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SARS-CoV-2 in Solid Organ Transplant Recipients: A Structured Review of 2020

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ABSTRACT

Background. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is challenging health systems all over the world. Particularly high-risk groups show considerable mortality rates after infection. In 2020, a huge number of case reports, case series, and consecutively various systematic reviews have been published reporting on morbidity and mortality risk connected with SARS-CoV-2 in solid organ transplant (SOT) recipients. However, this vast array of publications resulted in an increasing complexity of the field, overwhelming even for the expert reader.

Methods. We performed a structured literature review comprising electronic databases, transplant journals, and literature from previous systematic reviews covering the entire year 2020. From 164 included articles, we identified 3451 cases of SARS-CoV-2−infected SOT recipients.

Results. Infections resulted in a hospitalization rate of 84% and 24% intensive care unit admissions in the included patients. Whereas 53.6% of patients were reported to have recovered, cross-sectional overall mortality reported after coronavirus disease 2019 (COVID-19) was at 21.1%. Synoptic data concerning immunosuppressive medication attested to the reduction or withdrawal of antimetabolites (81.9%) and calcineurin inhibitors (48.9%) as a frequent adjustment. In contrast, steroids were reported to be increased in 46.8% of SOT recipients.

Conclusions. COVID-19 in SOT recipients is associated with high morbidity and mortality worldwide. Conforming with current guidelines, modifications of immunosuppressive therapies mostly comprised a reduction or withdrawal of antimetabolites and calcineurin inhibitors, while frequently maintaining or even increasing steroids. Here, we provide an accessible overview to the topic and synoptic estimates of expectable outcomes regarding in-hospital mortality of SOT recipients with COVID-19.

SINCE the World Health Organization declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak starting in 2019 a pandemic, many countries have been

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severely affected by continuously rising infection rates. This unprecedented situation has challenged health systems on a global scale, straining patient treatment inter alia because of an altered risk assessment for a variety of patient cohorts. Based on rapidly emerging data, factors such as age, diabetes mellitus, chronic lung disease, and hypertension have been identified to increase disease-related mortality [1]. This is why close attention has been paid to vulnerable patient populations. For instance, in patients undergoing surgery, an international cohort study has established an excessive mortality risk when patients became infected with SARS-CoV-2 directly before or during the first month after surgery [2]. Although this risk profile is most probably modulated by a variety of factors, the scale of these effects is unparalleled and calls for cautionary and preventative measures in regions affected by SARS-CoV-2 propagation.

Against this background, patients who received a solid organ transplant (SOT) have been identified as another high-risk group. An analysis of more than 17 million electronic health care records from the United Kingdom, including >10,000 deaths related to coronavirus disease 2019 (COVID-19), suggests a 6-fold increased sex- and age-adjusted risk of death (95% confidence interval, 4.73-7.61) in SOT recipients [3]. This relates both to patients who recently underwent transplantation and long-term SOT recipients. In addition to immunosuppression, transplant recipients frequently have additional risk factors that may favor detrimental outcomes. Meanwhile, an array of case reports, case series as well as case-control studies has been published, predominantly confirming an increased mortality risk for SOT recipients when infected with SARS-CoV-2 and developing COVID-19.

Multiple systematic reviews on the topic have become available throughout 2020, with steadily increasing case numbers. However, the massive increment of publications on SARS-CoV-2 has resulted in an unprecedented complexity of the field, which is overwhelming even for the expert reader [4]. This situation has also fostered a surge of non-peer−reviewed research published as preprints [5]. Although the rapid distribution of latest research findings represents a valuable tool to combat the pandemic, it is also linked to inherent limitations. Furthermore, pandemic pressure and the urge to catch up with the flood of information and findings already supplied by news and social media as well as in preprints has resulted in more rapid review by many scientific journals and the publication of preliminary reports. Taken together, revisiting available empirical data systematically seems highly relevant. Here, comprehensive synoptic analyses are a gateway to access the available literature, for example, allowing a broad-ranging overview and risk assessment for SARS-CoV-2 −infected SOT recipients, which may help with addressing the many urgent unanswered key questions arising in this context [6]. Thus, we performed a structured literature review, providing an overview that compiles all relevant scientific literature from January 1, 2020 until December 31, 2020, to produce a current synoptic assessment of mortality and clinical outcomes subsequent to infection and COVID-19 in SOT recipients, as well as a comprehensive summary of the relevant scientific literature that even a multitude of preceding systematic reviews falls short to provide so far [7-19].

