COVID-19 Mortality in Transplant Recipients

M. Alfishawy[1,2]*,
A. Elbendary[3],
M. Mohamed[4],
M. Nassar[5]

[1]*Infectious Diseases Consultants and Academic Researchers of Egypt (IDCARE), Cairo, Egypt*
[2]*Aswan Heart Centre, Aswan, Egypt*
[3]*Dermatology Department, Kasr Alainy Faculty of Medicine, Cairo University, Cairo, Egypt*
[4]*Nephrology Division, University of Tennessee Health Science Center, Memphis, TN, USA*
[5]*Internal Medicine Department, Beni Suef University, Beni Suef, Egypt*

ABSTRACT

Background: Organ transplant recipients are vulnerable to multiple infectious agents and in a world with a circulating SARS-CoV-2 virus, it would be expected that patients who are immunosuppressed would have higher mortality.

Objective: To determine the COVID-19 mortality in transplant recipients.

Methods: We conducted a search in PubMed and Google scholar databases using the keywords for COVID-19 and transplantation. All related studies between January 1, 2020 and May 7, 2020 were reviewed. All relevant published articles related to COVID-19 in transplant recipients were included.

Results: 46 articles were included; they studied a total of 320 transplant patients—220 kidney transplant recipients, 42 liver, 19 heart, 22 lung, 8 HSCT, and 9 dual organ transplant recipients. The overall mortality rate was 20% and was variable among different organs and different countries. 65 transplant recipients died of complications attributable to COVID-19; 33 were males (15% of males in this cohort), 8 females (8% of females in this cohort), and 24 whose sex was not determined. They had a median age of 66 (range: 32–87) years. The median transplantation duration was 8 years (range: 30 days to 20 years). The most frequent comorbidity reported was hypertensions followed by diabetes mellitus, obesity, malignancy, ischemic heart disease, and chronic obstructive pulmonary disease. The most frequent cause of death reported was acute respiratory distress syndrome.

Conclusion: Transplant recipients in our cohort had a high mortality rate. However, outcomes were not the same in different countries based on outbreak settings. Mortality was noted in elder patients with comorbidities.

KEYWORDS: COVID-19; Transplant recipients; Kidney transplant; Liver transplant; Heart transplant

INTRODUCTION

Organ transplantation is currently an established line of treatment for end-stage organ disease. As the recipients are under chronic immunosuppression, they become vulnerable to multiple infectious agents, particularly the emerging infectious diseases. Coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an emerging pandemic with over 6,000,000 confirmed cases worldwide and more than 390,000 deaths (reported case fatality 4%–14% in developed countries) [1]. Assessment of severity and outcome of SARS-CoV-2 infection in organ transplant recipients is required. Organ transplant recipients on chronic immunosuppression may alter the clinical presentation revealing atypical findings in such population [2]. Besides that, the course of the disease in the transplant patient population is unknown and it is unclear whether immunosuppres-

*Correspondence: Mostafa Alfishawy, MD, 1 Hassan Badrawi St, Haram, Giza, Egypt 12111.
ORCID: 0000-0002-9153-3237
Tel: +20-15-5007-9112
E-mail: malfishawy@kasralainy.edu.eg

sion results in a worse prognosis compared to the general population or not. On the other hand, immunosuppressive medication should be maintained in such patients to avoid transplant rejection.

Since the start of COVID-19 pandemic, several guidelines have recommended withdrawal of calcineurin inhibitors in transplant patients with severe SARS-CoV-2 infection [3, 4]. Yet, emerging evidence suggests that the severe form of the disease and the leading cause of death in such infection is a hyperinflammatory state and cytokine storm [5]. Therefore, theoretically immunosuppressive therapy could have a positive effect on transplant patients infected with SARS-CoV-2.

The objective of this review was to study the available information following almost 100 days since COVID-19 was reported and assess the risk of mortality of SARS-CoV-2 infection in transplant recipients.

MATERIALS AND METHODS

We conducted a PubMed search using the words "COVID-19 AND transplant"[All Fields] OR "severe acute respiratory syndrome coronavirus 2 AND transplant"[All Fields] OR "2019-nCoV AND transplant"[All Fields] OR "SARS-CoV-2 AND transplant"[All Fields] OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND transplant [All Fields]). We also included relevant articles from the references of manuscripts studied.

