Transplantation Reviews 35 (2021) 100588

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Review article

COVID-19 in solid organ transplant recipients: A systematic review and meta-analysis of current literature

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ARTICLE INFO

Keywords:
Solid organ transplant
COVID-19
SARS-CoV-2
Immunosuppression
Systematic review
Meta-analysis

ABSTRACT

Severe acute respiratory virus syndrome 2 (SARS-CoV-2) has led to a worldwide pandemic. Early studies in solid organ transplant (SOT) recipients suggested a wide variety of presentations, however, there remains a paucity of robust data in this population. We conducted a systematic review and meta-analysis of SOT recipients with SARS-CoV-2 infection from January 1[st] t October 9[th], 2020. Pooled incidence of symptoms, treatments and outcomes were assessed. Two hundred and fifteen studies were included for systematic review and 60 for meta-analysis. We identified 2,772 unique SOT recipients including 1,500 kidney, 505 liver, 141 heart and 97 lung. Most common presenting symptoms were fever and cough in 70.2% and 63.8% respectively. Majority (81%) required hospital admission. Immunosuppressive medications, especially antimetabolites, were decreased in 76.2%. Hydroxychloroquine and interleukin six antagonists were administered in59.5% and 14.9% respectively, while only few patients received remdesivir and convalescent plasma. Intensive care unit admission was 29% from amongst hospitalized patients. Only few studies reported secondary infections. Overall mortality was 18.6%. Our analysis shows a high incidence of hospital admission in SOT recipients with SARS-CoV-2 infection. As management of SARS-CoV-2 continues to evolve, long-term outcomes among SOT recipients should be assessed in future studies.

Contents

Abbreviation: AKI, Acute kidney injury; CI, Confidence interval; CNI, Calcineurin inhibitor; COVID-19, Coronavirus disease 2019; CRP, C-Reactive Protein; FEM, Fixed Effect Model; HSCT, Hematopoietic Stem Cell Transplant; ICU, Intensive Care Unit; IL-6, Interleukin Six; MERS, Middle East Respiratory Syndrome; NP, Nasopharyngeal; PRESS, Peer Review for Electronic Search Strategies; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; REM, Random Effect Model; RT-PCR, Reverse Transcriptase-Polymerase Chain Reaction; SARS, Severe Acute Respiratory Syndrome Coronavirus 1; SARS- CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SOT, Solid organ transplant.

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https://doi.org/10.1016/j.trre.2020.100588
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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19), has been an unmitigated worldwide pandemic, since the first case was reported in December 2019 [1,2]. Due to the high rate of transmissibility in the asymptomatic phase, the virus has continued to spread globally with catastrophic outcomes and has been a great challenge for clinicians all over the world [2,3]. Even though it causes mild disease in certain populations, to date it has led to 228,998 and 1,178,475 deaths in the U.S and worldwide, respectively [3].

Solid organ transplant (SOT) recipients are known to be vulnerable to several respiratory virus infections, such as influenza [4] due to a weakened T-cell mediated immune response [5]. The Centers for Disease Control and Prevention include SOT recipients amongst patients at increased risk for severe illness from SARS-CoV-2 [6]. Due to the novelty of this virus, there is still a paucity of data regarding many aspects including its natural course within immunocompromised hosts, the utility of current treatment regimens employed in non-transplant individuals for SOT recipients, the effect of immunosuppression on the course of the disease, and much more [7,8]. Even though presence of comorbidities, such as obesity, have been reported as risk factors for severe disease [9], an immunocompromised state has not yet been proven to have a worse clinical outcome with SARS-CoV-2 infection. Furthermore, as Vishnevetsky correctly points out, viruses that belong to the same coronavirus family such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome Coronavirus 1 (SARS) have not shown an increased risk of infection or worse outcome in immunocompromised patients [10–12]. Lai et. al. also published their systematic review comparing disease outcomes among the three major coronavirus diseases with preliminary data [13]. Furthermore, immunosuppression in the setting of hyperinflammation may even be beneficial, by blunting excessive cytokine release, which is still left to be established [14].

Since the first report of COVID-19 in SOT recipient from China was published in early 2020 [15], researchers from all over the world, have published their own experiences, especially from epidemic centers [16–18] to try and bridge the gap in knowledge, including several recently published registries [19–22]. COVID-19 presentation amongst SOT recipients has ranged from mild upper respiratory infection to severe acute respiratory distress and death [23,24]. Studies in the general population so far suggest a higher prevalence and severity of disease among middle-aged patients and in those with underlying comorbidities such as hypertension and obesity, however, data in SOT recipients is still lacking [25]. The wide variety in clinical presentation among SOT recipients is still not fully understood. Fung and Bebik recently published their narrative review that included SOT recipients and their manuscript broadly covered this area but did not assess present data quantitatively [24].

We performed a systematic review and meta-analysis of the existing literature to help expand our current limited knowledge base regarding COVID-19 in SOT recipients, especially looking at clinical presentations, treatment modalities and outcomes, with the aim to provide transplant physicians worldwide with important decision-making tools to manage these critically ill patients during this time of crisis.

2. Materials and methods

Our review was conducted according to the Methodological Expectations for Cochrane Intervention Reviews [26] and reported following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27].

2.1. Search methods

We conducted a comprehensive literature database search to find all relevant literature, published from January 1st to October 9th, 2020, on SARS-CoV-2 and SOT. The database search strategy was developed by an academic health science librarian (J.R.) in consultation with the project leader (Y.N.) and was reviewed using the Peer Review for Electronic Search Strategies (PRESS) tool through the PRESS forum [28].

We searched Ovid Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), Embase (Elsevier Embase.com), Scopus (Elsevier), Web of Science (Clarivate Analytics, using Science Citation Index Expanded, Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index- Science, Conference Proceedings Citation Index- Social Science & Humanities, Emerging Sources Citation Index, BIOSIS Citation Index, KCI-Korean Journal Database, Russian Science Citation Index, SciELO Citation Index, and Zoological Record), and LitCovid (National Center for Biotechnology Information, U.S. National Library of Medicine, without date restrictions). We searched clinical trial registries with Clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform for clinical trials with reported results. In lieu of handsearching, we also searched the online tables of contents of seven journals: *American Journal of Transplantation, Journal of Heart and Lung Transplantation, Liver Transplantation, Pediatric Transplantation, Transplant Infectious Disease, Transplant International,* and *Transplantation*. Databases and registries were searched between June 11th and June 15th, 2020, and individual journals were searched on June 19th, 2020. The database and journal site searches were updated on July 13th, 15th, August 20th, October 5th, as well as October 8th and again on October 9th 2020. The research team also monitored social media for new studies up to August 23rd, 2020. The search strategy was initially based on terms from 36 articles found by the research team prior to the comprehensive database search, and by refining, expanding, and adding to COVID-19 specific search strategies by Ellen Aaronson at the Mayo Clinic [29], and Michelle Volesko Brewer and Pieter van der Houwen, at Wolters Kluwer/Ovid [30].

The search strategy was written for Ovid Medline and translated using each database's syntax, controlled vocabulary, and search fields. MeSH terms, EMTREE terms, and text words were used for the search