MATERIALS AND METHODS

We performed a structured review searching for publications reporting on patients after SOT with confirmed SARS-CoV-2 infections and/or COVID-19. The search strategy conformed to applicable guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist [20] is available from the authors of this article on request). A total of 626 articles were identified by searching the electronic database MEDLINE through PubMed (https://pubmed.ncbi.nlm.nih.gov/) and the Cochrane library (https://www.cochranelibrary.com/). Respective search terms and search strings used to query electronic databases is available from the authors of this article on request. This search was complemented by screening reference lists as well as dedicated journals including the *American Journal of Transplantation* (Online ISSN: 1600-6143), *Transplantation* (Online ISSN: 1534-6080), and *Liver Transplantation* (Online ISSN: 1527-6473), identifying 160 additional articles through predefined search terms (including SARS-CoV-2, COVID-19, and transplantation). We searched for all articles published within the period from January 1, 2020, until December 31, 2020.

In addition, because of the high current interest in the topic, we also systematically searched PubMed for previously published systematic reviews relevant to the topic and identified 99 references from 13 systematic reviews (Table 1), totaling 728 references after duplicate removal to be screened.

In a first screening step, 519 of these publications were excluded and the 209 remaining articles were individually assessed and screened in detail for the relevant minimum required information defined by us. Characteristics searched for were SOT recipients 10 years or older with confirmed SARS-CoV-2 infection and/ or COVID-19. Additional essential information required before article inclusion were the number of SARS-CoV-2/COVID-19−positive SOT recipients, transplanted organs, and clinical outcomes. Review articles, unassignable registry data, surveys and non −English-language articles were excluded. After excluding 40 full-text-publications with reasons, 169 suitable articles were identified and 164 were included in the review (Fig 1). Five articles were removed because they are potentially reporting on the same set of patients.

Data were compiled and tabulated using Microsoft Excel (Microsoft Corporation, Redmond, Washington, United States); data analysis and visualization were performed by using the free and open-source programming language GNU R [21] with the additional packages easyPubMed [22] as well as ggplot2 [23]. Figures were drawn using Inkscape (https://inkscape.org) and Biorender (https://biorender.com/).

Data were processed to depict the relative number of cases up to each time point, both overall as well as separated by group (type of study as well as geographic area). Data are presented in total numbers and percentages. References to all included articles and extracted data used for evaluations with transparent and reproducible methodology are available from the authors on request.

RESULTS

Included Literature

This structured literature review identified 164 publications overall within our defined scope, which report on 3451 patients in total. The literature search strategy for the selection of scientific articles is illustrated in Fig 1. Most included studies were case reports (n = 89) [24-112], followed by cohort studies (n = 38) [113-150], case series (n = 26) [151-176], multicenter cohort studies or case series (n = 8) [177-184], and 3 case-control studies [185-187]. An overview on the largest patient cohorts is provided in Table 2.

Table 1. Characteristics of Previously Published Systematic Reviews

No.	Author	Period Until	Transplanted Organ(s)	Date Published	Included Articles, No.	Patients, No.	Mortality Rate, %
1	Gavriilidis et al. [9]	April 2020	Liver	06/25/2020	5	12	33.3
2	Hage et al. [11]	04/08/2020	SOT	05/07/2020	5	8	n.d.
3	Nacif et al. [16]	04/20/2020	SOT	06/03/2020	24	39	25.6
4	Imam et al. [12]	05/06/2020	Kidney	07/24/2020	21	58	15.5
5	González et al. [10]	05/15/2020	Kidney	06/05/2020	34	184	n.d.
6	Moosavi et al. [15]	05/22/2020	SOT	07/24/2020	50	337	22.8
7	Oltean et al. [17]	06/04/2020	Kidney	07/13/2020	12	204	21.2
8	Aziz et al. [7]	06/06/2020	SOT	09/15/2020	49	403	21
9	Fraser et al. [8]	06/15/2020	Liver	07/30/2020	15	223	19.3
10	Marinaki et al. [14]	07/07/2020	Kidney	09/16/2020	63	420	22.1
11	Mahaling-asivam et al. [13]	08/04/2020	Kidney	11/03/2020	20	1955	n.d.
12	Raja et al. [19]	10/09/2020	SOT	11/14/2020	60	2772	18.6
13	Phanish et al. [18]	10/15/2020	Kidney	12/19/2020	16	1494	24

n.d., no data; SOT, solid organ transplant.

Patient Demographics

Most included patients had received a kidney allograft (n = 2439; 70.7%), followed by liver (n = 499; 14.5%), heart (n = 274; 7.9%), and lung (n = 170; 4.9%) transplants. Only a minor fraction had multiple organ (n = 59; 1.7%) transplants (Fig 2A). An analysis of the global distribution revealed that the largest proportion of included patients were treated either in Europe (n = 1481; 42.9%) or North America (n = 1279; 37.1%), whereas a smaller number of patients was reported from countries located in Asia (538; 15.6%). Additionally, 153 patients (4.4%) were reported from other countries/regions or could not be allocated. Overall, only 2 patients were reported from South American countries (Fig 2B).