Google Scholar was also systematically searched, using the terms COVID-19 or SARS-CoV-2 AND transplant. Any reference list from eligible articles was reviewed to include any potential relevant article. The last search conducted was on May 7, 2020.

Retrospective studies, systematic and narrative reviews, case-series and case-reports were included in the review. Studies published in languages other than English were excluded. Three reviewers (MA, MM, and MN) independently screened the titles, abstracts, and full texts of the retrieved articles to assess the eligibility of studies for inclusion. Duplicate references were removed and a final list of articles was generated.

Among 605 articles found, 46 met the eligibility criteria. Included studies were published case of solid organ transplant recipients that were infected by SARS-CoV-2 confirmed by RT-PCR.

Patients were categorized as mild, moderate, and severe according to what was reported; when not reported, we categorized patients as either mild/asymptomatic according to symptoms with no evidence of pneumonia, moderate when there was evidence of pneumonia, and severe when SpO_2 was ≤93% on breathing room air or required intensive care unit (ICU) admission.

RESULTS

Forty-six of 605 retrieved articles were included; they studied a total of 320 transplant recipients; 218 (68.1%) were males and 99 (30.9%) were females; sex was not reported in three pediatric patients. In terms of epidemiology, 161 (50.3%) were reported from the USA, 52 (16.3%) from Spain, 43 (13.4) from Italy, 31 (9.7%) from China, 12 (3.8%) from Iran, 7 (2.2%) from UK, 7 (2.2%) from France, 2 (0.6%) from Germany, 2 (0.6%) from Korea, 1 (0.3%) from Brazil, 1 (0.3%) from Netherlands, and 1 (0.3%) from Turkey. Regarding the organs transplanted, 220 (69%) underwent kidney transplantation, 42 (13%) liver transplantation, 22 (7%) lung transplantation, 19 (6%) heart transplantation, 8 (3%) hematopoietic stem cell transplantation (HSCT), and 9 (3%) dual organ transplantation. Sixty-nine (21.7%) of cases were asymptomatic or mildly infected, 123 (38.7%) had moderate infection, and 126 (39.6%) had severe infection; two patients in one study had no severity report. Among the 320 transplant recipients studied, 64 (20%) died, all but two of them had severe SARS-CoV-2 infection (Tables 1 and 2).

Table 1: Characteristics of transplant recipients with COVID-19 in the included case reports

Reference	Country	No	Organ	Median age	Mild/ Asymptomatic	Moderate	Severe	Sex	Alive
Mathies *et al* [6]	Germany	1	Heart	77			1	M	1 (100%)
Chen *et al* [7]	China	1	Kidney	49			1	M	1 (100%)
Arpali *et al* [8]	Turkey	1	Kidney	28	1			F	1 (100%)
Guillen *at el* [2]	Spain	1	Kidney	50		1		M	1 (100%)
Zhong *et al* [9]	China	2	1 Kidney 1 liver	48, 37	1		1	2M	2 (100%)
Zhu *et al* [10]	China	10	Kidney	44.5	2		8	8M/2F	9 (90%)
Akalin *et al* [11]	USA	36	Kidney	60	8	17	11	26M/ 10F	26 (72%)
Lagana *et al* [12]	USA	1	Liver	1			1	F	1 (100%)
Hsu *et al* [13]	USA	1	Heart/ Kidney	39		1		M	1 (100%)
Wang *et al* [14]	China	1	Kidney	49	1			M	1 (100%)
D'Antiga [15]	Italy	3	Liver	pediatric	3				3 (100%)
Donato *et al* [16]	Italy	8	Liver	70	6	2		6M/2F	8 (100%)
Marx *et al* [17]	Italy	1	Kidney	58	1			M	1 (100%)
Huang *et al* [18]	China	1	Liver	59			1	M	0
TCUKTP [19]	USA	15	Kidney	51	5	6	4	10M/ 5F	13 (86%)
Kates *et al* [20]	USA	4	1 Kidney 1 Liver 1 Heart 1 Lung	62.5	2	1	1	3M/1F	4 (100%)
Fontana *et al* [21]	Italy	1	Kidney	61		1		M	1 (100%)
Periera *et al* [22]	USA	90	46 Kidney 13 Liver 9 Heart 17 Lung 5 Dual	57	22	41	27	53 M/ 37 F	74 (82%)
Fernandez-Ruiz *et al* [23]	Spain	18	8 Kidney 6 Liver 4 Heart	71	5	8	5	13M/ 5F	13 (72%)*
Huang *et al* [24]	China	2	1 Kidney 1 HSCT	55			2	2M	0
Bhoori *et al* [25]	Italy	3**	Liver	>65***			3	3M	0
Chen *et al* [26]	China	3	Lung╪	66			3	3M	2 (66%)
Alberici *et al* [27	Italy	20	Kidney	59		11	9	16M/ 4F	15 (75%)
Ning *et al* [28]	China	1	Kidney	29			1	M	1 (100%)
Qin *et al* [29]	China	1	Liver	37		1		M	1 (100%)