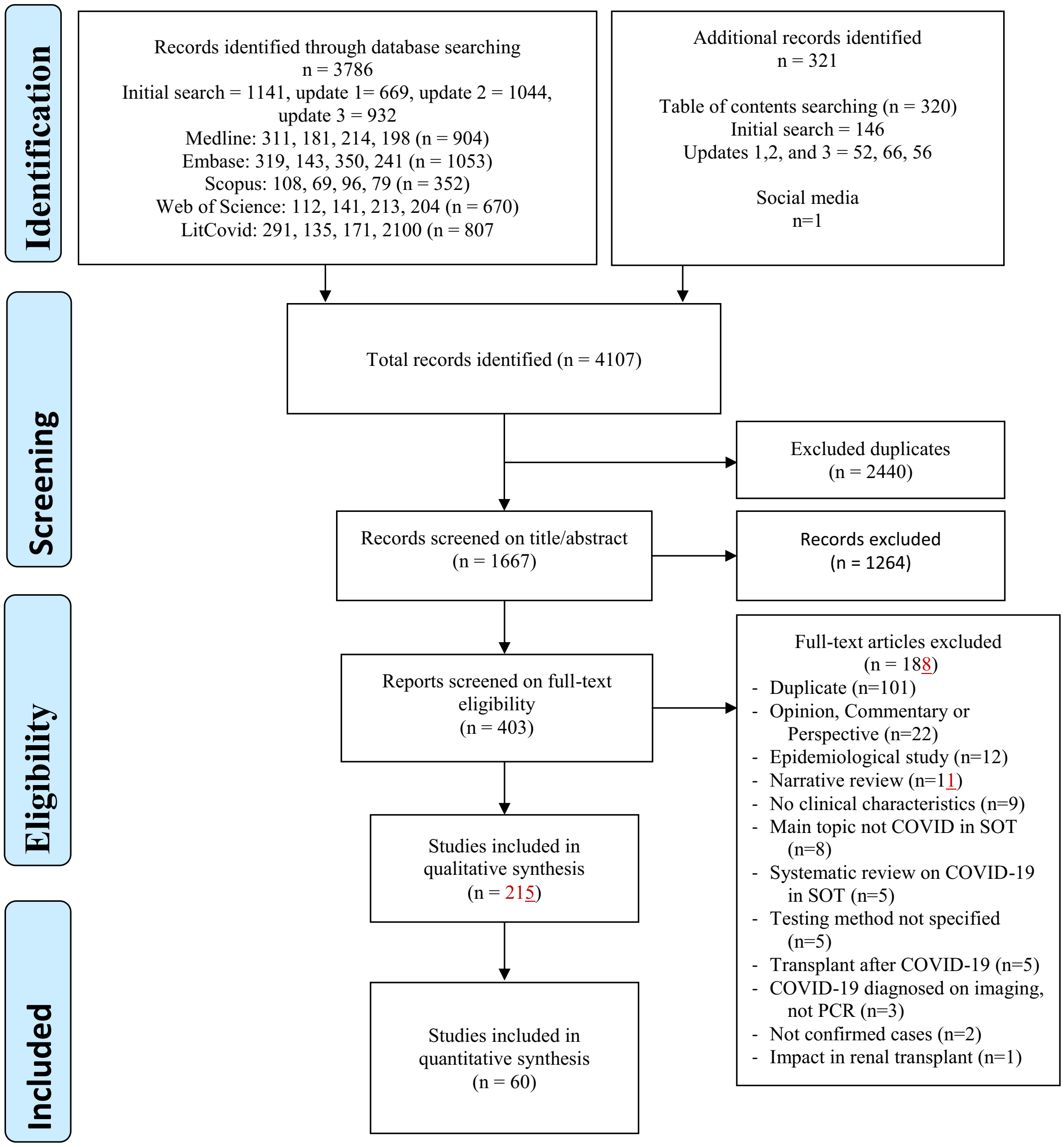

Fig. 1. Study selection flow. Majority of the cases were excluded due to opinion commentaries for COVID-19 or related to other viruses. Abbreviations: COVID; Coronavirus disease 2019, SOT; Solid organ transplant, RT-PCR; Reverse transcriptase-polymerase chain reaction.

concepts of Covid-19/SARS-Cov-2 and solid organ transplantation and their synonyms. No language, study type, or publication type limits were applied at the search phase. Animal studies were excluded. Except for LitCovid, searches were limited by date from January 1, 2020 to the present to allow for broader search terms while still focusing on SARS-Cov-2.

For full search strategies, see Appendix 1. All database records were downloaded to EndNote X9, then uploaded to Covidence web-based software for deduplication, screening, and data extraction. We contacted several authors whose cases potentially can be used several times in the different articles. Two reviewers (MAM and APV) independently assessed all studies for risk of bias. Any discrepancies in data extraction were resolved with discussion with the third and fourth reviewers (M.R. and Y.N.). After study selection, one author (J.R.) checked for retractions at The Retraction Watch Database and individual journal websites.

Table 1
Summary of symptoms with COVID 19 in Solid Organ Transplant Recipients.

Symptoms	No. of Studies	Model	Pooled incidence (%) (95% CI)	Heterogeneity (I^2), *p value*
Fever	38	REM	70.2 (61.0-79.5)	96.2, p<0.01
Cough	38	REM	63.8 (55.0-72.6)	94.4, p<0.01
Shortness of breath	36	REM	49.1 (41.1-57.1)	92.1, p<0.01
Diarrhea	36	REM	30.4 (23.6-37.2)	85.4, p<0.01

Abbreviations: CI, confidence interval, REM, random effect model

2.2. Inclusion and exclusion criteria

We included all randomized controlled trials, cohort studies, case reports, and letters to the editor that included targeted data in SOT and reverse transcriptase-polymerase chain reaction (RT-PCR) or antibody testing confirmed SARS-CoV-2 infection. As previously mentioned, animal studies and articles where the main topic was other than COVID-19 in SOT patients were excluded. We excluded studies dealing with patients with suspected infection (eg. chest imaging abnormality and symptoms), without positive RT-PCR or antibody testing. We also excluded other non-SARS-CoV-2 coronavirus related studies such as MERS and SARS. If the study subject was published more than once, we entered in the analysis only once using all available sources. For the meta-analysis, we only included articles with 5 or more patients to minimize small study effect. From included studies, the following variables were collected: number of subjects, organ transplant types, symptoms, laboratory data, treatment modalities used, type of immunosuppression, modification to the immunosuppression, graft loss, follow up period, duration from first positivity to negativity of nasopharyngeal (NP) swab RT-PCR, and all-cause mortality. After obtaining these results we excluded studies for hospital admission, intensive care unit (ICU) admission, mechanical ventilation, and all-cause mortality, for studies dealing only with critically ill patients, to avoid selection bias and avoid heterogeneity.

2.3. Data analysis

We conducted this data analysis using STATA/IC 14.0 (StataCorp LP, College Station, TX, USA). Dichotomous data were shown as relative risk ratio (RR, event/total) and their confidence interval (CI), where relevant. Pooled incidence was calculated with either random effect model or fixed-effect model, wherever appropriate. Heterogeneity among studies was graphically shown and checked with I^2 values, which show the variation among studies that are not due to chance. I^2 values of 75%, 50%, and 25% correspond to a high, medium, and low level of heterogeneity. Fixed-effect model (FEM) was used if I^2 was less than 50%, otherwise random effect model (REM) was used. To visually inspect the publication bias, we created both forest and funnel plots.

3. Results

With this search strategy, we found 1,667 potential studies, after excluding the duplicates. Of these, 1,263 studies were excluded during the abstract and title review as they did not meet eligibility criteria. The most common reasons for exclusion were perspective or opinion commentaries regarding COVID-19 and articles reporting viruses other than COVID-19. As a result, we conducted a full-text review for 403 articles, of which 188 were excluded with reasons shown in Fig. 1. Finally, a total of 215 studies were included in the systematic review [8,15–24,31–235], and 60 studies were included in a meta-analysis [16,18,21,22,24,31,32,38,40,43,50,51,55,59,60,65,69,70,79,81,85,88,96,100,102,108,114,117,128,133,135,136,141–143,149,151,153,157,158,162,166,175,179,183,185,189,190,192,199,210,212,216,217,219,228,229,231].