Clinical Course and Outcome

Among 3451 patients reported with confirmed SARS-CoV-2 infection and/or COVID-19, data on the clinical course and outcome were available for 3353 patients (97.2%). According to this, 84% required hospitalization, whereas the remaining 536 patients were treated in an outpatient setting. For one study, respective data were unavailable [156] and hospitalization was assumed as the default option. Among all included 2817 hospitalized patients, 53.6% recovered from SARS-CoV-2 infection or could be discharged. Altogether 21.1% (n = 709) of patients were deceased at the time of data reporting and 10.2% of the patients remained affected by the disease, whereas 15.1% remained with an unknown outcome (Fig 2C). For 57.9% of the patients, changes in immunosuppressive medication were reported, and for at least 22.6% of SOT recipients disease progression involved an impaired allograft function (Fig 2D).

Development of Publications on COVID-19 and Transplantation Over Time

We further analyzed the types of publications and the geographical origin of the included studies throughout the year 2020, thereby revealing clear longitudinal trends for both origin and publication type. Starting with the SARS-CoV-2 outbreak, first reports on disease outcomes in SOT recipients became available from Asia. In spring 2020, when Europe was severely hit by a first SARS-CoV-2 wave, this resulted in increasing publication numbers reporting on SOT recipients. By mid-April 2020, also sizeable numbers of publications on SARS-CoV-2 and SOT recipients from North America were published. Relevant publications from other continents were only published late in 2020 and remained scarce compared with the publication output from Asia, Europe, and North America (Fig 3A).

Similar longitudinal trends can also be shown when analyzing the type of data published. Although early in the pandemic data on SARS-CoV-2 in SOT recipients were derived mainly from case reports, this was later followed by case series, with steadily increasing patient numbers reported in each publication and then succeeded by publications of cohort studies starting in late April 2020. Ultimately, also case-control studies became available but only in the second half of the year. However, their number remained small, thus accounting only for a minor proportion of patients reported (Fig 3A, B).

Management of Immunosuppressive Therapy

Among a subgroup of 1192 transplant recipients from 5 large cohorts [119,132,164,177,179], we analyzed the available data on modification and management of the immunosuppressive therapies. Accordingly, the most frequent measure mentioned was the reduction or withdrawal of antimetabolites in 81.9% of SOT recipients with SARS-CoV-2 infection initially receiving this treatment. Reduction or withdrawal of calcineurin inhibitors was also reported frequently (48.9%). In contrast, steroids have been increased in 46.8% of respective patients, while reporting a reduction or withdrawal remained an exception (1.3%) (Table 3).

To obtain a more conclusive picture, we additionally screened the most recent recommendations from national and international transplantation societies regarding the immunosuppressive management of SOT recipients with SARS-CoV-2 infection. We identified 6 clinical guidelines generally based on expert opinion and summarized their

