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REVIEW

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COVID-19 clinical manifestations and treatment strategies among solid-organ recipients: A systematic review of cases

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Abstract

Background: COVID-19 has been spreading worldwide with a significant death toll. Solid-organ transplantation (SOT) recipients are at higher risk due to their suppressed immune system. In this study, we aimed to conduct a systematic review on COVID-19 clinical manifestations and treatment strategies in SOT recipients.

Methods: We searched three databases for relevant terms related to COVID-19 and transplantation. 50 studies, including 337 patients, were reviewed.

Results: Two hundred thirty six patients were male, with a mean age of 49.9 years. The most prevalent group was the kidney 57.0%, followed by 17.2% heart and 13.6% liver. Fever and cough were the most reported clinical presentations. Infiltration (55.4%) in chest x-ray and ground-glass opacity (67.1%) in CT scans were the most radiological findings. It was found that 96.8% and 72.4% of patients present with CRP level and lymphocytopenia, respectively, and 70.6% of kidney recipients patients presented with high creatinine levels. The most common baseline immunosuppressants were calcineurin inhibitors (88.9%) and antimetabolites (73.2%). Antimetabolites (84.3%) and calcineurin inhibitors (54.3%) were discontinued/decreased 84.3% whereas glucocorticoids dosage almost has no change (77.9%) or even increased. 18.4% of cases had died, and 65.9% were discharged.

Conclusions: Patients' demographics, signs, symptoms, and radiographic findings in SOT recipients are almost similar to the general population. However, gastrointestinal symptoms appear to be more common. There are different treatment strategies, but in most of them, antimetabolite and calcineurin inhibitors were decreased or discontinued, while corticosteroids were increased. Finally, COVID-19 seems to be more severe and has higher mortality in SOT recipients compared to the general population.

KEYWORDS

clinical manifestation, COVID-19, radiography, systematic review, transplantation, treatment

1 | INTRODUCTION

Coronavirus disease (COVID-19) is caused by a single-stranded RNA virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first human case was reported in Wuhan, Hubei province of China in December 2019, and by a few weeks, the COVID-19 infection has the characteristics of a "pandemic".[1]

According to the World Health Organization (WHO), fever, fatigue, and dry cough are the most common symptoms of COVID-19. Patients may also experience shortness of breath, myalgia, sore throat, and gastrointestinal (GI) symptoms. Real-time polymerase chain reaction (RT-PCR) is the most accurate detection method by now; however, some centers have chosen chest x-ray (CXR) or computerized tomography (CT) investigations as first-line triage tools due to long RT-PCR turnaround times.[2,3]

There are several threats for transplant recipients, but one particularly significant threat is emerging of infectious diseases. There have been several new viral diseases since 1980, including HIV, SARS-CoV, West Nile Virus, Influenza A/H1N1, Zika, Ebola, and now COVID-19.[4,5]

Since the outbreak, there is increasing evidence that those with existing comorbidities, older age, or a compromised immune system are at higher risk of developing severe and even fatal respiratory diseases. Solid-organ transplant (SOT) recipients are also considered to be in this risk group, especially as they get treated with immune-suppressive drugs.[3,6] It is also assumed that transplant recipients may have a more significant viral burden and shedding, resulting in higher infectivity and potential spread to other individuals, including healthcare professionals. Moreover, they have shown atypical clinical manifestations and worse prognosis in comparison to the general population; hence, different treatment approaches may be needed.[7-10]

COVID-19 has immediately and dramatically impacted the world. Considering the early nature of the pandemic, knowledge about COVID-19 and its impact on SOT patients is limited to case reports and experts' discussions.[11] In the present study, we aimed to perform a thorough systematic review aiming at collecting any clinical evidence accrued to date on the impact of COVID-19 on SOT recipients.

2 | METHODS

2.1 | Study design and search strategies

The present study was conducted along with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and it has been listed in the International Prospective Register of Systematic Reviews (PROSPERO) database (ID CRD42020181465). A comprehensive literature review of PubMed, Embase, and Scopus entries between December 1, 2019 and May 22, 2020 was conducted for relevant terms related to COVID-19 and SARS-CoV2 in transplant patients and setting (Appendix 1).