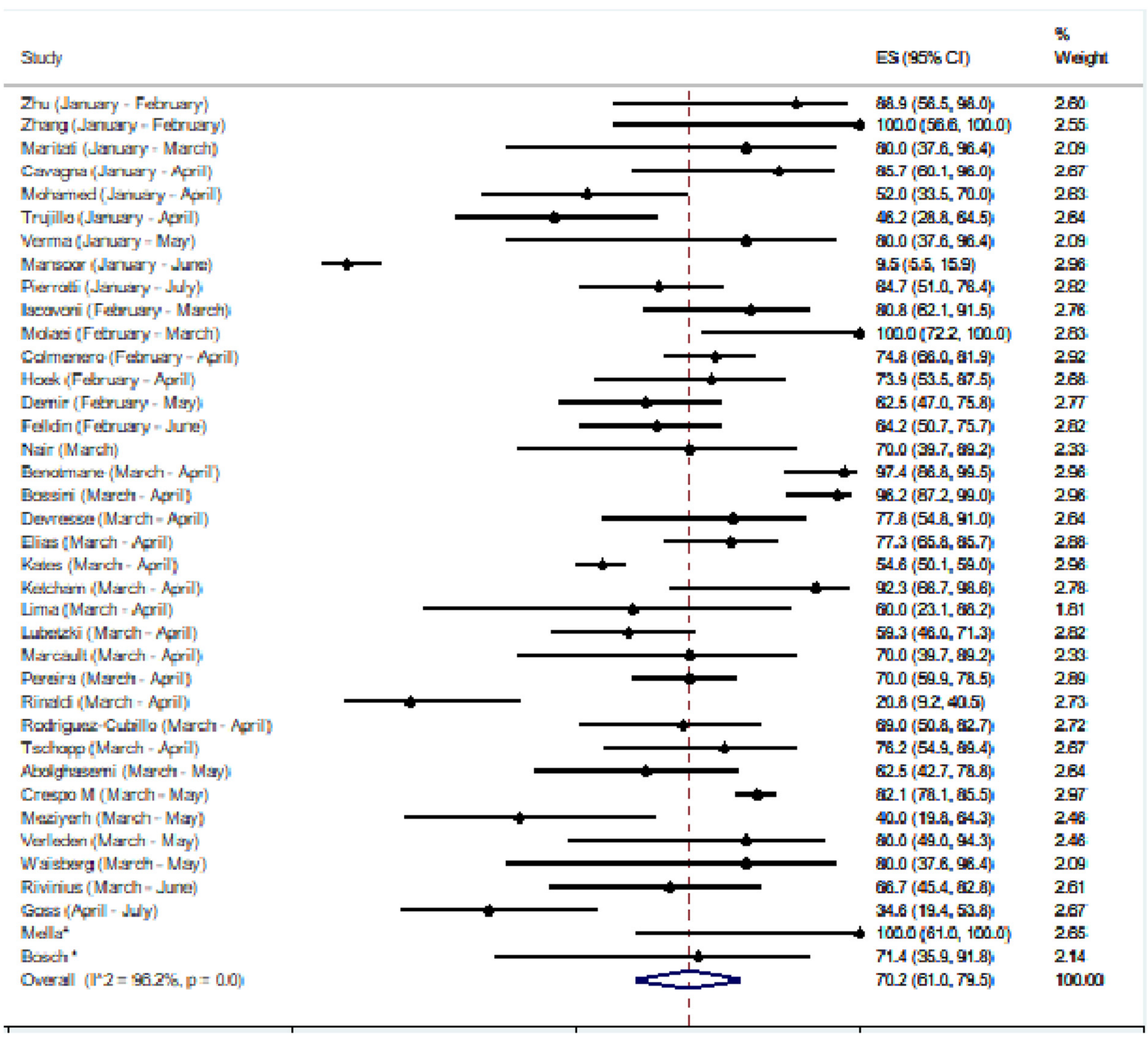

Fig. 2A. Pooled incidence of fever showing the absolute risk and 95% confidence intervals of each study (n=38) [18,20,22,31,56,59,60,65,70,79,81,85,88,96,102,108,117,133,136,141–143,151,152,156,158,166,179,189,190,192,210,212,216,217,219,229,231]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

3.1. Patient background

In total, 2,772 unique SOT recipients were identified including 1,500 kidney, 505 liver, 141 heart, 97 lung, 1 face and 43 unidentified combined transplants. One thousand seven hundred sixty four (63.63%) patients were male. Calcineurin inhibitor (CNI) and corticosteroids were used in the majority of the patients at the time of diagnosis, 91%, (95% Confidence Interval [CI], 87.6%-94.3%, REM, I^2 86.4%) and 70.1%, (95% CI, 61.5%-78.7%, REM, I^2 96.2%) respectively. Antimetabolite, such as azathioprine and mycophenolate mofetil, were used in 76.9% (95% CI, 71.3%-82.4%, REM, I^2 87.6%). Time from transplant to diagnosis of SARS-CoV-2 widely varied from 4 days to 31 years. Of note, no donor derived SARS-2 COVID infection was reported.

3.2. Symptoms with COVID-19 in solid organ transplant recipients

At first, we assessed the most common presenting symptoms among SOT recipients with COVID-19. A summary is shown in table 1. Of note, pooled incidence of fever, shortness of breath, cough and diarrhea were 70.2% (95% CI, 61.0%-79.5%, REM, I^2 96.2%), 49.1% (95% CI, 41.1%-57.1%, REM, I^2 92.1%), 63.8% (95% CI, 55.0%-72.6%, REM, I^2 94.4%) and 30.4% (95% CI, 23.6%-37.2%, REM, I^2 85.4%), respectively (Fig. 2A-2D) [16,18,20,22,24,31,38,40,43,51,55,56,59,60,65,69,70,79,81,85, 88,96, 100,102,108,117,133,136,141–143,149,151,152,156,158,162,166,179, 185,189,190,192,210,212,216,217,219,228,229,231].

3.3. Laboratory results and radiologic findings

We then analyzed laboratory results at and after diagnosis of COVID-19. Leukopenia (white blood cell count <4000/mm^3) was noted in 19 studies with pooled incidence of 17.8% (95% CI 10.7%-24.8%, REM, I^2 57.2%) [24,31,40,51,88,96,108,133,135,143,151,152,158,162,166,216, 217,219,229]. C-reactive protein (CRP) level was documented in 161 studies [8,14,16–19,21,23–25,31–38,40,42–48,50–52,55,56,59,60,62, 63,66–69,71–73,76–82,84–89,92–98,100–104,106,108–110,112,115, 116,118–121,124–130,133–139,141,143,146,147,151–156,158,159, 161–167,169,171,174,177–179,185,187–192,194,196–200,203,204, 206,207,210–214,216,218–221,224–226,228–232,234–240]. Cravedi et. al. reported a median CRP level of 41.0 (interquartile range 11.5-125.3) mg/L amongst 144 patients [19], while Pereira et. al. reported a median CRP level of 68.5 (interquartile range 15.4-126) mg/L from among 90 patients [18].

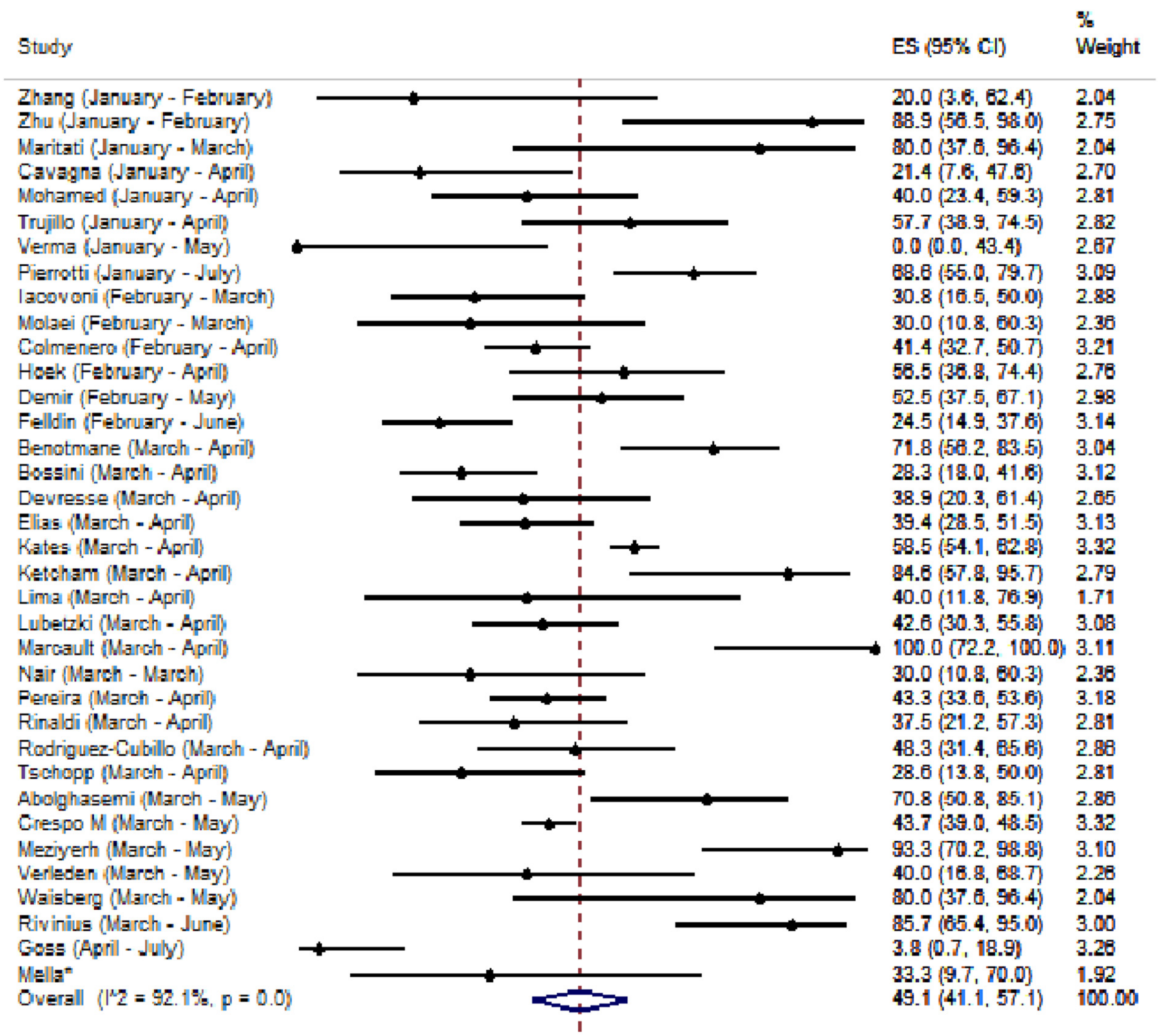

Fig. 2B. Pooled incidence of shortness of breath showing the absolute risk and 95% confidence intervals of each study (n=36) [18,20,22,31,55,60,65,70,79,81,85,88, 96,102,108,117,133,136, 142,143,151,152,156,158,166,179,189,190,192,210,212,216,217,219,229,231] Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

Radiological abnormalities on chest imaging, either radiography or computerized tomography, was found in 28 studies with pooled incidence of 79.7% (95% CI 69.5%-89.9%, REM, I^2 96.0%) [22,31,59,65,79,81,85,96,102,114,117,133,143,152,156,158,166,179,189,190,192,210,212,216,217,219,229,231] (Fig. 3).

