bologna, Italy
[3] Division of Infectious Diseases, Department of Diagnostics and Public Health, University of Verona, Verona, Italy
[4] Infectious Diseases and Microbiology Unit, Hospital Universitario Virgen Macarena and Department of Medicine, University of Sevilla/Biomedicines Institute of Sevilla, Sevilla, Spain
[5] Centro de Investigación Biomédica en Red en Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain

ARTICLE INFO

Article history:
Received 16 December 2021
Received in revised form
16 February 2022
Accepted 24 February 2022
Available online 12 March 2022

Editor: L Leibovici

Keywords:
30-Day mortality rate
Clinical outcome
COVID-19
Solid organ transplant recipients
Superinfections

ABSTRACT

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 with COVID-19 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; $I^2 = 33.9\%$). 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.
Milo Gatti, Clin Microbiol Infect 2022;28:1057

* Corresponding author. Maddalena Giannella, Infectious Diseases Unit, IRCCS Policlinico Sant'Orsola, Via Massarenti 11, 40137 Bologna, Italy.
E-mail address: maddalena.giannella@unibo.it (M. Giannella).

https://doi.org/10.1016/j.cmi.2022.02.039
1198-743X/

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 term 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 searched a predefined group for removal of duplicates. The reference lists of included studies were screened to identify any potentially relevant article.

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 χ^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 for Windows (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 preponderance (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, 0.35–3.52), 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

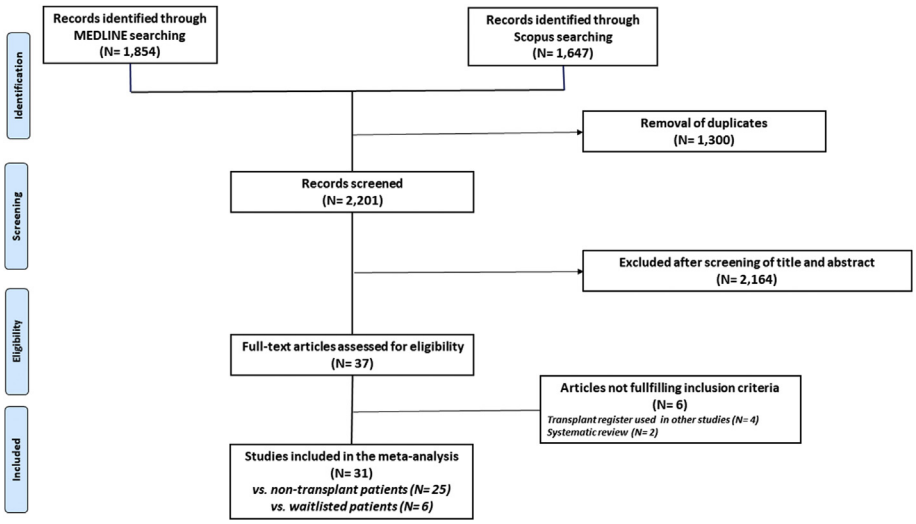

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram for study selection.

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), Miarons 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