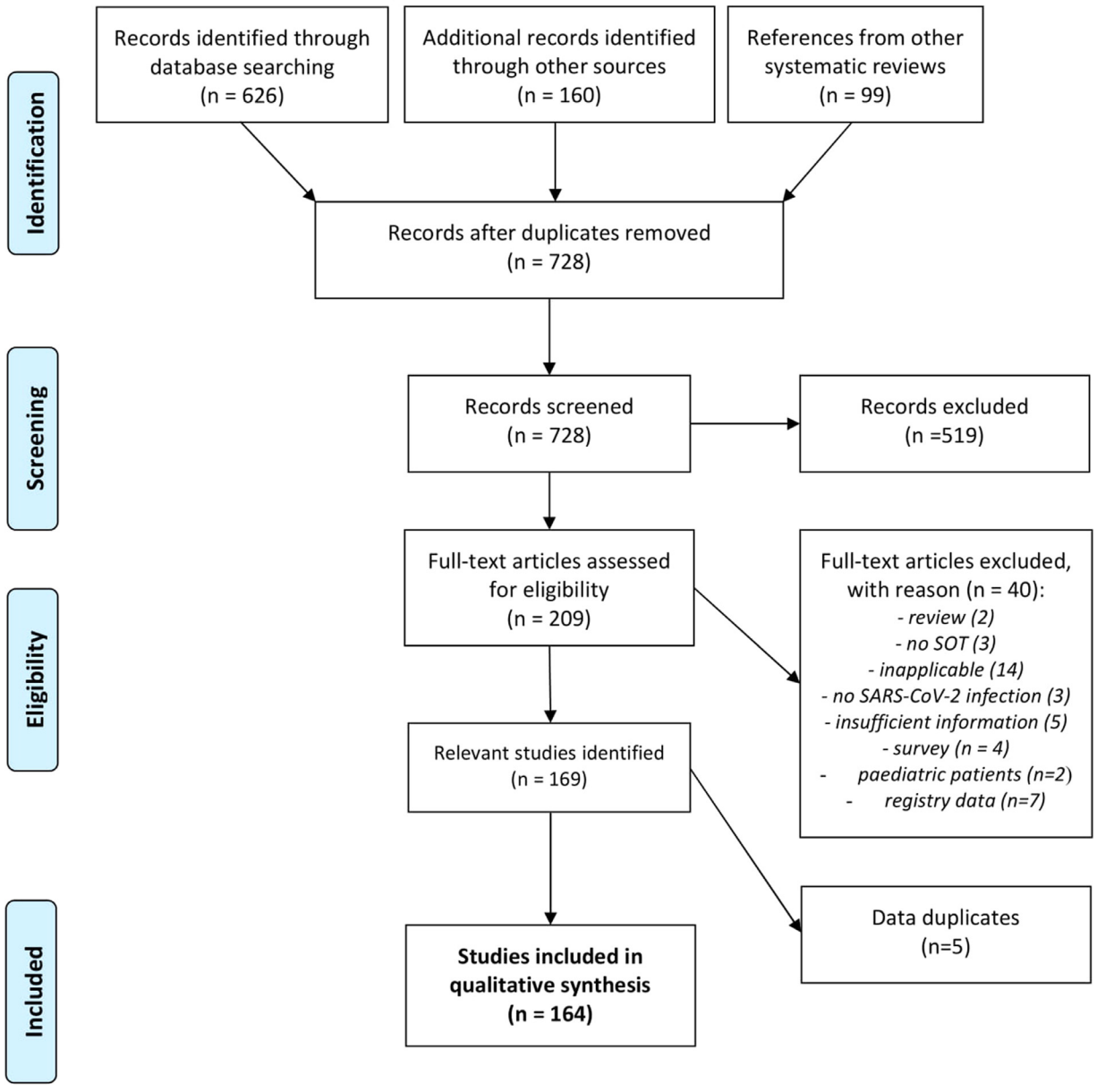

Fig 1. Flow diagram outlining the literature search strategy and selection of articles. The diagram depicts the different stages of our structured review including identification, screening, and selection of suitable articles. Articles were identified through searching MEDLINE, PubMed, and Cochrane databases, as well as additional sources for articles reporting on SOT recipients with SARS-CoV-2 infection or COVID-19. The used search strategy conforms to PRISMA guidelines [6]. Precise search terms and a PRISMA checklist as well as extracted data are available from the authors of this article on request. COVID-19, coronavirus disease 2019; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.

recommendations (Table 4) [188-193]. A broad consensus prevails, suggesting a critical consideration of the overall level of immunosuppression in SARS-CoV-2−infected SOT recipients based on established principles for managing infections in those patients. In patients with low risk of allograft rejection, decreasing immunosuppressive medication should be considered, especially in patients with severe COVID-19 disease. Here, guidelines consistently recommend withdrawal or reduction of antimetabolites as a first step, followed by reduction of calcineurin inhibitors. Although no guideline recommends the reduction of steroids, some do recommend the administration of dexamethasone (6 mg daily) for up to 10 days in patients who require oxygen supplementation or are mechanically ventilated.

Table 2. Overview of Cohort Studies and Largest Published Data Sets on Kidney, Liver, Heart, and Lung Transplant Recipients Infected With SARS-CoV-2

Author	Study Design	Origin	Patients, No.	Transplanted Organ(s)	Mortality Rate, %
Coll et al. [177]	Multicenter cohort study	Europe	665	Kidney/liver/heart/lung/other	23.5
Kute et al. [179]	Multicenter cohort study	Asia	250	Kidney	11.6
Azzi et al. [118]	Cohort study	North America	229	Kidney	20.5
Webb et al. [184]	Multicenter cohort study	Other	151	Liver	18.5
Cravedi et al. [127]	Cohort study	North America	144	Kidney	31.9
Favà et al. [131]	Cohort study	Europe	104	Kidney	26.9
Molnar et al. [180]	Cohort study	North America	98	Kidney/liver/heart/lung/other	39.8
Ozturk et al. [181]	Multicenter cohort study	Asia	81	Kidney	11.1
Craig-Schapiro et al. [126]	Cohort study	North America	80	Kidney	16.3
Ali et al. [117]	Cohort study	Asia	67	Kidney/liver/lung	3.0