2.2 | Study selection

First, two reviewers (A.M, AH) independently screened the title and abstracts of all eligible studies. Inclusion criteria for studies were the description of SOT recipients who got infected with COVID-19. Excluding criteria were pediatric transplantation, guidelines, unavailable full texts, and lack of sufficient data. Non-English publications were translated into English, using Google's translation service. If eligibility was indeterminable, the full text was considered, and disagreements were resolved by consensus. Of all articles, 50 were regarded as relevant to this review.[3,7,12-57] PRISMA flow chart of study selection is shown in Figure 1.

2.3 | Data extraction

Three authors (A.M, S.M, AH) then separately extracted data from all relevant manuscripts using a pre-defined data extraction sheet. Parameters such as patients' demographics including age, sex, country of residency, comorbidities, past medical history including the transplanted organ and post-transplant time, baseline immunosuppressant therapy regimen, COVID-19 clinical manifestations (Signs, Symptoms), intensive care unit (ICU) admission and intubation, abnormal laboratory data (WBC count, C-reactive protein (CRP) serum level and serum Creatinine level (Cr), RT-PCR tests, reported radiographic findings, and patients' outcome were extracted.

2.4 | Statistical analysis

The statistical analysis was performed using SPSS version 21.0 (SPSS Inc). Continuous variables were displayed as mean ± standard deviation, and categorical variables were reported as counts and percentages.

3 | RESULTS

3.1 | Description of included studies

We found 1047 references by applying the search strategy in the databases. We then discarded 499 duplicate citations. 426 articles were also excluded due to apparent irrelevancy of their topics in primary screening (Figure 1). In the secondary screening of 122 full texts, we excluded 72 papers. Finally, 50 studies, including 36 case reports, and 14 case series which overall have presented 337 patients were included in this systematic review.[3,7,12-57] The studies of Qin, L et al and Zhong, z et al reported a same case; to avoid duplication bias, we excluded (Qin, L et al) from our review. Table 1 has summarized the studies and patients' characteristics.

3.2 | Demographic data and comorbidities

A total of 337 patients who met the criteria were included in the current systematic review. More than two-thirds (236 patients) were male, and 101 were female. Regarding the available clear data, the mean ± SD age of patients was 49.9, with a range of 24