Table 1
Main features of included studies

Study reference	Stud design	Country	Time period	No. of enrolled patients (SOT vs. general population)	Age (y), mean or median	Sex (male), %	Intervention group (SOT)					Comparator group (general population)
							Liver	Kidney	Heart	Lung	Combined	
Chavarot et al. [31]	Retrospective case-control study	France	26/02/2020–22/05/2020	83 vs. 83	64.7 vs. 67.5	64.0 vs. 57.9	0	83	0	0	0	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
Hilbrands et al. [32]	Prospective multicentre cohort study	The Netherlands	01/02/2020–01/05/2020	305 vs. 768	60 vs. 67	62.0 vs. 60.0	0	305	0	0	0	Patients undergoing scheduled intermittent haemodialysis
Colmenero et al. [33]	Prospective nation-wide study	Spain	28/02/2020–07/04/2020	111 vs. 146 690	65.3 vs. N/A	71.2 vs. N/A	111	0	0	0	0	General population from national COVID-19 database balanced for age and sex
McClenaghan et al. [34]	Retrospective cohort study	Worldwide	Beginning pandemic–13/06/2020	32 vs. 149	38 vs. 24	62.5 vs. 47.7	2	0	0	28	2	Patients affected by cystic fibrosis included in an international register and affected by COVID-19
Monreal et al. [35]	Retrospective case-control study	Spain	Beginning pandemic–15/04/2020	9 vs. 687	65.5 vs. 64	66.7 vs. 74.1	2	7	0	0	0	Hospitalized patients affected by COVID-19 with no autoimmune disease or receiving immunosuppressant agents
Najafi et al. [36]	Retrospective cohort study	Iran	21/02/2020–02/08/2020	35 vs. 451	N/A	N/A	0	35	0	0	0	Hospitalized patients affected by COVID-19 with no chronic kidney disease
Ravanan et al. [37]	Retrospective cohort study	UK	01/02/2020–20/05/2020	597 vs. 197	56 vs. 53	64.8 vs. 61.4	64	470	23	13	3	SOT waitlisted patients affected by COVID-19
Craig-Schapiro et al. [38]	Retrospective case-control study	United States	13/03/2020–20/05/2020	80 vs. 56	57 vs. 60	70.0 vs. 66.0	0	80	0	0	0	Kidney transplant waitlisted patients affected by COVID-19
Webb et al. [6]	Prospective multicentre cohort study	United Kingdom/ United States	25/03/2020–26/06/2020	151 vs. 627	60 vs. 73	68.0 vs. 52.0	151	0	0	0	0	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
Fisher et al. [9]	Prospective cohort study	United States	10/03/2020–01/09/2020	128 vs. 3907	60 vs. 60	61.7 vs. 61.7	12	113	6	0	3	Patients hospitalized with COVID-19 matched for age, sex, race, ethnicity, BMI, hypertension, diabetes mellitus, congestive heart failure, and obesity
Hadi et al. [25]	Retrospective cohort study	United States	20/01/2020–30/09/2020	2289 vs. 2289	54.5 vs. 55.2	59.3 vs. 61.1	418	1740	262	180	0	General population affected by COVID-19 retrieved from health care databases including large academic organization, tertiary care facilities, and outpatient satellite clinics. Patients were matched for race, age, diabetes, hypertension, chronic lung disease, nicotine dependence, heart failure, ischaemic heart disease, BMI, and sex
Molnar et al. [26]	Retrospective multicentric cohort study	United States	04/03/2020–05/06/2020	98 vs. 288	58 vs. 61	73.0 vs. 71.0	14	67	17	4	4	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
Pereira et al. [27]	Retrospective case-control study	United States	10/03/2020–30/05/2020	117 vs. 350	61 vs. N/A	65.0 vs. 67.0	12	92	22	25	34	Adults hospitalized with COVID-19 matched 3:1 for age categories, sex, BMI, race, ethnicity, hypertension, and diabetes
Hardesty et al. [28]	Retrospective case-control study	United States	01/03/2020–18/05/2020	11 vs. 44	55 vs. 55	36.3 vs. 38.6	0	11	0	0	0	Adults hospitalized with COVID-19 matched for age and sex
Trapani et al. [13]	Retrospective cohort study	Italy	21/02/2020–22/06/2020	450 vs. 238 895	59.1 vs. 61.4	75.6 vs. 45.7	89	285	53	15	8	All Italian patients affected by COVID-19 retrieved from national COVID-19 database up to 22/06/2020
Avery et al. [14]	Retrospective case-control study	United States	01/03/2020–21/08/2020	45 vs. 2427	59 vs. 59	53.3 vs. 51.9	N/A	N/A	N/A	N/A	N/A	Dataset of inpatient patients matched for age, sex, race, oxygen therapy requirement at admission, and severity score at admission

(*continued on next page*)

Table 1 (*continued*)