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

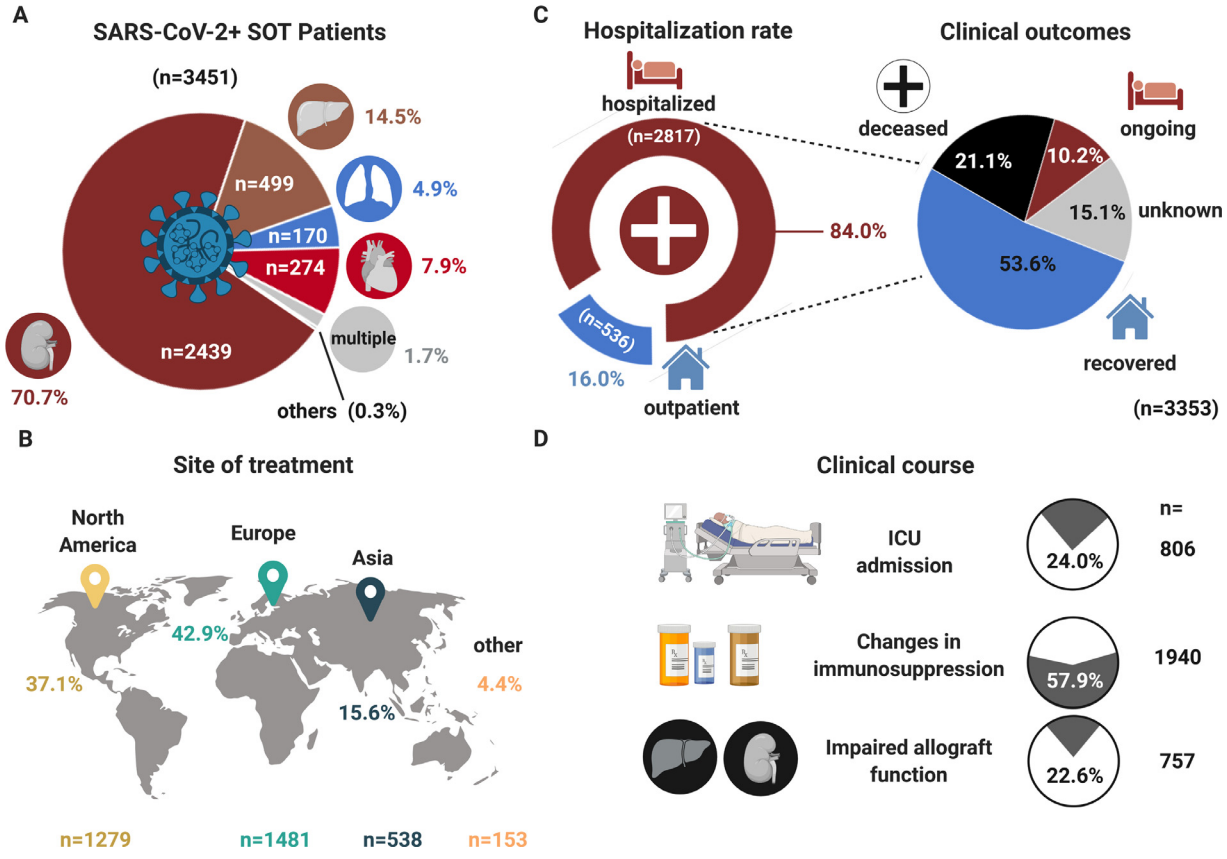

Fig 2. Synthesis of structured review results assessing SARS-CoV-2 infections in solid organ transplant recipients. Our structured review comprises 3451 cases of SOT recipients with confirmed SARS-CoV-2 infection (SARS-CoV-2+) and/or COVID-19 presented as a synopsis (respective source data are available from the authors). **(A)** The pie chart depicts % fractions of infected SOT recipients (subdivided into liver, lung, heart, and multiple organs). **(B)** Assigns numbers and % fractions of infected SOT recipients according to the local origin of the reports/their site of treatment. **(C)** Presents respective SOT recipients according to treatment, categorized either as hospitalized or as outpatient, as well as outcomes at the time of reporting, categorized into deceased/recovered and ongoing treatment. **(D)** Clinical outcomes of SOT recipients are presented as % fractions and numbers of patients among all cases requiring ICU admission, changes in immunosuppression, and patients experiencing an impaired transplant function linked to infection. COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT, solid organ transplant.