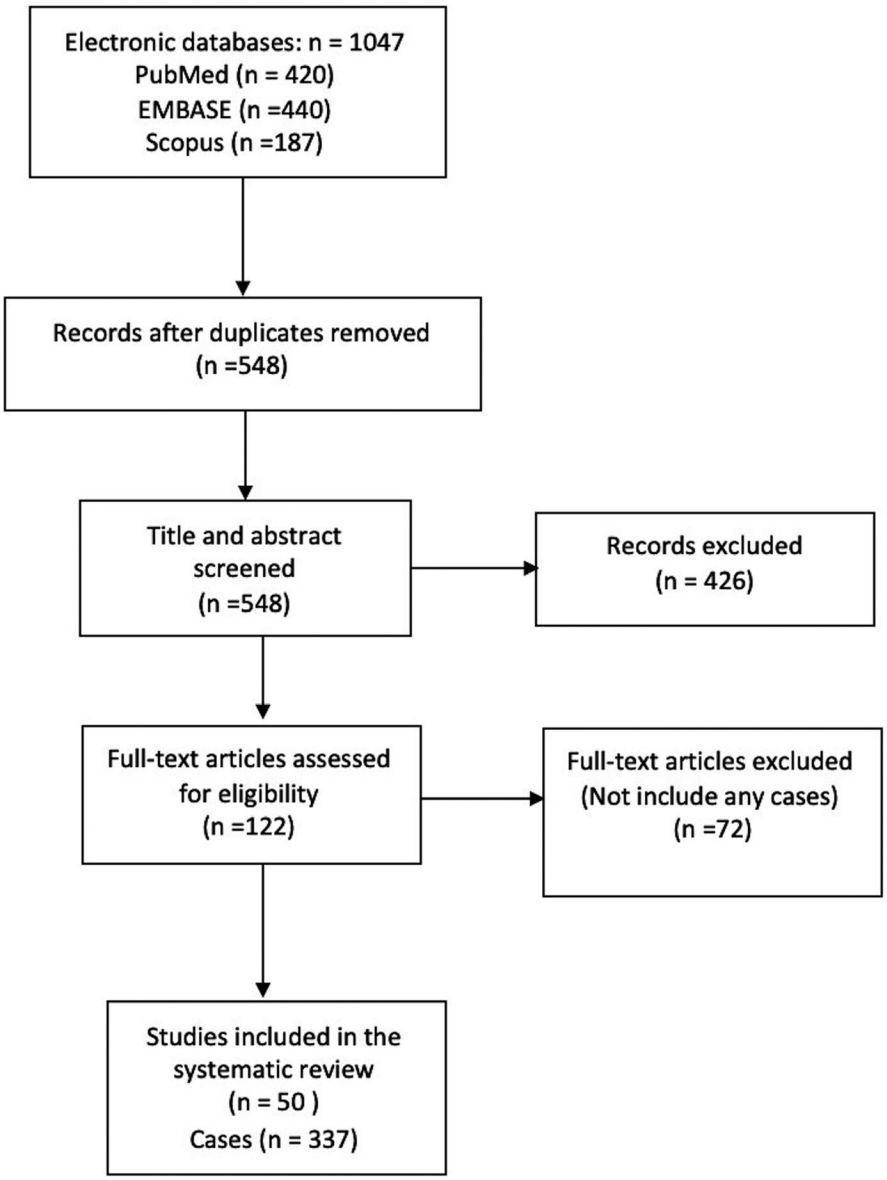

FIGURE 1 PRISMA flowchart of literature search

to 80 years in different studies. The most prevalent patient group was the kidney transplant recipients with a population of 192 (57.0%), followed by 58 (17.2%) with heart, 46(13.6%) with liver, 25 (7.4%) with lung, eight (2.4%) with heart-kidney, three (0.9%) with pancreas-kidney, one (0.3%) with heart-kidney, and one (0.3%) with lung-kidney, with an average of 10.6 (0.2-31) years transplant history among the clearly reported data. Forty-six cases were defined with their donor status; fourteen (30.4%) cases were mentioned that had a living donor, and 32 (69.6%) got their transplanted organ from deceased donors.

one hundred sixty four patients were mentioned to have hypertension, 114 diabetes mellitus, and 10 malignancies. The patients were under medication for these underlying diseases, such as antihypertensive or antihyperglycemic treatments. All patients were under immunosuppressive treatment due to history of transplantation; calcineurin inhibitors were used by 88.9% of patients; it was followed by glucocorticoids for 62.8% of patients. The baseline immunosuppressive treatment of patients is summarized in Table 2.

3.3 | Primary signs and symptoms, and diagnostic measures (RT-PCR, radiographic findings, and laboratory data)

The most reported clinical presentation was fever (228 cases) followed by cough (181 cases). The frequency of reported sign/symptoms is shown in Figure 2.

It was stated that 209 RT-PCR tests were done for the studied patients; all had a positive PCR test except one with a negative test who was diagnosed via CT scan. 189 cases were evaluated through CXR, and there were 21 cases of normal CXR, while 168 (88.9%) were not; among these abnormal cases, 74 cases were reported with details of findings that included 41 (55.4%) cases of infiltrations, 15 (20.3%) cases of consolidations, 11 (14.7%) cases of opacities, 2 (2.7%) cases of haziness, and 5 (6.8%) cases with other findings.

Chest CT scan is mentioned to be performed for 76 cases, and 68 were reported with details. Sixty-seven (98.5%) patients were reported to have abnormal findings; 45 (67.1%) cases were reported with ground-glass