Study reference	Stud design	Country	Time period	No. of enrolled patients (SOT vs. general population)	Age (y), mean or median	Sex (male), %	Intervention group (SOT)					Comparator group (general population)
							Liver	Kidney	Heart	Lung	Combined	
Caillard et al. [15]	Retrospective case-control study	France	01/03/2020–30/04/2020	273 vs. 273	62 vs. 63	66.3 vs. 63.4	0	273	0	0	0	Nonimmunosuppressed adults with COVID-19 hospitalized at Strasbourg Hospital and matched for age, BMI, cardiovascular and respiratory diseases, cancer, and diabetes
Ozturk et al. [16]	Retrospective multicentre study	Turkey	17/04/2020–06/06/2020	81 vs. 450	48 vs. 51	59.3 vs. 50.2	0	81	0	0	0	Patients admitted to nephrology clinics exhibiting no intermittent haemodialysis/chronic kidney disease status, and matched for age, sex, diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease, and renal function
Mamode et al. [17]	Retrospective cohort study	United Kingdom	01/03/2020–30/04/2020	121 vs. 52	56.2 vs. 54.4	71.1 vs. 63.5	0	121	0	0	8	Kidney or kidney/pancreas transplant candidates affected by COVID-19
Linares et al. [7]	Prospective cohort study	Spain	06/03/2020–24/05/2020	41 vs. 220	58 vs. 63	65.9 vs. 65.5	4	32	3	0	2	Patients hospitalized with COVID-19 and matched for age, sex, hypertension, lung disease, severity of COVID-19, and use of anticytokine agents
Chaudhry et al. [18]	Retrospective case-control	United States	20/03/2020–18/04/2020	35 vs. 100	62 vs. 60	65.7 vs. 50.0	0	26	5	4	0	Convenience sample of consecutive hospitalized non-transplant recipients affected by COVID-19
Darilmaz Yuce et al. [19]	Retrospective case-control	Turkey	03/2020–01/2021	23 vs. 336	49.8 vs. 57.5	78.3 vs. 57.8	6	17	0	0	0	Patients hospitalized for COVID-19 without pre-existing comorbidities
Mansoor et al. [20]	Retrospective cohort study	United States	01/01/2020–23/06/2020	125 vs. 125	57.0 vs. 59.8	65.6 vs. 68.0	125	0	0	0	0	Patients with COVID-19 retrieved from health research network balanced for age, race, and key comorbidities
Nair et al. [21]	Retrospective case-control study	United States	01/03/2020–27/04/2020	82 vs. 1625	61.8 vs. 62.7	68.3 vs. 68.7	3	69	6	1	3	Patients hospitalized with COVID-19 during the same period and matched for age, sex, diabetes, hypertension, and cardiovascular disease
Ge et al. [22]	Retrospective cohort study	Canada	15/01/2020–31/12/2020	176 vs. 167 324	N/A	N/A	N/A	N/A	N/A	N/A	N/A	All patients living in Ontario, Canada, affected by COVID-19 during the study period retrieved from dedicated electronic database
Ringer et al. [23]	Retrospective cohort study	United States	10/03/2020–15/05/2020	30 vs. 60	60.0 vs. 60.5	53.3 vs. 60.0	3	26	1	0	0	Hospitalized patients affected by COVID-19 matched for age, BMI, diabetes, and hypertension
Santos et al. [24]	Retrospective cohort study	United States	01/11/2019–31/01/2021	62 vs. 20	58 vs. 52	66.1 vs. 75.0	0	57	0	0	5	Kidney or kidney/pancreas waitlisted patients
Rinaldi et al. [29]	Prospective multicentre cohort study	Italy	15/03/2020–30/04/2020	24 vs. 861	62 vs. 70	62.5 vs. 70.0	2	22	0	0	0	Adults hospitalized with COVID-19
Miarons et al. [5]	Retrospective cohort study	Spain	11/03/2020–25/04/2020	46 vs. 166	62.7 vs. 66.0	71.7 vs. 73.5	3	30	0	13	0	Adults hospitalized with COVID-19 and matched for age, sex, and age-adjusted Charlson's index
Arya et al. [4]	Retrospective cohort study	United States	15/03/2020–16/09/2020	58 vs. 14 975	57.4 vs. 52.3	62 vs. 45	8	38	5	0	7	General patients with COVID-19 retrieved from health care system
Sharma et al. [30]	Retrospective case-control study	United States	10/03/2020–15/05/2020	41 vs. 121	60.0 vs. 60.0	83.0 vs. 49.6	8	16	9	3	5	Adults non-SOT, non-waitlisted affected by COVID-19 and matched for age, race, and admission status

BMI: body mass index; N/A: not available; SOT; solid organ transplant.

different immunosuppressive 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

Table 2
Results of meta-analysis for primary and secondary outcomes

Outcome	Studies, *n*	No. of patients (transplant patients vs. comparators)	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
Secondary outcome							
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	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