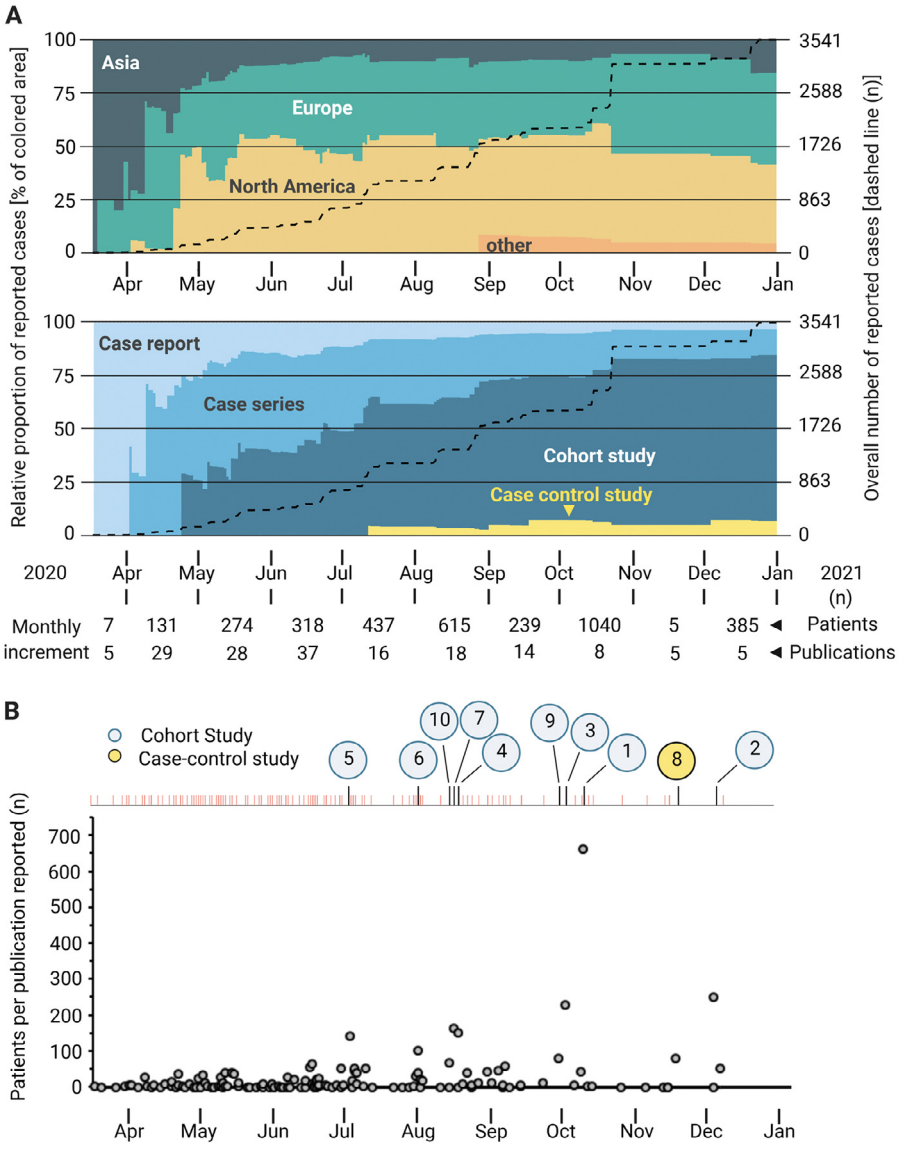

Fig 3. Comparison of publications on COVID-19 and transplantation over time. **(A)** The diagram illustrates the course of scientific information about COVID-19 made available (dates of first publication). A distinction is made between the origin of the studies (graph above) the types of publication (graph below). The dashed line represents overall numbers of patients; the colored area represents the relative number of patients reported until that time. **(B)** The graph depicts the number of patients per publication reported over time. The numbers from 1 to 10 illustrate the 10 studies with the largest patient collective, as presented in Table 2. COVID-19, coronavirus disease 2019.

DISCUSSION

Based on data from other patient cohorts, it was reasonable to assume early on in the pandemic that SOT recipients do also exhibit a high-risk profile after infection with SARS-CoV-2 because of indispensable immunosuppressive medication and a high rate of additional medical risk factors. Data from first small cohort studies that had become available in kidney transplant recipients confirmed this notion, with reported mortality rates of up to 30% [168]. A case-control study with a more robust study design conducted in 151 liver transplant recipients and 627 hospitalized control patients who were not transplant recipients surprisingly concluded that SOT status by itself was not independently associated with higher mortality. Instead, multivariate analysis established that mortality was primarily associated with age and disease severity [184]. These two examples may demonstrate the broad range of published information on SARS-CoV-2 in SOT recipients, while at the same time calling for careful synoptic assessment of the available literature to support a better understanding of the overall risk involved for SARS-CoV-2−infected SOT recipients.

Here, our comprehensive evaluations confirm that during the course of 2020 better studies with a more robust scientific design have increasingly become available. However, the SARS-CoV-2 pandemic has also fundamentally impacted research publishing, as reflected by increasing submission numbers, preprint rush, expedited review, and in some cases retractions, even in high-profile peer-reviewed journals [5]. Therefore, our work may provide a robust overview and facilitate orientation within the tsunami of information linked to COVID-19.

Table 3. Adjustments of Immunosuppressive Drug Regimen in Selected Cohort Studies/Case Series of Transplant Recipients Infected With SARS-CoV-2

Author	Transplanted Organ(s)	Study Cohort, No.	Antimetabolites, n/N (%)*				Calcineurin Inhibitors, n/N (%)†				Steroids, n/N (%)‡			
			↔	X	↓	↑↔	X	↓	↑	↔	X	↓	↑
Coll et al. [177]	Kidney, HSCT, liver, lung, pancreas, multivisceral	778	92/389 (23.7)	273/389 (70.2)	24/389 (6.2)	0175/495 (35.4)	181/495 (36.6)	134/495 (27.1)	5/495 (1)	197/460 (42.8)	8/460 (1.7)	2/460 (0.4)	253/460 (55)
Kute et al. [179]	Kidney	250	0	188/250 (75.2)	62/250 (24.8)	0165/236 (69.9)	21/236 (8.9)	50/236 (21.2)	0	150/250 (60)	0	0	100/250 (40)
Bechetti et al. [119]	Liver	57	15/26 (57.7)	10/26 (38.5)	1/26 (3.8)	031/50 (62)	7/50 (14)	12/50 (24)	0	10/10 (100)	0	0	0
Lubetzky et al. [164]	Kidney	54	13/52† (25)	24/52 (46.2)	15/52 (28.8)	035/52 (67.3)	0	17/52 (32.7)	0	22/27 (81.5)	0	0	5/27 (18.5)
Felldin et al. [132]	Kidney, liver, heart, lung, liver-kidney, kidney-heart	53	17/41 (41.5)	19/41 (46.3)	5/41 (12.2)	042/53 (79.2)	3/53 (5.7)	8/53 (15.1)	0	30/40 (75)	0	0	10/40 (25)
Total		1192	137/758 (18.1)	514/758 (67.8)	107/758 (14.1)	0448/886 (50.6)	212/886 (23.9)	221/886 (24.9)	5/886 (0.6)	409/787 (52)	8/787 (1)	2/787 (0.3)	368/787 (46.8)