TABLE 1 Summary of all included articles

Author	Cases	country	Gender	Age	TX. Organ	Outcome
Abrishami, A. et al[12]	12	Iran	9 males, 3 females	47.6 (Mean)	Kidney	8 expired, 4 recovered
Aigner, C. et al[13]	1	Germany	Female	59	Lung	Recovered
Alberici, F. et al[14]	20	Italy	16 males, 4 females	59 (Mean)	Kidney	5 expired, 12 hospitalized, 3 discharged
Arpali, E et al[15]	1	Turkey	Female	28	Kidney	Recovered
Banerjee, D. et al[16]	7	England	4 males, 3 females	57.42 (mean)	Kidney	1 expired, 2 recovered, 2 hospitalized, 2 intubated
Bartiromo, M et al[7]	1	Italy	Female	36	Kidney	Recovered
Billah, M. et al[17]	1	USA	Male	44	Kidney	Hospitalized
Bin, L et al[18]	1	China	Male	50	Liver	Recovered
Bussalino, E et al[19]	1	Italy	Male	32	Kidney	Recovered
Chen, S et al [20]	1	China	Male	49	Kidney	Recovered
Cheng, D. R. et al[78]	2	China	1 male, 1 female	56.5 (Mean)	Kidney	Recovered
Cozzi, E. et al[21]	2	Italy	2 males	58.5 (Mean)	Lung	1 expired, 1 recovered
de Barros Machado, D. J. et al[22]	1	Brazil	Male	69	Liver-kidney	Recovered
Donato, M. F. et al[23]	8	Italy	6 males, 2 females	63(Mean)	Liver	6 recovered, 2 hospitalized
Farfour, E. et al[24]	1	France	Male	35	Lung	Not stated
Fernandez-Ruiz, M et al[25]	18	Spain	14 males, four females	66.33 (Mean)	8 kidneys, 6 livers, 4 hearts	5 Expired, 4 hospitalized, 1 intubated, 8 recovered
Fontana, F. et al[26]	1	Italy	Male	61	Kidney	Recovered
Gandolfini, I et al[27]	2	Italy	1 male, 1 female	63.5 (Mean)	Kidney	1 expired, 1 recovered
Gao, F. et al[28]	3	China	3 males	48.6 (Mean)	Liver	1 expired, 2 recovered
Guillen, E et al[29]	1	Spain	Male	50	Kidney	Intubated
Hammami, M. B. et al[30]	1	USA	Male	63	Liver	Recovered
Holzhauser, L. et al[31]	2	USA	1 male, 1 female	67 (Mean)	Heart	1 expired, 1 recovered
Hsu, J. et al [32]	1	USA	Male	39	Kidney-Heart	Recovered
Huang J et al[33]	1	China	Male	58	Kidney	Expired
Johnson, K et al[34]	1	USA	Male	57	Kidney	Recovered
Kates, O et al[35]	4	USA	3 males, 1 female	62 (Mean)	1 kidney, 1 liver, 1 heart, 1 lung	Recovered
Ketcham, S. et al[36]	13	USA	13 males	61 (Mean)	10 hearts, 2 heart-kidney, 1 heart-lung	2 expired, 2 hospitalized, 9 recovered
Kim, Y et al[37]	2	Korea	2 males	46 (Mean)	Kidney	Recovered
Kocak, B. et al[38]	2	Turkey	2 females	41.5 (Mean)	kidney	Recovered
Koczulla, R. A. et al[39]	1	Germany	Female	64	Lung	Recovered

(Continues)

TABLE 1 (Continued)

Author	Cases	country	Gender	Age	TX. Organ	Outcome
Latif, F. et al [40]	28	USA	22 males, 6 females	64.0 (Median)	Heart	7 expired, 4 hospitalized, 17 recovered
Li, F. et al[79]	2	China	2 males	47 (Mean)	Heart	Recovered
Marx, D et al[41]	1	France	Male	58	Kidney	Recovered
Mathies, D et al[42]	1	Germany	Male	77	Heart	Recovered
Meziyerh, S et al[43]	1	The Netherlands	Male	35	Kidney	Recovered
Montagud-Marrahi, E et al[44]	33	Spain	19 males, 14 females	57.3 (Mean)	Kidney	2 expired, 2 hospitalized, 28 recovered
Nair, V. et al[45]	10	USA	6 males, 4 females	56.3 (Mean)	Kidney	3 expired, 7 recovered
Namazee, N. et al[46]	1	Iran	Female,	63	Kidney	Expired
Ning, L et al[80]	1	China	Male	29	Kidney	Recovered
Pereira, M et al[47]	90	USA	53 male, 37 female	57 (Median)	46 kidneys, 17 lung, 13 livers, 9 heart, 3 heart-kidney, 1 liver-kidney,1 pancreas-kidney	16 expired, 15 hospitalized, 59 recovered
Seminari, E et al[48]	1	Italy	Male	50	Kidney	Recovered
Travi, G. et al[49]	13	Italy	9 males, 4 females	59 (Median)	4 kidneys, 7 livers, 2 heart-kidney	3 expired, 10 not stated
Tschopp, J. et al[50]	21	Switzerland	15 males, 6 females	56 (Median)	10 kidney, 5 liver, 2 kidney-pancreas, 1 kidney-lung, 1 pancreas, 1 lung, 1 heart	2 expired, 3 hospitalized, 16 recovered
Wang, J et al[51]	1	China	Male	49	Kidney	Recovered
Xuan, T. M. et al[52]	1	China	Male	70	Lung	Recovered
Zhang, H et al[53]	5	China	4 males, 1 female	44.8 (Mean)	Kidney	3 recovered, 2 hospitalized
Zhang, M, et al et al[54]	1	China	Male	49	Kidney	Recovered
Zhong, Z et al[55]	2	China	2 Males	42.5 (Mean)	Liver, Kidney	Recovered
Zhu, L.; Gong, N et al[56]	10	China	8 males, 2 females	45 (Mean)	Kidney	1 expired, 8 recovered, 1 hospitalized
Zhu, L; Xu, X et al[57]	1	China	Male	52	Kidney	Recovered