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

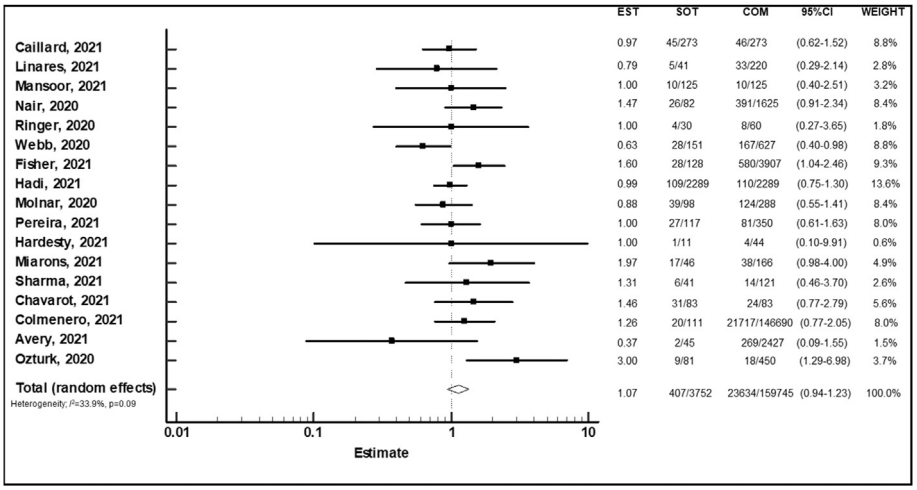

Fig. 2. Forest plot of mortality rate in solid organ transplant recipients compared with the general population for the main analysis, including only studies providing adjusted outcome data.

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; EC: review and editing of original draft; ZPB: review and editing of original draft; GC: data curation; ERV: data curation; ET: conceptualization, review and editing of manuscript; JRB: conceptualization, review and editing of manuscript; PV: conceptualization, review, and editing of manuscript; MaGi: conceptualization, data curation, writing original draft, review and editing of final manuscript.