3.4. Treatment method

We also analyzed the different treatment modalities used in SOT patients with COVID 19 and findings are summarized in table 2 [18,20,22,24,31,55,59,60,65,70,79,81,85,88,96,102,108,114,117,133,136,142, 143,151,156,158,166,179,183,189,192,210,212,216,219,231]. Immunosuppressive medications, especially antimetabolites, were decreased in 76.2% (95% CI, 68.4%-84.1%, REM, I^2 91.9% ,Fig. 4A) [18,21,22,55,59,79,85,88, 108,114,117,133,135,143,151,156,166,179,183,189,190,192,212,216,217,229,231]. On the other hand, reduction in CNI highly varied from 0%-100% with pooled incidence of 38.7% (95% CI, 29.0%-48.4%, REM, I^2 93.0, Fig. 4B) [16,18,21,23,24,38,40,51,55,69,81,85,88,100,114,117,128,133,136,143,151,166,179,183,189,212,216,217,228,229,231]. Corticosteroids were very seldom reduced in 1.7% (95% CI, 0.1%-3.5%, FEM, I^2 0.0%, Fig. 4C) [18,21,51,59,69,88,100,114,128,133,151,166,192,212,216,217,229].

Majority of cases were treated with hydroxychloroquine (59.5% 95% CI, 45.0%-74.0%, REM, I^2 98.7%, supplemental Fig. A) [18,20,22, 31,55,59,60,65,70,81,85,88,96,102,108,114,117,133,143,151,158,166,183,189,190, 192,210,212,216,219]. Forty eight percent of cases were also placed on azithromycin (95%CI, 35.2%-62.0%, REM, I^2 97.4%, supplemental Fig. B) [18,20,22,55, 59,60,65,70,88, 96,102,114,158,166, 179,183,189,190,210,216,219]. Interleukin Six (IL-6) antagonists were used in 14.9% (95% CI, 9.9%-19.9%, REM, I^2 86.7% supplemental Fig. C) [18,20,22,55,60,70,79,85,88,117,133,136,189,192,210]. Protease inhibitors were used in 28.8% (95% CI, 19.1%-38.5%, REM, I^2 82.8% supplemental Fig. D) [20,24,31,56,70,108,143,151,189,210,212]. Use of high dose steroids, [defined as prednisone at least 1mg/kg, hydrocortisone at least 100mg/day, methylprednisolone at least 200mg/daily, dexamethasone (>2mg/day)], was reported in 19 studies with a pooled incidence of 38.9% (95% CI, 27.9%-49.8%, REM, I^2 97.0% ,supplemental Fig. E) [18,20,22,55,60,70,81,108,117,133,142,156,158,179,183,189,192, 210,

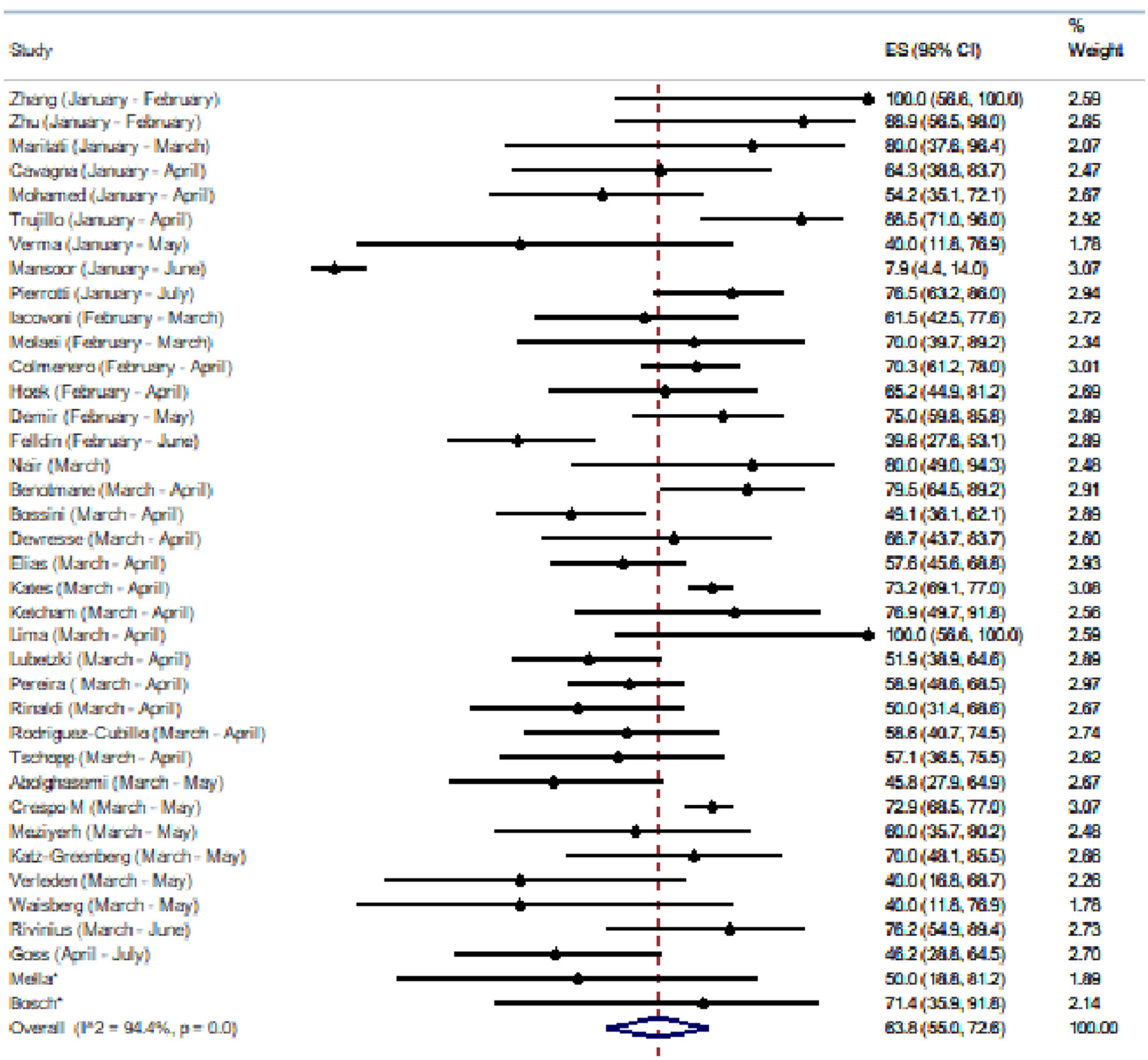

Fig. 2C. Pooled incidence of cough showing the absolute risk and 95% confidence intervals of each study (n=38) [18,20,22,31,55,59,60,65,70,79,81,85,88,96,102,108,114,117,133,136,141,143,151,152,156,158,166,179,189,190,192,210,212,216,217,219,229,231]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

231]. Concurrent antibiotic use was seen in 69.4% (95% CI, 58.9%-79.9%, REM, I^2 94.9%) [16,24,32,40,50,51,55,60,79, 81,102,108,136,151, 162,166,179,185,190,199,210,212,216,219,229].

Fourteen studies, excluding potential duplicates, documented use of remdesivir with a total of 36 unique patients [18,22,50,69,70,114, 127,133,136, 165,183,217,228,240], of which 9 studies documented mortality with 2 deaths amongst 14 patients [50,69,114,127,133,136, 165,217,228]. Thirteen studies, excluding potential duplicates, mentioned use of convalescent plasma with a total of 33 unique patients [24,33,46,69,90,110,114,133,136,165,185,199,228], of which 11 studies documented about mortality with a total of 4 deaths from among 31 patients [24,33,46,69,90,110,114,133,165,185,228].