↔, no (substantial) change; ↓, dose reduction; ↑, dose increase; HSCT, hematopoietic stem cell transplant; n, quantity; N, patient population among study cohort that initially received the respective treatment; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; X, withdrawal.

* Azathioprine and/or mycophenolate mofetil.

† Cyclosporine and/or tacrolimus.

‡ No reduction/≤50% reduction.

Our synoptic review incorporates 3451 cases of SOT recipients with confirmed SARS-CoV-2 infection and/or COVID-19, predominantly from the Unites States and Europe, and therefore sheds additional light on key issues in SOT recipients exposed to SARS-CoV-2, facilitating an easy overview. In contrast, the largest patient cohort previously reported on in a systematic review were considerably smaller with 2772 SOT recipients [19] and 1955 and 223 for kidney [13] and liver [8] transplant recipients, respectively. About 70.7% of patients included by us were kidney transplant recipients, which is relevant since chronic kidney disease has been implicated in COVID-19−related mortality [194]. The overall mortality in our data set was 21.1%, which is well in line with previous work [7,8,14,15,17]. Compared with the status quo before the pandemic, these data are alarming, even when assuming the very low end of estimates concerning the COVID-19−related case fatality rate reported at only 8.1% and 4.6% in men and women, respectively [195]. However, a large observational study in more than 10,000 hospitalized patients in Germany found in-hospital mortality rates at 22% among the general population [196], which is in line with our review findings among SOT recipients.

Our compiled data suggest that SARS-CoV-2 infection and COVID-19 resulted in a hospitalization rate of 84% with 24% of patients requiring intensive care unit admission. We may speculate that the hospitalization rate derived from respective articles published in 2020 is most likely an overestimation resulting from reporting bias, which is inherent to this kind of evaluation. Nonetheless, our findings tend to concur with previous reports, for example, in 36 infected adult kidney transplant recipients from the United States, where the hospitalization rate was 78%, and 39% of patients required mechanical ventilation, with a resulting mortality rate of 28% [114]. Then again, a single-center report from Italy, which had been severely impacted early on in the pandemic, has reported unanimous hospitalization (100%), frequent occurrence of acute respiratory distress syndrome (55%), and 25% mortality among 20 SARS-CoV-2−infected renal allograft recipients [152], suggesting the local situation may likely have impacted reporting.

The management of immunosuppressive therapies in COVID-19−positive SOT recipients is crucial but has not been conclusively addressed until now. Here, balancing the risks of allograft rejection and viral infection is paramount for the affected patients, yet the available data are scarce and scattered so far. Therefore, current guidelines from transplantation societies are mainly based on expert opinion, consistently recommending the withdrawal or reduction of antimetabolites followed by a reduction in calcineurin inhibitor dosage, depending on disease severity. Those recommendations are in line with the summary results of our literature overview, considering available retrospective clinical evidence.

Along the same lines, tacrolimus could be linked with a positive independent effect on survival in liver transplant recipients [197], whereas baseline immunosuppression containing mycophenolate mofetil was an independent predictor of severe COVID-19 [198].

Table 4. Recommendations From National and International Transplantation Societies