opacity (GGO), 8 (11.9%) with mixed patterns, 3 (4.5%) with viral infection presentation, 2 (3.0%) with patchy consolidation, and one (1.5%) with regular patterns. Eight cases (11.9%) were reported with other findings.

Among the studies that had reported the definite laboratory results of CRP or lymphocyte counts, 72.4% (71/98) of cases were reported with lymphocytopenia and 96.8% (92/95) with an increased CRP. Among the 68 cases of kidney transplant with available creatinine (Cr) level data, 48 (70.6%) had presented with high Cr level.

3.4 | Treatment strategies

Seventy-nine of 291 reported cases, (27.1%) patients were reported to have an ICU admission, and 85/239 (35.6%) cases were intubated. The most discontinued/decreased therapies were antimetabolites 177/210 (84.3%), while the highest number of newly prescribed treatments was immunoglobulin-based therapies with 41 cases. In 4.1% of the patients who were using glucocorticoids, it was stopped using or the dosage was decreased, and in 77.9%, the dosage was not changed. The baseline and final immunosuppressant therapies with their changes for patients are summarized in Table 2.

Twenty cases (6.7%) were reported with IVIG prescription post-COVID-19 infection. Hydroxychloroquine was prescribed for 200/ 297 (67.3%) of patients, 137/ 221 (62.0%) consumed antibiotics, and 118/ 224 (52.7%) received other treatments, including 222 Lopinavir/Ritonavir (LPV/r) and two cases of unknown antiviral.

TABLE 2 Summary of available immunosuppressant therapies

	Baseline treatment frequency (%)	Treatment changes after COVID-19 infection			
	Total available Cases = 325	Not Changed**	Decreased or discontinued**	Increased**	Newly prescribed (number of reported cases)
Glucocorticoids	204 (62.8%)	113/145 (77.9%)	6/145 (4.1%)	26/145 (17.9%)	21
Antimetabolites					
Mycophenolate mofetil	227 (69.8%)	33/210 (15.7%)	177/210 (84.3%)	0/210 (0%)	0
Azathioprine or Mizoribine	11 (3.4%)				
Calcineurin inhibitors	289 (88.9%)	139/256 (54.3%)	116/256 (45.3%)	1/256 (0.4%)	3
Immunoglobulin-based therapies	7 (2.1%)	2/2 (100%)	0/2 (0%)	0/2 (0%)	41
mTOR Inhibitor	22 (6.8%)	2/18 (11.1%)	16/18 (88.9%)	0/18 (0%)	0
Cept (TNF Inhibitor—Belatacept)	6 (1.8%)	Data are only available about one discontinued case			

**Number of cases with the change status/total case under the regimen as their baseline treatment (with pre- and post-COVID-19 infection available data).