3.5. Outcomes

Finally, we analyzed outcomes in SOT recipients post COVID-19 infection.

Twenty two studies showed 81.0% pooled incidence of hospital admission (95% CI 75.2%-86.7%, REM, I^2 91.4%) [18,20,22, 55,60, 65,70, 79,81,85,88,96,102,108,114,136,141,156, 166,190, 212,216], while 30 studies showed a 29.3% pooled incidence (95% CI 22.6%-36.1%, REM, I^2 89.2%) of admission to the ICU from amongst hospital admissions [18,20,22,31,59,60,70,79,81,85,88,96, 102,108,114, 117,133, 143,151, 152,158,166,179,183,189,190,210,212,216,229]. Overall, 25.9% of patients required mechanical ventilation (95% CI 20.1%-31.8%, REM, I^2 74.4%) from among hospital admissions [18,20,22,31,59,60,65, 70,79,81,85,88,96,102,108,114,117,133,142,143, 151,152,158,166, 179, 183,190,192,212,216,217,219,229,231].

Thirty-four studies addressed secondary or co-infections [22,24, 50,51,89,91,92,96,105,106, 110,127,133,143,145,151,157,158, 162,163, 165,166,177,182,185,189–191,194,199,200,212,217,219]. The majority of reported cases were bacterial urinary tract infection in kidney transplant recipients [89,96,151,165,166,212] Of note, Nair et. al documented that 3 recipients, out of 10 kidney transplant patients, developed positive urine culture (*Enterococcus*, *Klebsiella* and *E.coli*) [166] and while Goss et. al report a culture with Group B streptococcus [96]. Respiratory secondary bacterial infections due to gram negative bacteria, including *Eschericia coli, Pseudomonas aeruginosa*, *Acinetobacter baumanni*, *Klebsiella pneumoniae*, *Morganella morganii*, *Stenotrophomonas maltophilia*, as well as gram positive bacteria, including *Enterococcus faecalis*,

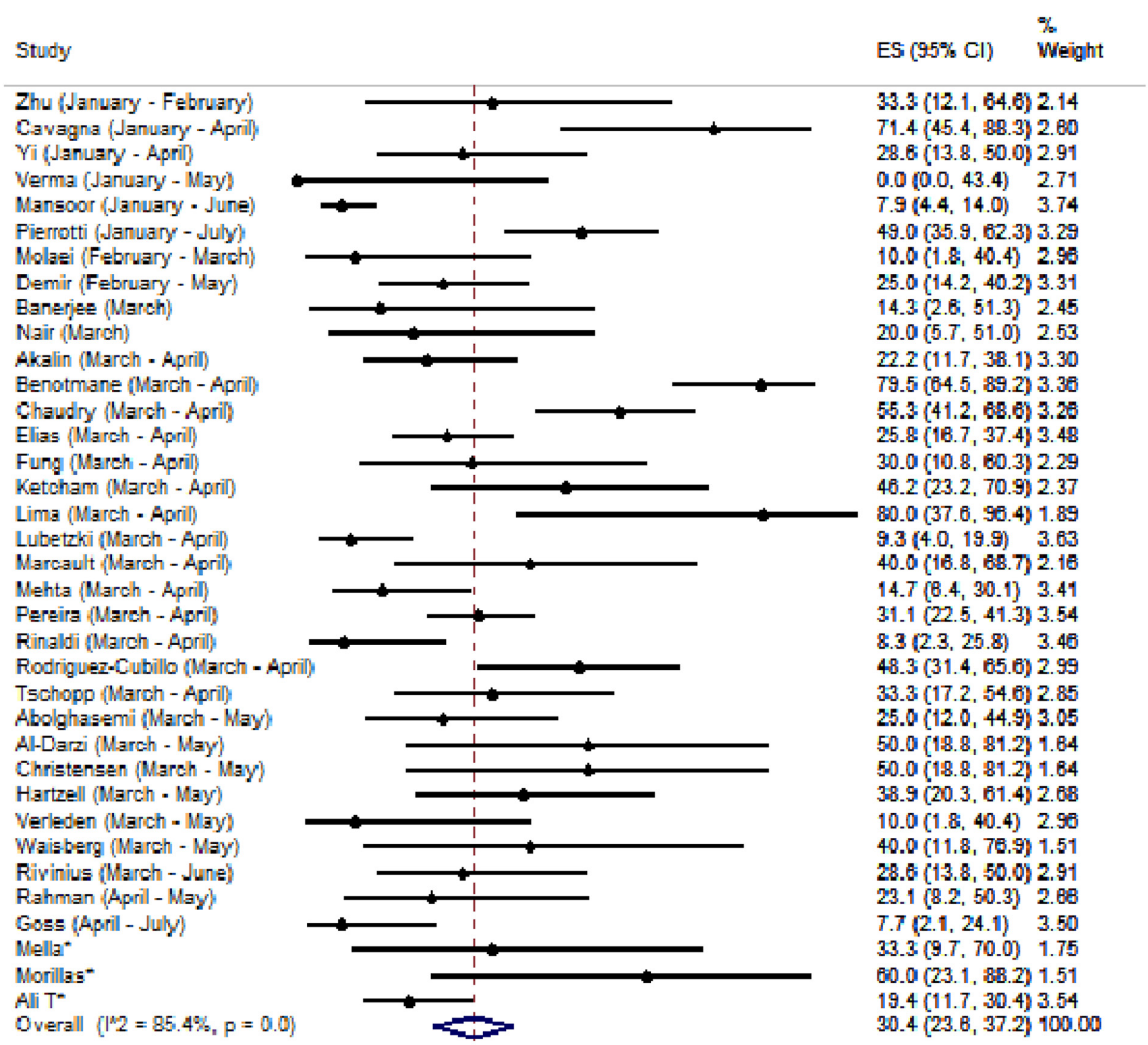

Fig. 2D. Pooled incidence of diarrhea showing the absolute risk and 95% confidence intervals of each study (n=36) [16,18,24,31,38,40,43,51,55,65,69,79,85,96,100,117,133,136, 141,142,149,151,158,162, 166,179,185,189,190,192,212,216,217,219,228,231]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