Continued

Table 1: Characteristics of transplant recipients with COVID-19 in the included case reports

Reference	Country	No	Organ	Median age	Mild/Asymptomatic	Moderate	Severe	Sex	Alive
Seminari *et al* [30]	Italy	1	Kidney	50			1	M	1 (100%)
Zhu *et al* [31]	China	1	Kidney	52		1		M	1 (100%)
Liu *et al* [32]	China	1	Liver	50			1	M	1 (100%)
Maggi *et al* [33]	Italy	2	Liver	61, 69				2M	1 (50%)
Bartiromo *et al* [34]	Italy	1	Kidney	36		1		F	1 (100%)
Zhang *et al* [35]	China	5	Kidney	45		5		4M/1F	5 (100%)
Li *et al* [36]	China	2	Heart	51, 43		1	1	2M	2 (100%)
Gandolfini *et al* [37]	Italy	2	Kidney	75, 52			2	1M/1F	1 (50%)
Banerjee *et al* [38]	UK	7	Kidney	54	2		5	4M/3F	6 (85%)
Kim *et al* [39]	Korea	2	Kidney	56, 36		2		2M	2 (100%)
Nair *et al* [40]	USA	10	Kidney	57	3	2	5	6M/4F	7 (70%)
Meziyerh *et al* [41]	Netherlands	1	Kidney	35			1	M	1 (100%)
Hammami *et al* [42]	USA	1	Liver	63		1		M	1 (100%)
Aigner *et al* [43]	Germany	1	Lung	59		1		F	1 (100%)
Billah *et al* [44]	USA	1	Kidney	44			1	M	1 (100%)
Machado *et al* [45]	Brazil	1	Kidney/ Liver	69		1		M	1 (100%)
Bussalino *et al* [46]	Italy	1	Kidney	32		1		M	1 (100%)
Abrishami *et al* [47]	Iran	12	Kidney	47			12	9M/ 3F	4 (25%)
Malard *et al* [48]	France	7	HSCT	61		4	3	5M/2F	6 (86%)
Montagud-Marrahi *et al* [49]	Spain	33	31 Kidney 2 Dual	57	7	13	13	19M/14F	31 (94%)
Holzhauser *et al* [50]	USA	2	Heart	67			2	M/F	1 (50%)

*Mortality 2 Kidney, 2 Lung, 1 Heart

**148 patient data was not available (only report 3 male patients were reported)

*** This was the age reported

ǂ Patients received lung transplants for COVID-19

F: Female; M: Male; NA, not available; TCUKTP: The Columbia University Kidney Transplant Program

In our cohort, 65 transplant recipients died of complication attributable to COVID-19; 33 were males (15% of males in this cohort), 8 females (8% of females in this cohort), and 24 whose sex was not determined [11, 22]. Periera, *et al* [22], reported 16 deaths without

Table 2: Detailed number of patients in different organs transplanted and their mortality percentages

Total	320	174*	29*	10*	5*	8	4*
Total mortality	64 (20%)	36 (20%)	5 (17.2%)	2 (20%)	3 (60%)	2 (25%)	0

*These are the total number of patients excluding the patients described in Periera et al as these details were not mentioned

mentioning the age of patients, clinical characteristics or cause of death. The median age of the remaining patients was 66 (range: 32–87) years. Regarding the time since transplantation to the time of COVID-19, there was no information for 27 (41%) patients; one had lung transplantation 40 days after COVID-19; the remaining cases had a median transplantation duration of 8 years (range: 30 days to 20 years). Comorbidities were reported in 38 cases (58% of total mortality), and included hypertension in 22 patients (58%), diabetes mellitus in 11 (29%), obesity in 5 (13%), malignancy in 5 (13%), ischemic heart disease in 4 (11%), chronic obstructive pulmonary disease in 2 (5%), hepatitis B in 2 (5%), asthma in 1 (3%), hepatitis C in 1 (3%), HIV in 1 (3%), and chronic kidney disease in 1 (3%). Nine (14%) patients did not have comorbidities.