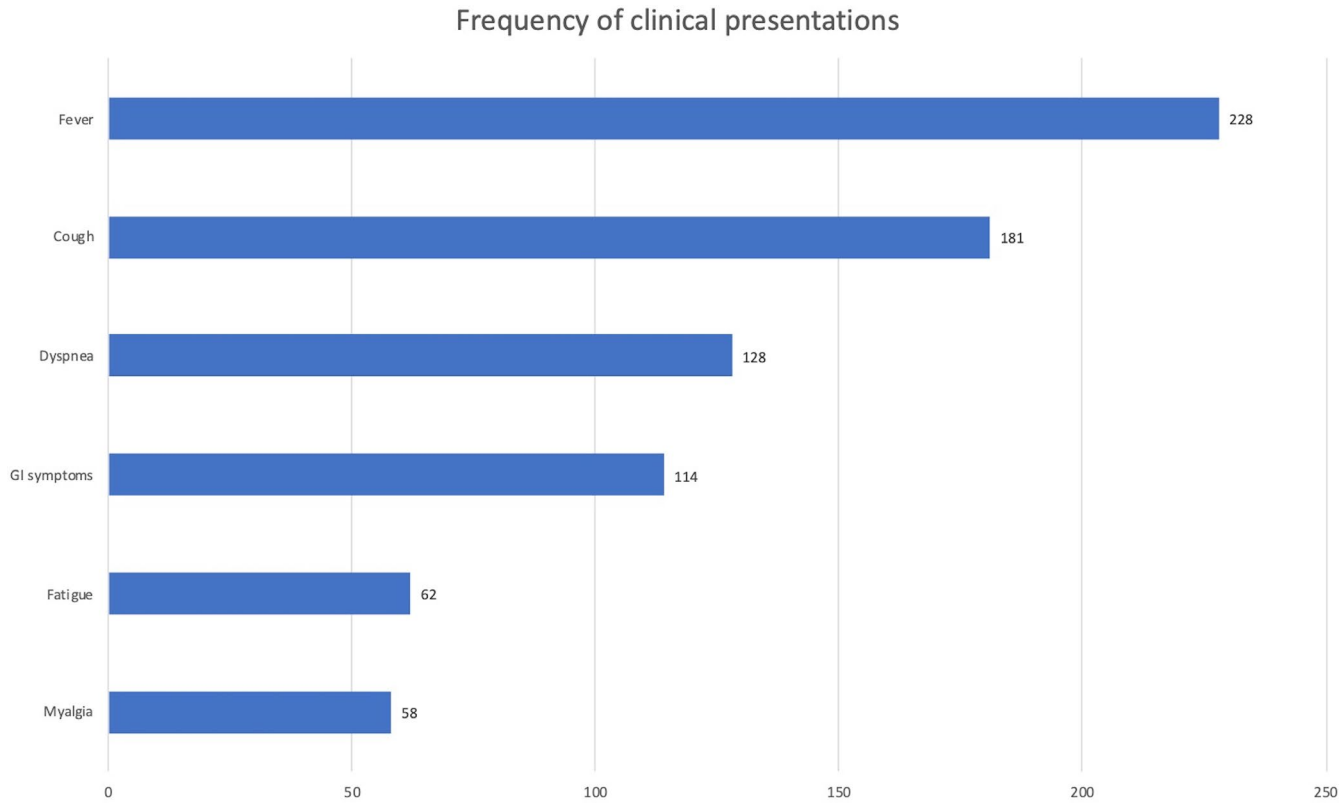

FIGURE 2 Most common signs and symptoms

3.5 | Outcomes

Sixty-one (18.4%) cases were reported to be expired among all the studied patients with reported outcomes (333 cases). 218 (65.9%) patients were discharged, and 54 (16.3%) were reported by the Authors to be still hospitalized.

The available mean ± SD age of expired patients was 61.3 ± 11.7 years, and the available sex proportion was 17/7 for male to female. Excluding studies, in which their data about expired patients were not clear in details, the mortality rate was 18/79 (22.8%), 3/21 (14.3%), 2/10 (20.0%), and 1/6 (16.7%) among patients with kidney, liver, heart, and lung transplantations,

respectively; among these 18 expired patients with kidney transplantation, high creatinine level was noted in 14 of 16 (85.7%) cases with available reports.

4 | DISCUSSION

The infection caused by SARS-CoV-2 was declared as a global pandemic by WHO. Previously, other coronaviruses caused epidemic outbreaks such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) were also seen in SOT recipients.[58,59] Considering the fact that they belong to high-risk groups due to their immunosuppressive medications, it is vital to determine COVID-19 manifestations in them.