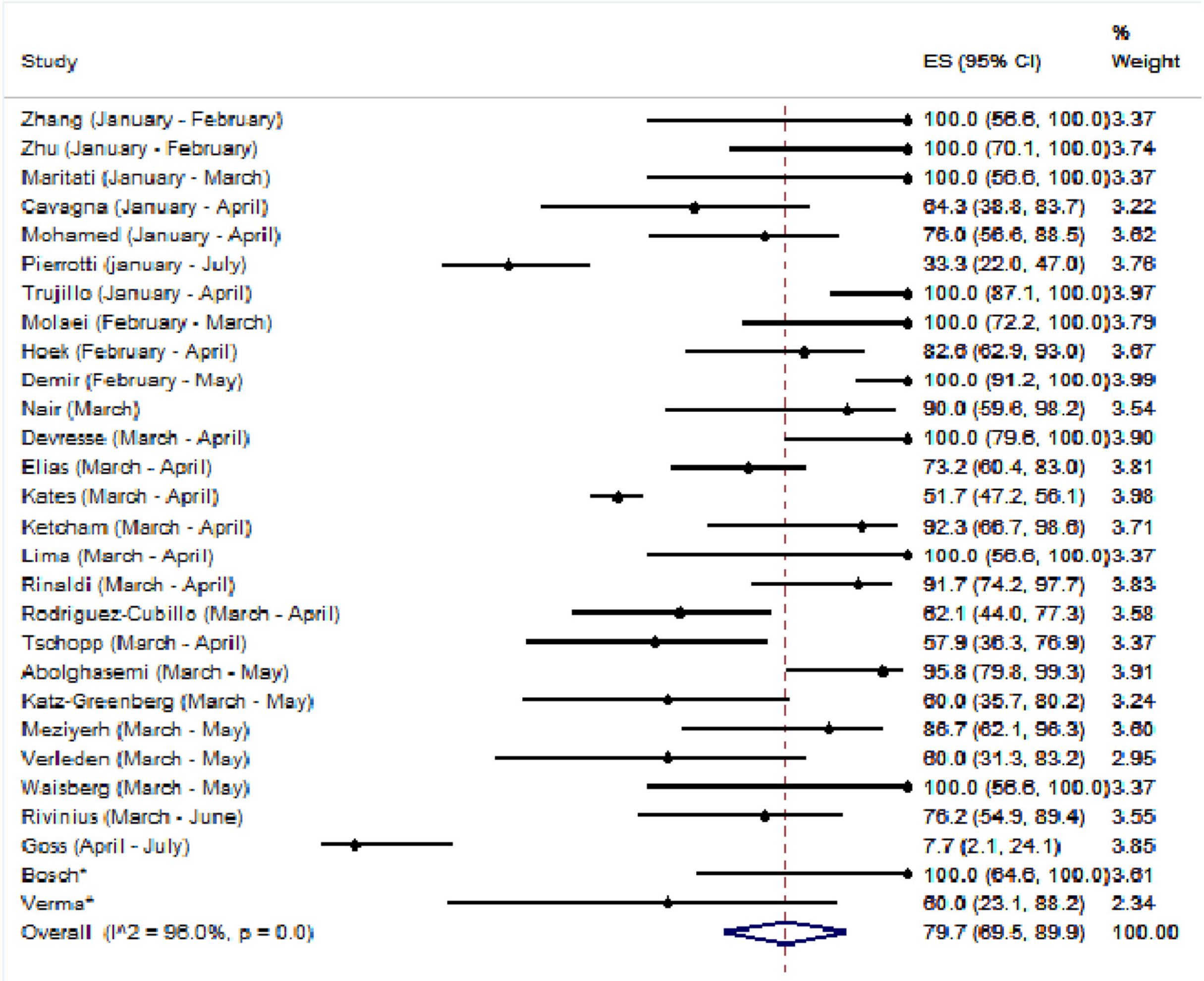

Fig. 3. Pooled incidence of abnormal chest imaging (either radiography or computerized tomography) in solid organ transplant recipients and COVID-19, showing the absolute risk and 95% confidence intervals of each study (n=28)[22,31,59,65,79,81,85,96,102,114,117,133,143,152,156,158,166,179,189,190,192,210,212,216,217,219,229,231]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

Staphylococcus aureus, *Streptococcus haemolyticus* were also noted [22,50,92,127,157,169,177,185,219][22,50]. Bacteremia was reported in 4 cases with different pathogens [50,91,133,143]: 2 patients with *Klebsiella pneumoniae*, *Staphylococcus epidermidis* and two patients with *Staphylococcus aureus* [143]. Clostridium difficile colitis was reported in three patients [177,185].

Regarding viral secondary infection we six reports of Cytomegalovirus infection [50,51,143,158,177,190]. Molaei et. al reports four patients having COVID-19 and CMV co-infection with a viremia of 412-592 IU/mL [158], on the other hand, Pereira et. al also reports five patients with CMV with a median of 1469 (1326-8994) IU/mL [177] while Pierroti et. al reports 9 patients with CMV viremia [179]. Only one case of Influenza A co-infection was reported [200]. Two other patients had co-infections with HHV-6 and EBV [177]. There is also a report on a patient with a recent history of slight BK viremia that largely increased after COVID-19 infection [145].

Fungal secondary infections were also reported. Candidemia was reported in 1 liver transplant recipient [106] and other solid organ transplant patients with *Candida glabrata* candidemia [177] and *Candida krusei* bacteremia [185] while Rinaldi et al. reported 3 invasive candidiasis as well as 12 pulmonary aspergillosis [189]. Morlacchi et. al. reported on 4 lung transplant recipients with a bronchoalveolar lavage from 1 patient with *Aspergillus fumigatus* [163] while Pereira et. al reported another solid organ transplant recipient with aspergillus infection [177]. Also, Roberts et. al. reported 2 fungal infections with *Aspergillus versicolor* and severe cutaneous candidiasis [191]. Finally, Kates et. al. reported a pneumonia due to cryptococcus species as well as a patient with Pneumocystis pneumonia [22].

There are 62 studies documented about the duration of viral shedding and time to negativity of RT-PCR on NP specimens [1,15,24,35,36,39,45,47,55,60,61,66,67,70,72,75,80,91,92,96–98,105,106,110,113,115,118–122,125,130,134,136–138,140,147,148, 161–164, 170,174,176,180,182,197,198,200,207,213, 218,220,221,226, 229,230, 232,241] Majority of patients achieved negativity around 3 to 5 weeks from the initial positive result. The NP swab RT-PCR methods varied from

Table 2
Summary of treatment modalities with COVID 19 in Solid Organ Transplant Recipients.

Treatment Modalities	No. of Studies	Model	Pooled incidence (%) (95% CI)	Heterogeneity (I^2), *p value*
Hydroxychloroquine	30	REM	59.5 (45.0-74.0)	98.7, p<0.01
Azithromycin	21	REM	48.6 (35.2-62.0)	97.4, p<0.01
IL-6 antagonist	15	REM	14.9 (9.9-19.9)	86.7, p<0.01
Protease inhibitors	11	REM	28.8 (19.1-38.5)	82.8, p<0.01
Steroids	19	REM	38.9 (27.9-49.8)	97.0, p<0.01

Abbreviations: CI, confidence interval, REM, random effects model, IL-6, interleukin six study to study and the time from onset of symptoms to first positive RT-PCR result was not assessed. However, we identified that SOT recipients achieved RT-PCR negativity on day 5 at the earliest [170] and day 56 at the latest [182] in this systematic review. No studies were found documenting viral culture of SARS-CoV-2 among SOT recipients.

Also, 52 articles documented about rejection after COVID-19 [18,22–24,31,40,43,50,65,69,70, 81,84,88,92,98,101,103–105, 108,114, 116,118,120,123,125,130,133–135, 143,145,154,165,171,173,175,179, 183,186,191,192,199,201,205,207,210,220,224,230,231][18, 22–24,65, 81, 84,92,98,101,103–105,108,116,118,120,123, 125,130,133–135, 143,173,175,186,191,192,199,201,210,224,230,231]. During the follow up period, the pooled incidence of rejection was calculated only at 1.0% (95% CI, 0.2%-1.7%, FEM, I^2 0.0%) [22,23,65,81,88,108,114,133,135, 143,179,183,192,210,231].

Finally, we assessed all-cause mortality after COVID-19 in SOT recipients. We identified 37 articles and 18.6% died from any cause (95% CI, 14.8%-22.3%, REM, I^2 72.4%) during their follow-up period [18,20, 22,31,55,59,60,65,70,79,81,85,88,96, 102,108,114,117,133,141–143, 151,152,156,158,166,179,189,190,192,210,212,216,219,229,231]

3.6. Kidney transplant recipients

We conducted the same analysis for the subset of kidney transplant recipients [16,18,20–24,31,32,38,43, 51,55,60,65,79,81,85,88, 96,100, 102, 114,136,142,143,149,151,152,156,158, 166,179,185,189,192, 210, 212,228,229,231]. Fever, cough, and shortness of breath were seen in 70.3% (95% CI, 62.5%-78.2%, REM, I^2 90.6%), 65.3% (95% CI, 58.9%-71.7%, REM, I^2 74.3%), and 49.3% (95% CI, 40.5%-58.2%, REM, I^2 87.8%), respectively. Of note, acute kidney injury (AKI) in this group was seen in 45.4% (95% CI, 35.7%-55.1%, REM, I^2 85.5%) [21,24,40,43, 51,60,81,85, 100,114,136,149,156,166,179,189,192,210,229,231] during entire follow-up. Anti-metabolites were reduced in 85.5% (95% CI, 79.4%-91.6%, REM, I^2 84.0%), while change in CNI were seen in 48.2% (95% CI, 31.4%-65.0%, REM, I^2 95.5%), and steroids only among 1.8% 95% CI, 0.6%-4.1%, FEM, I^2 0.0%), In regards to treatment modalities, majority of cases were treated with hydroxychloroquine in 75.6% (95% CI, 62.3%-88.8%, REM, I^2 97.1%), with azithromycin use among 50.8% (95% CI, 38.7%-62.8%, REM, I^2 89.0%). IL-6 antagonists were used in 17.3% (95% CI, 10.0%-24.6%, REM, I^2 88.1%), protease inhibitors in 37.7% (95% CI, 23.2%-52.2%, REM, I^2 89.1%), with high dose steroids in 44.4% (95% CI, 27.3%-61.4%, REM, I^2 96.5%). All-cause mortality in the subset of kidney transplant recipients was noted to be 22.0% (95% CI, 19.5%-24.4%, FEM, I^2 47.1%).