The most frequent cause of death reported was acute respiratory distress syndrome (ARDS). None of the patients faced issues regarding hospital resource availability that may have affect cause of death. All the deceased cases with reported detailed characteristics had reduced or stopped their immunosuppressive therapy apart from steroids. None had graft rejection (Table 3). There were no any post-mortem exams reported in our cohort.

We compared transplant mortality by 10-year age intervals to data from Richardson, *et al* [51], on mortality in New York similar to most of our patients who were reported from same city. It was evident that mortality increased with increasing age among transplant recipients (Fig 1).

Our transplant recipient cohort mortality was categorized into different countries reported from, and contrasted to the general population

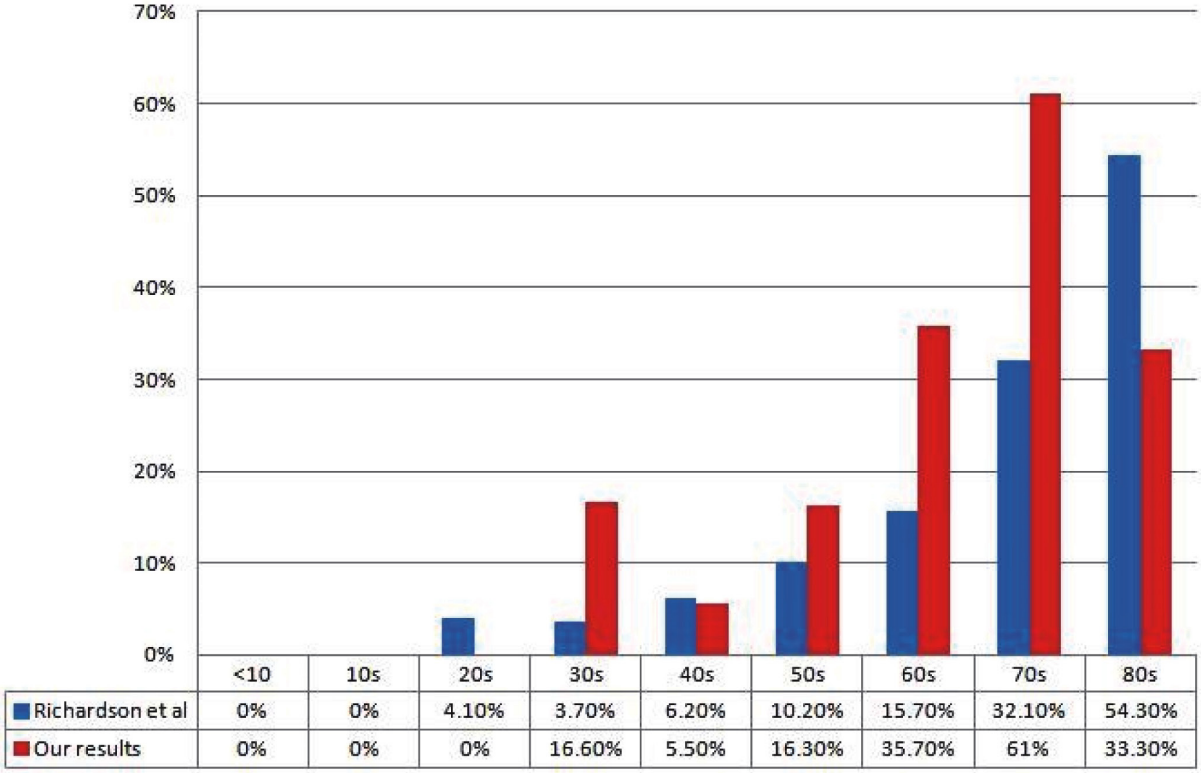

Figure 1: Comparison of mortality rates in transplant recipients and mortality rates reported by Richardson, *et al* [51].