Appendix A. Supplementary data

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

References

[1] Baek MS, Lee MT, Kim WY, Choi JC, Jung SY. COVID-19-related outcomes in immunocompromised patients: a nationwide study in Korea. PLoS One 2021;16. e0257641.
[2] Suárez-García I, Perales-Fraile I, González-García A, Muñoz-Blanco A, Manzano L, Fabregate M, et al. In-hospital mortality among immunosuppressed patients with COVID-19: Analysis from a national cohort in Spain. PLoS One 2021;16. e0255524.
[3] Danziger-Isakov L, Blumberg EA, Manuel O, Sester M. Impact of COVID-19 in solid organ transplant recipients. Am J Transplant 2021;21:925–37.
[4] Arya A, Li M, Aburjania N, Singh P, Royer T, Moss S, et al. COVID-19 in solid organ transplantation: disease severity and clinical update. Transplant Proc 2021;53:1227–36.
[5] Miarons M, Larrosa-García M, García-García S, Los-Arcos I, Moreso F, Berastegui C, et al. COVID-19 in solid organ transplantation: a matched retrospective cohort study and evaluation of immunosuppression management. Transplantation 2021;105:138–50.
[6] Webb GJ, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, et al. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. Lancet Gastroenterol Hepatol 2020;5:1008–16.
[7] Linares L, Cofan F, Diekmann F, Herrera S, Marcos MA, Castel MA, et al. A propensity score-matched analysis of mortality in solid organ transplant patients with COVID-19 compared to non-solid organ transplant patients. PLoS One 2021;16. e0247251.
[8] Mansour O, Keller S, Katz M, Townsend JL. Outpatient parenteral antimicrobial therapy in the time of COVID-19: the urgent need for better insurance coverage. Open Forum Infect Dis 2020;7. ofaa287.
[9] Fisher AM, Schlauch D, Mulloy M, Dao A, Reyad AI, Correll M, et al. Outcomes of COVID-19 in hospitalized solid organ transplant recipients compared to a matched cohort of non-transplant patients at a national healthcare system in the United States. Clin Transplant 2021;35. e14216.
[10] Moher D, Liberati A, Tetzlaff J, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6. e1000097.
[11] Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355. i4919.
[12] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[13] Trapani S, Masiero L, Puoti F, Rota MC, Del Manso M, Lombardini L, et al. Incidence and outcome of SARS-CoV-2 infection on solid organ transplantation recipients: a nationwide population-based study. Am J Transplant 2021;21:2509–21.
[14] Avery RK, Chiang TPY, Marr KA, Brennan DC, Sait AS, Garibaldi BT, et al. Inpatient COVID-19 outcomes in solid organ transplant recipients compared to non-solid organ transplant patients: a retrospective cohort. Am J Transplant 2021;21:2498–508.
[15] Caillard S, Chavarot N, Francois H, Matignon M, Greze C, Kamar N, et al. Is COVID-19 infection more severe in kidney transplant recipients? Am J Transplant 2021;21:1295–303.
[16] Ozturk S, Turgutalp K, Arici M, Odabas AR, Altiparmak MR, Aydin Z, et al. Mortality analysis of COVID-19 infection in chronic kidney disease, haemodialysis and renal transplant patients compared with patients without kidney disease: a nationwide analysis from Turkey. Nephrol Dial Transplant 2020;35:2083–95.
[17] Mamode N, Ahmed Z, Jones G, Banga N, Motallebzadeh R, Tolley H, et al. Mortality rates in transplant recipients and transplantation candidates in a high-prevalence COVID-19 environment. Transplantation 2021;105:212–5.
[18] Chaudhry ZS, Williams JD, Vahia A, Fadel R, Acosta TP, Prashar R, et al. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: a cohort study. Am J Transplant 2020;20:3051–60.
[19] Darılmaz Yüce G, Ulubay G, Tek K, Bozbaş SS, Erol C, Büyükaşık P, et al. Clinical features of SARS-CoV-2 infection in patients undergoing solid-organ transplant. Exp Clin Transplant: Baskent University experience; 2021 [Epub ahead of print].
[20] Mansoor E, Perez A, Abou-Saleh M, Sclair SN, Cohen S, Cooper GS, et al. Clinical characteristics, hospitalization, and mortality rates of coronavirus disease 2019 among liver transplant patients in the United States: a multicenter research network study. Gastroenterology 2021;160:459–62. e1.
[21] Nair V, Jandovitz N, Hirsch JS, Abate M, Satapathy SK, Roth N, et al. An early experience on the effect of solid organ transplant status on hospitalized COVID-19 patients. Am J Transplant 2021;21:2522–31.
[22] Ge E, Li Y, Wu S, Candido E, Wei X. Association of pre-existing comorbidities with mortality and disease severity among 167,500 individuals with COVID-19 in Canada: a population-based cohort study. PLoS One 2021;16. e0258154.
[23] Ringer M, Azmy V, Kaman K, Tang D, Cheung H, Azar MM, et al. A retrospective matched cohort single-center study evaluating outcomes of COVID-19 and the impact of immunomodulation on COVID-19-related cytokine release syndrome in solid organ transplant recipients. Transpl Infect Dis 2021;23. e13556.
[24] Santos CAQ, Rhee Y, Hollinger EF, Olaitan OK, Schadde E, Peev V, et al. Comparative incidence and outcomes of COVID-19 in kidney or kidney-pancreas transplant recipients versus kidney or kidney-pancreas waitlisted patients: a single-center study. Clin Transplant 2021;35. e14362.
[25] Hadi YB, Naqvi SFZ, Kupec JT, Sofka S, Sarwari A. Outcomes of COVID-19 in solid organ transplant recipients: a propensity-matched analysis of a large research network. Transplantation 2021;105:1365–71.
[26] Molnar MZ, Bhalla A, Azhar A, Tsujita M, Talwar M, Balaraman V, et al. Outcomes of critically ill solid organ transplant patients with COVID-19 in the United States. Am J Transplant 2020;20:3061–71.
[27] Pereira MR, Arcasoy S, Farr MA, Mohan S, Emond JC, Tsapepas DS, et al. Outcomes of COVID-19 in solid organ transplant recipients: a matched cohort study. Transpl Infect Dis 2021;23. e13637.
[28] Hardesty A, Pandita A, Vieira K, Rogers R, Merhi B, Osband AJ, et al. Coronavirus disease 2019 in kidney transplant recipients: single-center experience and case-control study. Transplant Proc 2021;53:1187–93.
[29] Rinaldi M, Bartoletti M, Bussini L, Pancaldi L, Pascale R, Comai G, et al. COVID-19 in solid organ transplant recipients: No difference in survival compared to general population. Transpl Infect Dis 2021;23. e13421.
[30] Sharma P, Chen V, Fung CM, Troost JP, Patel VN, Combs M, et al. COVID-19 outcomes among solid organ transplant recipients: a case-control study. Transplantation 2021;105:128–37.
[31] Chavarot N, Gueguen J, Bonnet G, Jdidou M, Trimaille A, Burger C, et al. COVID-19 severity in kidney transplant recipients is similar to nontransplant patients with similar comorbidities. Am J Transplant 2021;21:1285–94.
[32] Hilbrands LB, Duivenvoorden R, Vart P, Franssen CFM, Hemmelder MH, Jager KJ, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. Nephrol Dial Transplant 2020;35:1973–83.
[33] Colmenero J, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. J Hepatol 2021;74:148–55.
[34] McClenaghan E, Cosgriff R, Brownlee K, Ahern S, Burgel PR, Byrnes CA, et al. The global impact of SARS-CoV-2 in 181 people with cystic fibrosis. J Cyst Fibros 2020;19:868–71.
[35] Monreal E, Sainz de la Maza S, Fernández-Velasco JI, Natera-Villalba E, Rita CG, Rodríguez-Jorge F, et al. The impact of immunosuppression and autoimmune disease on severe outcomes in patients hospitalized with COVID-19. J Clin Immunol 2021;41:315–23.
[36] Najafi N, Akbari R, Lotfi Z, Makhough A, Vahedi M, Asgharpour M, et al. The clinical course and prognostic factors of COVID-19 in patients with chronic kidney disease, a study in six centers. Iran J Kidney Dis 2021;15:279–87.
[37] Ravanan R, Callaghan CJ, Mumford L, Ushiro-Lumb I, Thorburn D, Casey J, et al. SARS-CoV-2 infection and early mortality of waitlisted and solid organ