3.7. Non-kidney solid organ transplant recipients

We also looked at similar outcomes in non-kidney transplant recipients. However, due to small sample size, stratification per organ type was difficult. In terms of all-cause mortality, a pooled incidence of 11.8% (95% CI, 4.2%-19.3%, REM, I^2 73.4%) among liver transplant recipients [43,50,70,96,128,141,212,219] and a pooled incidence of 15.6%

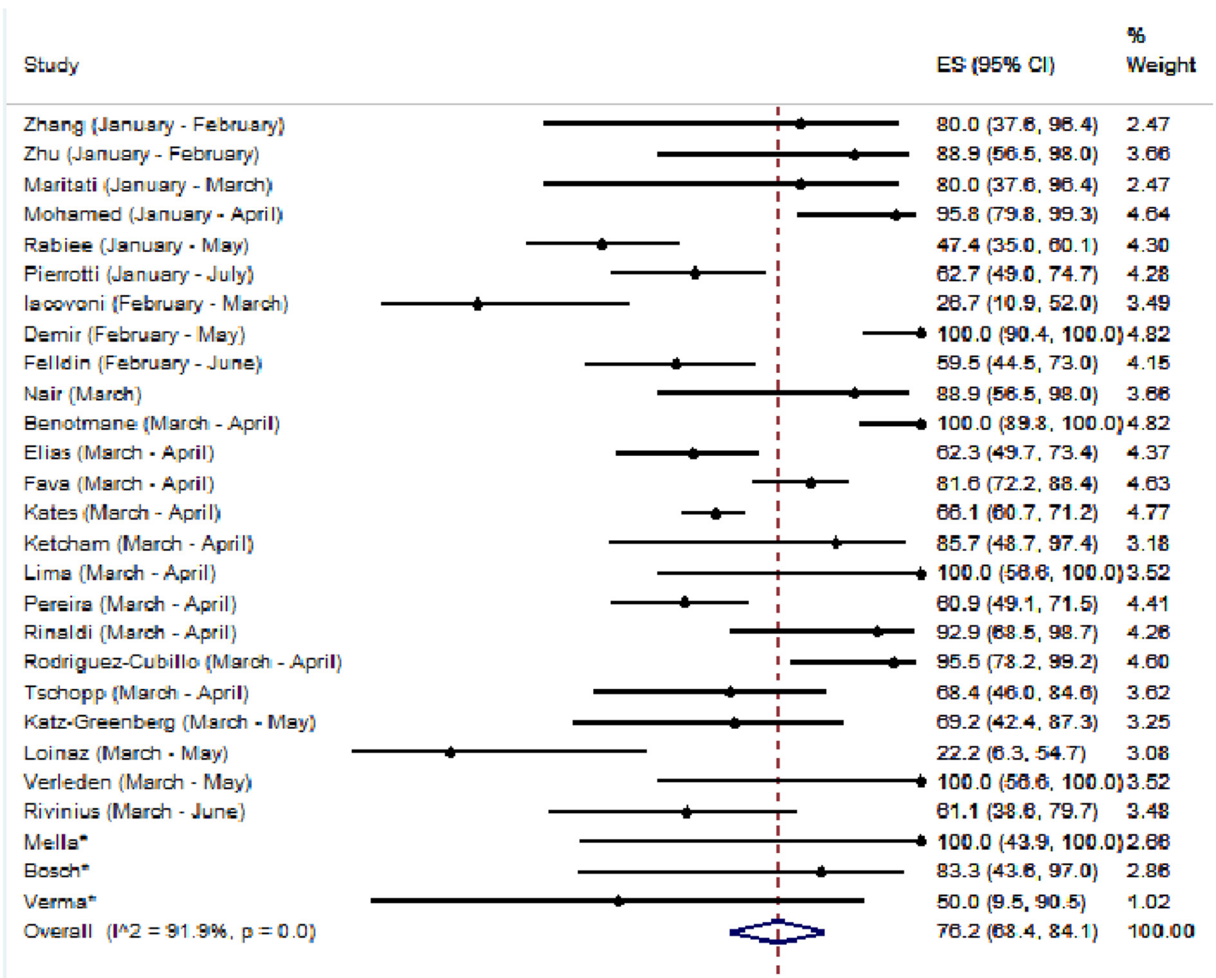

Fig. 4A. Pooled incidence of reduction in anti-metabolite showing the absolute risk and 95% confidence intervals of each study (n=27)[18,20–23,55,59,79,81,108,117,133,135,143,156, 166,175,189–192,212,216,229,231]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

(95% CI, 8.5%-22.7, FEM, I^2 48.5%) among heart transplant recipients was seen [40,65,96,108,117,133,190,199].

4. Discussion

This is the first full systematic review and meta-analysis regarding COVID-19 in SOT recipients during the first wave of the pandemic in terms of symptoms, treatment strategy (including reduction in immunosuppression), and short-term outcomes. First, one fifth of this vulnerable population died after COVID-19 in a short term. Next, fever was common and reported in 70.2% but respiratory symptoms (cough and shortness of breath) were found in 63.8% and 49.1% respectively. Non-respiratory symptoms such as diarrhea were also seen in 30.4%. Also, we found that in the majority of SOT recipients, antimetabolites were either reduced or stopped completely.

In the general population, risk factors for severe COVID-19 infection have been well documented, such as hypertension, older age, and diabetes mellitus. Immunosuppressive medications have been thought to be a risk factor for severe illness from COVID-19 [6]. Even our meta-analysis showed a significantly higher admission rate (81.0%) as compared to the general population, which may not entirely reflect disease severity but rather the management strategy as employed by treating physicians who may prefer closer inpatient monitoring. Our meta-analysis showed incidence of lower respiratory tract infection (based on abnormal imaging), ICU admission rate and mortality of 79.7%, 29%, and 18.6% respectively, which are all comparable to the large published data in non-SOT, general population [242]. Even though T-cell immunity against respiratory viruses in SOT recipients is thought to be lower than the general population, viral clearance for SARS-CoV-2 in SOT recipients was around a median of 3-5 weeks, which again, is almost comparable to general population [242].

Similarly, as compared to oncology patients, which were also recognized as immunocompromised and high risk for severe COVID-19, our data showed comparable outcomes especially for hospital admission rate and mortality [243]. Even though this meta-analysis shows high incidence of mortality in SOT recipients when compared with the general population [242], it is important to note that these studies are not entirely comparable given the differences in associated comorbidities within the cohorts, such as incidence of diabetes or obesity.

On the other hand, hematopoietic stem cell transplant (HSCT) recipients are treated with immunosuppressive medications as well, and sometimes even at higher doses as compared to SOT recipients. Few reports have been published regarding COVID-19 in HSCT population and Malard et. al. documented a mortality of around 40%[244], which is significantly higher than SOT recipients.

In general, secondary infection was reported and found to be rare. In our study, some authors reported bacterial infection, especially urine culture positivity in kidney transplant recipients [89,151,165,166,212]. We cannot conclude if these infections occurred due to COVID-19 or were simply hospital acquired. Six reports of Cytomegalovirus infection