Society/Reference	Origin	Date	Guideline	Recommendation
British Transplantation Society [188]	UK	January 2021	Guidance on the management of transplant recipients diagnosed as having or suspected of having COVID-19	Outpatients: - Stop antiproliferative agents (MMF/azathioprine) - Review total burden of immunosuppression and consider reduction of CNIs - High or increased dose steroid is NOT recommended at this stage Hospitalized patients: - Stop antiproliferative agents (MMF/azathioprine) Consider reducing or stopping CNIs - Dexamethasone 6 mg daily for 10 d Patients requiring ventilatory support: - Stop antiproliferative agents (MMF/azathioprine) - Dramatically reduce or stop CNIs - Consider dexamethasone, as above
International Society of Heart and Lung Transplantation [189]	International	February 2021	Guidance from the International Society of Heart and Lung Transplantation regarding the SARS-CoV-2 pandemic	- For transplant recipients, consider holding MMF, mTOR inhibitors, or azathioprine while admitted with moderate/severe illness.
Transplantation Society [190]	International	March 2021	Guidance on Coronavirus Disease 2019 (COVID-19 for Transplant Clinicians	- Dexamethasone 6 mg daily for up to 10 d can be considered in patients who require supplemental oxygen or are mechanically ventilated. - Attention should be paid to the potential drug interactions with current immunosuppression and the potential for increased risk of infectious complications when immunomodulatory agents are added to existing immunosuppressive therapy.
American Association for the Study of Liver Diseases [191]	US	March 2021	Clinical Best Practice Advice for Hepatology and Liver transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement	- Consider lowering the overall level of immunosuppression, particularly antimetabolite dosages (eg, azathioprine or MMF) based on general principles for managing infections in transplant recipients and to decrease the risk of superinfection. - Monitor kidney function and CNI levels. - Adjust immunosuppressive medications based on severity of COVID-19 and risk of graft rejection and renal injury.
Canadian Society of Transplantation [192]	Canada	April 2021	Consensus guidance and recommendations for organ donation and transplantation services during COVID-19 pandemic	- Based on current evidence, we suggest a temporary adjustment of maintenance immune suppression for hospitalized patients with severe COVID-19. - Data on optimal immune-suppression adjustment in patients with COVID-19 are lacking, may vary, and may not be required depending on disease severity and physician judgment.
American Society of Transplantation [193]	US	June 2021	2019-nCoV (Coronavirus): FAQs for Organ Transplantation	- The impact of immunosuppression on COVID-19 is not currently known but decreasing immunosuppression may be considered for infected recipients who have not had recent rejection episodes. - Many providers have decreased or discontinued cell cycle inhibitors or reduced CNI levels, but comparative data regarding these interventions are not yet available. - Whether adjunctive corticosteroid therapy for patients with severe ARDS may be beneficial is also unknown.

AASLD, American Association for the Study of Liver Diseases; ARDS, acute respiratory distress syndrome; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; FAQs, frequently asked questions; MMF, mycophenolate mofetil; mTOR, mammalian target of rapamycin; UK, United Kingdom; US, United States of America; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Some guidelines even recommend dexamethasone administration for up to 10 days in patients who require supplemental oxygen or are mechanically ventilated, thus conforming with the Randomised Evaluation of COVID-19 Therapy Trial (RECOVERY) results [199] and treatment guidelines for the general population. The only review of guidelines addressing the use of immunosuppressants during the coronavirus pandemic for diverse indications also concluded that steroid use should not be stopped and emphasized the role of an individualized risk-benefit assessment, weighing the risk of COVID-19 infection and drug-induced immunosuppression for each patient [200].

Another critical aspect in COVID-19−diseased SOT recipients is the preservation of transplant function. Graft impairment or failure has been reported for about 22.6% of the cases we have compiled. Such complications were frequently reported for kidney and liver transplant recipients. Corresponding data for acute kidney injury have been reported to range between 25% and 57% in COVID-19−diseased kidney transplant recipients [41,65,152,154,185], linking it with a particularly poor prognosis [201].

We believe that the presented overview should be fairly comprehensive because of the amount of data compiled, while at the same time providing a representative number regarding clinical outcomes and in-hospital mortality rates that may be expectable in COVID-19−diseased SOT patients. Our data are unfortunately not suitable for a general assessment because of inherent study limitations. Here, especially asymptomatic SARS-CoV-2−infected SOT recipients may not be reflected by our evaluations, and any deductive conclusions should therefore be avoided.

As a potential limitation of our aggregate findings, a relevant selection bias is probable because of the design of our work. In detail, we assume, for example, mortality rates may be overestimated and most probably apply only to the in-hospital setting. Another limitation is that follow-up duration was inhomogeneous and ranged widely, with many included cases having ongoing disease at time of reporting or unknown outcomes, which may render results premature. Nevertheless, most patients had a sufficiently long follow-up period in our view, considering mortality in infected SOT recipients is mainly observed within the first 15 days after hospitalization [185]. We intentionally refrained from any meta-analyses of data or reporting estimates of uncertainty, which was deliberately not within the scope of our work. We believe that preceding publications have proven this attempt to be most likely futile, while at the same time lacking significant added value [19]. Hence, the aggregated data presented here come with limitations that are defined by the nature of the available data and should therefore be considered as rough ballpark estimates rather than detailed outcomes.

CONCLUSIONS

In conclusion, we provide a topical, comprehensive overview of the literature on SARS-CoV-2 and/or COVID-19 comprising more than 3400 SOT recipients, aggregating their clinical outcomes, setting the available findings into a larger context, and providing entry points to a vast body of results published over one year.

Therefore, this overview adds substantially to the hitherto available studies and comparable previous work. Because the data support the notion that clinical outcomes after SARS-CoV-2 infections in SOT recipients are poor, maintaining adequate precautionary measures seems reasonable.

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