transplant recipients in England: a national cohort study. Am J Transplant 2020;20:3008–18.
[38] Craig-Schapiro R, Salinas T, Lubetzky M, Abel BT, Sultan S, Lee JR, et al. COVID-19 outcomes in patients waitlisted for kidney transplantation and kidney transplant recipients. Am J Transplant 2021;21:1576–85.
[39] Nandy K, Salunke A, Pathak SK, Pandey A, Doctor C, Puj K, et al. Coronavirus disease (COVID-19): a systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. Diabetes Metab Syndr 2020;14:1017–25.
[40] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
[41] Fung M, Babik JM. COVID-19 in immunocompromised hosts: what we know so far. Clin Infect Dis 2021;72:340–50.
[42] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
[43] Romanelli A, Mascolo S. Immunosuppression drug-related and clinical manifestation of Coronavirus disease 2019: a therapeutical hypothesis. Am J Transplant 2020;20:1947–8.
[44] Raja MA, Mendoza MA, Villavicencio A, Anjan S, Reynolds JM, Kittipibul V, et al. COVID-19 in solid organ transplant recipients: a systematic review and meta-analysis of current literature. Transplant Rev (Orlando) 2021;35:100588.
[45] Heldman MR, Kates OS. COVID-19 in solid organ transplant recipients: a review of the current literature. Curr Treat Options Infect Dis 2021:1–16.
[46] Ventura-Aguiar P, Campistol JM, Diekmann F. Safety of mTOR inhibitors in adult solid organ transplantation. Expert Opin Drug Saf 2016;15:303–19.
[47] Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. Int J Antimicrob Agents 2020;55:105946.
[48] Ao G, Wang Y, Qi X, Nasr B, Bao M, Gao M, et al. The association between severe or death COVID-19 and solid organ transplantation: a systematic review and meta-analysis. Transplant Rev (Orlando) 2021;35:100628.
[49] Iuliano AD, Brunkard JM, Boehmer TK, Peterson E, Adjei S, Binder AM, et al. Trends in disease severity and health care utilization during the early Omicron variant period compared with previous SARS-CoV-2 high transmission periods–United States, December 2020–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:146–52.