In our study, nearly two-thirds of the patients were male. Also, the mean age was around 50. A recent meta-analysis of more than 2500 COVID-19 patients showed a mean age of about 52 years and the male proportion of 56%.[60] This finding shows that there is no noticeable difference in the mean age of COVID-19 patients between the general population and transplant patients. It is also reported that male patient proportion was greater than women in a case series study of 5700 COVID-19 patients from New York City.[61] However, the higher male proportion of COVID-19 in transplant recipients might be due to the higher male proportion in transplant patients based on the previous studies.[62]

According to Global observatory on donation and transplantation, kidney, liver, heart, and lung are the most frequently transplanted organs in the world[63]; however, the published cases from heart recipients seem to be more than liver recipients. Besides, 164 patients were reported to have hypertension, and 114 have diabetes mellitus. Comparing the data to the normal population as reported in Yang, J et al, the normal hosts of COVID-19 represented hypertension, diabetes mellitus, cardiovascular, and respiratory system disease as the most prevalent comorbidities, which is consistent with our results.[64]

The reported clinical manifestations in the reviewed studies are quite variable. Manuel, O et al[65] reported that transplant recipients often present with mild or atypical symptoms, and sometimes fever may be absent. However, our total result matches the same clinical profile of the general population with the most common clinical symptoms of fever, cough, and dyspnea.[66] Nevertheless, it should be noted that about one-third of the studied patients presented with GI symptoms. A recently published, multicenter study of 204 patients with confirmed COVID-19 suggests that approximately 18.5% of patients presented with GI symptoms, including diarrhea, vomiting, or abdominal pain.[67] Therefore, SOT patients may suffer from GI symptoms more often than the general population.

Since SOT patients are on medications that modulate the inflammatory response, symptoms associated with community-acquired respiratory viruses are typically less severe and less frequent than in regular healthy hosts, especially in patients with severe lymphocytopenia.[68] We found that about 72% of the patients with available data show lymphocytopenia in their blood tests. Tan, Li et al[69] suggest that lymphocytopenia is an effective and reliable indicator of the severity and hospitalization in COVID-19 patients. Furthermore, in our review, among the patients with reported CRP, almost 97% have shown high plasma concentration. Wang L. found that CRP levels were positively correlated with lung lesions and disease severity and, it can be a factor to consider for estimating the prognosis.[70]

Among the 68 cases of kidney transplant with available Cr level data, nearly 70% had presented with high Cr level. This may be due to acute kidney injury (AKI) in COVID-19 infection. It is reported that AKI in COVID-19 can accompany by sepsis, multi-organ failure, and shock, suggesting the cause of AKI can be due to acute tubular necrosis (ATN).[71] Furthermore, Cheng Y et al[72] found that AKI is a predictor of mortality in COVID-19 infection, and previously, it was reported that kidney injury was associated with an increased chance of death in patients with H1N1 and SARS as well.

Our study shows that nearly 89% of the patients had shown abnormality in their CXR, and the most frequent findings were infiltrations, consolidations, opacities, and haziness. Wong, HYF et al[2] reported that 65% of the confirmed COVID-19 cases had abnormal CXR findings, and consolidation was the most common one. This can indicate that SOT recipients have shown more abnormality in their CXR and this can be used for primary screening for the disease by seeing infiltrations or consolidations. Besides, our chest CT evaluations demonstrate abnormalities in about 98% of patients; GGO in 67% of cases, 12% mixed, 4.5% with viral infection presentation, and 3% with patchy consolidation which is consistent with a case series of 81 patients with COVID-19 from the general population.[73] However, Ju, CR et al reported that the imaging demonstrations of COVID-19 in SOT patients do not share standard features with the majority of the general population.[3]