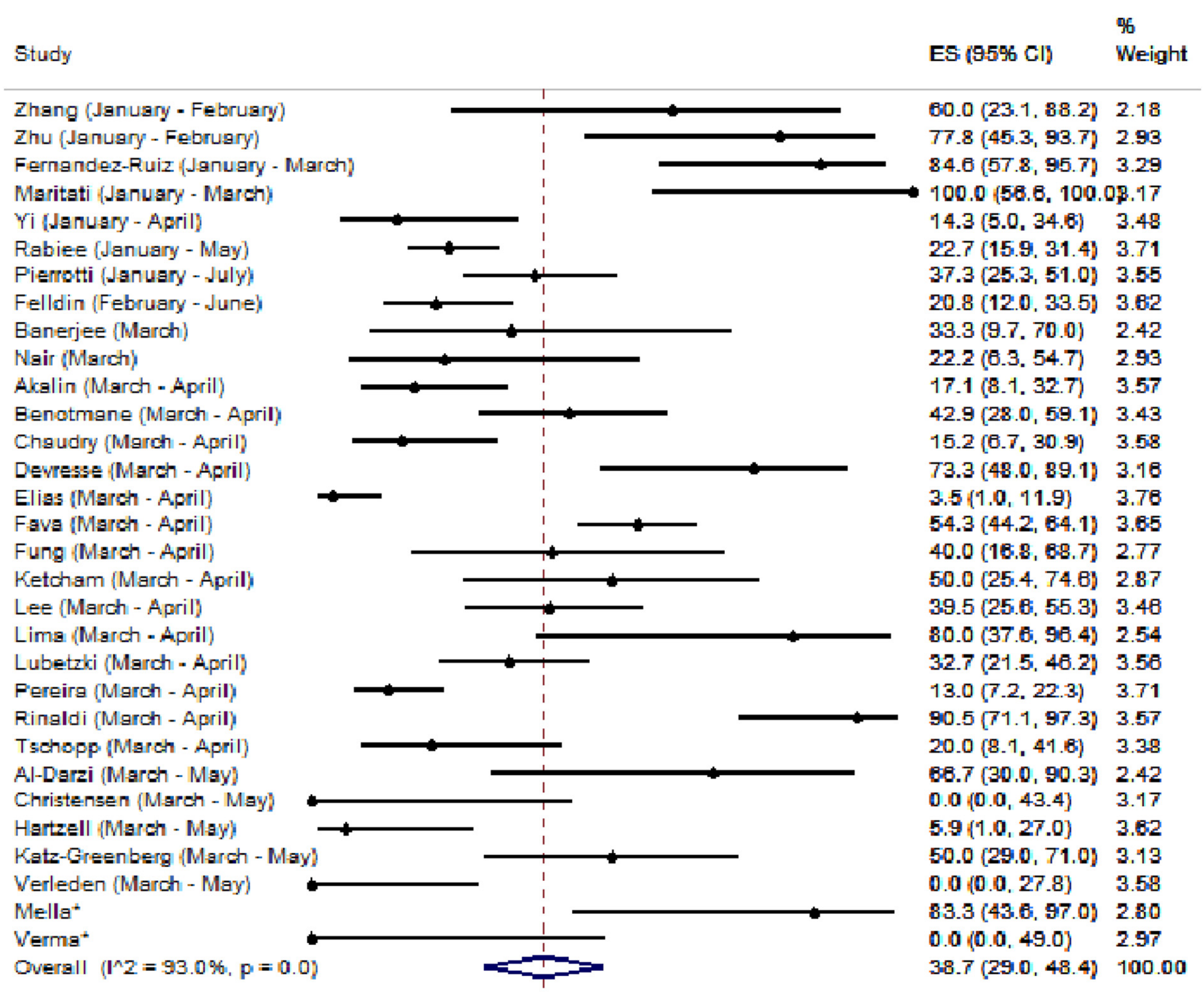

Fig. 4B. Pooled incidence of reduction in calcineurin inhibitor showing the absolute risk and 95% confidence intervals of each study (n=31)[16,18,20,21,23,24,38,51,55,79,81,117,128,133,143,151,166,175,189,191,212,216,228,229,231]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

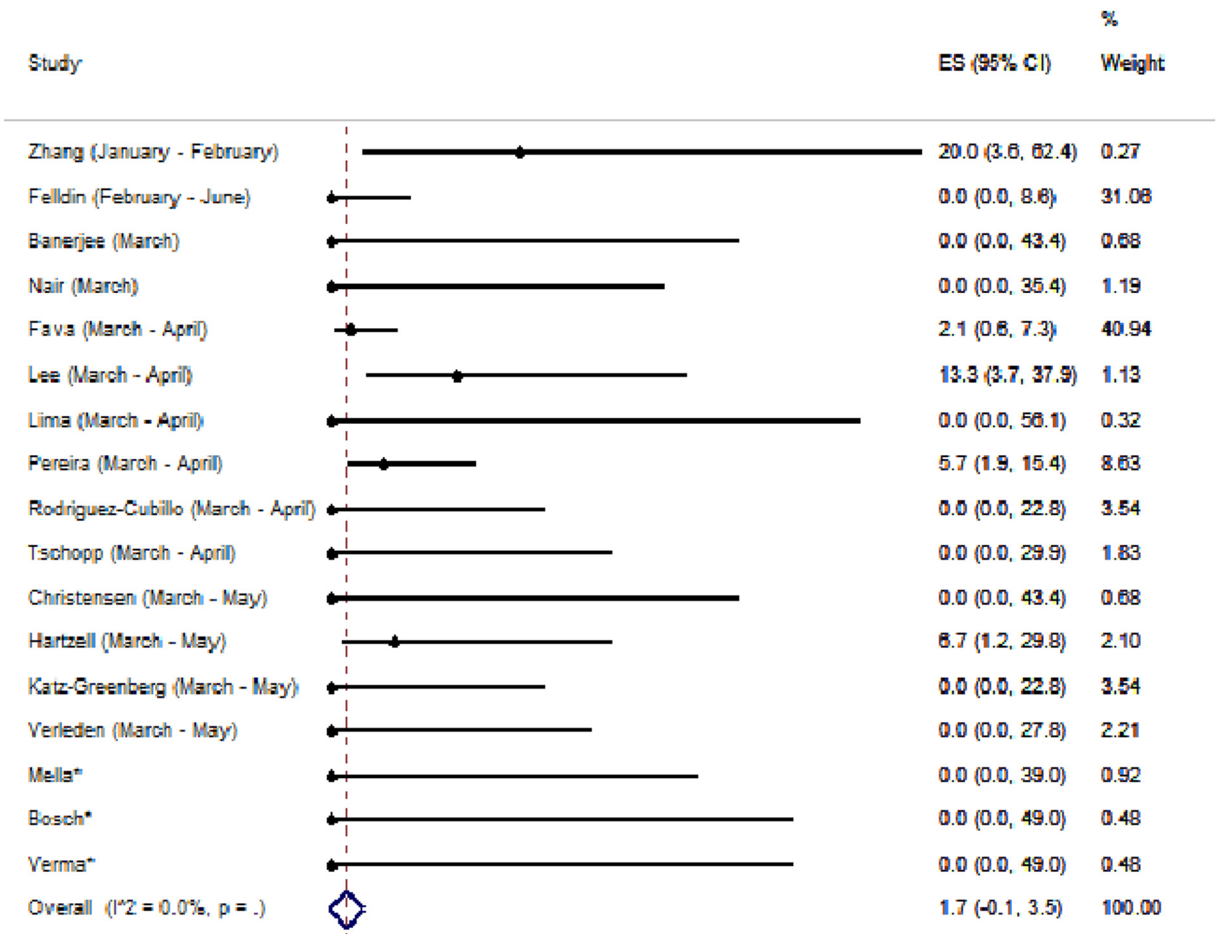

Fig. 4C. Pooled incidence of reduction in steroid showing the absolute risk and 95% confidence intervals of each study (n=17)[18,21,23,51,81,100,128,151,166,191,192,212,216,229]. Abbreviations. ES; Effect Size, CI; Confidence Interval, *=study period not defined.

were found in our study [50,51,143,158,177,190]. In general, Aspergillus co-infection was also reported, Rinaldi et. al reported twelve pulmonary aspergillosis [189], Pereira et.al reported also a patient with aspergillus infection [177], while other authors report a case of a lung transplant recipient with a positive bronchoalveolar lavage for *Aspergillus fumigatus* [163] *and a case of Aspergillus versicolor* [191]. Even though SOT recipients, especially lung transplant, are at highest risk for Aspergillosis, we found a relatively lower rate of Aspergillosis after COVID-19. This may be due to a short follow-up period or use of post-lung transplant antimold prophylaxis, even prior to COVID-19.

This systematic review and meta-analysis has several limitations. First, we found significant heterogeneity between studies. This may be in part due to a wide variety of different transplant types, immunosuppressive agents, and a lack of uniform treatment of COVID-19. Definition of certain clinical presentations, such as fever, also varied from study to study, giving rise to further heterogeneity. Even after factoring in heterogeneity into our analyses, we could not completely overcome it. Secondly, we could only perform analyses in the subset of kidney transplant recipients. Due to sample size limitations, we could not perform the same for other transplant types. Next, the follow-up period varied significantly from study to study and that prevented us from capturing certain outcomes, such as rate of rejection, allograft dysfunction, secondary infection, and even mortality. Finally, it is important to note that this systematic review and meta-analysis reflects our initial experience with this ever rapidly growing pandemic, and as treatment modalities and strategies evolve in the coming months, this is likely to change. Moreover, differences in the available resources, epidemiology and demographics, from country to country, also play an important factor when it comes to the management of these highly immunosuppressed patients.

In conclusion, we performed a systematic review and meta-analysis of COVID-19 in SOT recipients regarding symptoms, treatment options, and outcomes. Based on this review and meta-analysis, we conclude that a higher admission rate was noted but overall outcome was similar to the general population. Further studies are still required to assess the long-term outcomes including allograft rejection, secondary infections and mortality in this highly immunocompromised patient population.

Funding

The authors declare no-funding for this study.

Disclosure

Authors of this manuscript do not have any conflicts of interest to disclose.

Authorship

M.R, MAM, APV, J.R. and Y.N. performed the literature search. M.R., MAM, V.K. and Y.N. performed the data analysis. All authors were responsible for the study design, data interpretation, and writing.

Declaration of Competing Interest

The authors of this manuscript declare no competing conflicts of interest.

Acknowledgement

The authors would like to thank Tara Brigham, MLIS, from the Mayo Clinic Libraries in Jacksonville, FL, for peer review of the Medline database search strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2020.100588.

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