Calcineurin inhibitors, antimetabolites, and corticosteroids are most frequently used as baseline immunosuppressants; however, in COVID-19-confirmed cases, antimetabolites were mostly ceased whereas prescription of corticosteroids was kept in treatment or even increased in dosage. It was considered essential to use appropriate doses of corticosteroids throughout the process, as it could suppress inflammatory storms and promote the recovery from pneumonia without severe side effects as described in Zhong, Z et al[55] Furthermore, Fix, O.K et al suggest that the immune response may be the main reason for pulmonary injury due to COVID-19, and immunosuppression may be protective.[74] However, the World Health Organization recommends avoiding corticosteroids for treatment of COVID-19 unless for another therapeutic purpose.[75] Overall, use of steroids is still controversial and the efficacy has not been proven in clinical trials in the general population or in transplant recipients specifically.[20] In addition, it is a common strategy when treating pneumonia caused by opportunistic virus infections to reduce or even discontinue immunosuppressant drugs to allow recipients the opportunity to reacquire anti-infection immunity within a short period in post-transplant settings.[57] Besides, IVIG was administered to 20 patients. Jawhara, S[76] reported that immunotherapy with IgG combined with antiviral medications could provide an alternative treatment against COVID-19 infection. These immune IgG

antibodies collected from the healed patients will boost the immune response in newly infected patients.

This study shows that almost 27% of the patients were admitted to ICU, and around 36% were intubated. Besides, Richardson, S et al[61] study on patients with COVID-19 admitted to different hospitals in New York City showed that 14.2% of the patients were hospitalized in ICU, 12.2% underwent invasive ventilation, and almost 21% died. However, Cascella, M et al[77]suggest that the death rate ranges from 1% to 2% depending on the study and country. Comparing ICU admission and intubation can indicate that the course of the disease is more severe in SOT patients than in the normal hospitalized population. In addition, our results explicate that the mortality is around 18% among all patients. It is important to note that many of these SOT patients who contracted COVID-19 may still be in hospitals, some even in the ICU, and the outcome is still not predictable. These findings show that SOT patients are at a higher risk of mortality than the general population but lower in comparison with normal hospitalized patients as mentioned in Richardson, S et al.[61]

4.1 | Limitations and suggestions on future study

To best of our knowledge, this is the only systematic review on SOT recipients with COVID-19 that has evaluated the different aspects of the disease from diagnosis, to treatment modifications. The emergence of the outbreak and lack of high-level evidence in the reviewed literature makes this study much more critical, which may shed light on the better management of transplant patients, who should be considered as a vulnerable group during this pandemic.

There are several limitations to making comparisons, generalizations, or concluding the currently reported cases of SOT patients treated for COVID-19. These recently published cases present a considerable variation in transplant and clinical characteristics as well as treatment strategies. Most of the currently published cases do not describe patients' incubation periods, and days of hospital stay thoroughly to allow for comparison. Additionally, very limited data regarding medication interactions and reasons for changing some drugs were available. Besides, given the fact that a significant number of individuals may not present with symptoms until the disease progresses to advanced stages, the overall generalizability of results and conclusions may somewhat be hampered by publication bias. Another limitation was that performing pooled data analyses was impossible due to the lack of information from the studies retrieved and their design, which are mostly case study and series. At the time of writing this study, many cases were still at the hospital, some even intubated, and the reported mortality can be higher since the outcome of these patients is not completely reported yet. In addition, it is too soon for evaluation of the long-term effects of immunosuppressant discontinuation or dose reduction in SOT patients on graft rejection, and there is an essential need for more comprehensive clinical studies including short- and long-term follow-up cohort assessments. Also, more concentration is needed on prolonged viral shedding since there is a potential of putting the lives of other patients and health workers at risk.

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AUTHOR CONTRIBUTION

Seyed Ali Moosavi and Amirali Mashhadiagha designed the study, collected the data, and drafted the manuscript. Alireza Hashemazar contributed to design the study, collected the data, participated in data analyses, and participated in drafting the manuscript. Amir Human Hoveidaei analyzed the data and participated in drafting the manuscript. Nasrin Motazedian, and Davide Bolignano contributed to design the study, participated in drafting the manuscript, reviewed the manuscript, and edited the final version.

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APPENDIX 1

SEARCH STRATEGY

Embase: (((((COVID-19) OR SARS-CoV-2) OR coronavirus) OR corona-virus)) AND ((graft*) OR transplant*)

Scopus: (((((COVID-19) OR SARS-CoV-2) OR coronavirus) OR corona-virus)) AND ((graft*) OR transplant*)

PubMed: (((((COVID-19) OR SARS-CoV-2) OR coronavirus) OR corona virus)) AND ((graft*) OR transplant*)