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbidities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
Zhu *et al* [10] China	Kidney	1/10 (10%)	59	M	ND	HTN, HHD, COPD	Severe (ICU)	-CT chest: Multiple bilateral ground glass opacities -Significant serum creatinine elevation -Significant decrease in urine volume	-MPA cessation -CNI cessation -IV MP -IVIG -Antiviral (not specified) -Mechanical Vent.	6 days	-Acute renal allograft failure -Sudden acute respiratory failure
Akalin *et al* [11] #1* USA	Kidney	10/36 (28%)	60	M	5 weeks	None	Mild (home isolation)	ND	MMF cessation	None	-Sudden death
Akalin *et al* [11] #2* USA	Kidney	10/36 (28%)	72	M	3 months	DM, HTN	Mild (home isolation	ND	Decrease IS (not specified)	None	-Sudden death
Huang *et al* [18] China	Liver	1/1 (100%)	59	M	3 years	History of HBV and HCC	Mild Complicated in day 4 by nosocomial infection	-Chest CT scan showed bilateral ground-glass opacities -Day 4: Marked lung inflammation, blood culture positive for candida albicans, alveolar lavage positive for Ps.	At admission: lopinavir/ritonavir , piperacillin tazobactam Decrease in MMF, CNI -ECMO at later period - Cefperazone-sulbactam and caspofungin	45 days	Multiple organ failure

Continued

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
TCUKTP [19] #1 USA	Kidney	2/15 (13%)	70	M	5 years	ND	Severe	Lymphopenia (500) CRP=100mg/dL IL-6=89.5pg/mL	Held MPA, postponed belatacept HQ, azithromycin	ND	Severe acute respiratory distress syndrome
TCUKTP [19] #2 USA	Kidney		78	M	10 years	ND	Severe	CXR: bilateral patchy opacity Lymphocytes=860 CRP=208mg/dL IL-6=10 pg/mL	Held MMF HQ, azithromycin	ND	Severe acute respiratory distress syndrome
Periera *et al* [22] USA	ND	16/90 (17.8%)	ND	ND	ND	ND	ND	ND	ND	ND	ND
Fernandez-Ruiz *et al* [23] #1 Spain	Kidney	5/18 (27.8%)	78	M	8.3 years	HTN, prostatic adenocarcinoma	Severe	CXR; Unilateral diffuse consolidation	Lopinavir/ritonavir Reduction of tacrolimus dose High flow O therapy	5 days	ARDS
Fernandez-Ruiz *et al* [23] #2 Spain	Kidney		71	F	6 years	HTN	Severe	CXR: Bilateral interstitial pneumonia, patchy consolidations	Lopinavir/ritonavir HQ, Reduction of tacrolimus dose, discontinuation of MPA and prednisone Metilprednisolone (day +10), IVIg (day +10)	16 days	ARDS

Continued

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
Fernandez-Ruiz *et al* [23] #3 Spain	Liver		72	M	5.5 years	HTN, DM, obesity	Severe	CXR: Multifocal consolidation	HCQ (day +1), LPV/r, IFN-β, HFOT, Transitory conversion from MMF to tacrolimus	7 days	Progressive respiratory failure with ARDS, renal failure,
Fernandez-Ruiz *et al* [23] #4 Spain	Liver		73	M	16.4 years	HBV cirrhosis, diabetes, asthma, bronchiectasis, splenectomy	Severe (ICU)	CXR: multifocal consolidation	Discontinuation of MMF Mechanical vent.	24 days	ARDS, refractory shock
Fernandez-Ruiz *et al* [23] #5 Spain	Heart		63	M	17.9 years	IHD, HTN, DMs, lung cancer, peripheral artery disease	Severe	CXR: bilateral diffuse consolidation	Discontinuation of cyclosporine and MMF LPV/r, HQ, IFN-β (day +6)	10 days	ARDS

Continued

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
Huang *et al*[24] #1 China	HSCT	2/2 (100%)	51	M	2 years	History of acute myeloid leukemia	Severe	Chest CT: multiple patchyground glass opacities bilaterally. Lymphopenia (258)	Cessation of IS (Cs) LPV/r, MP, Mechanical vent. linezolid, meropenem, and caspofungin for nosocomial infection	22 days	ARDS
Huang *et al*[24] #2 China	Kidney		58	M	12 years	None	Severe	Chest CT: multiple patchy ground glass opacities Lymphopenia (376)	Cessation of IS (MMF), LPV/r Methylprednisolone, Mechanical vent. linezolid, meropenem, and caspofungin when nosocomial infection ECMO	40 days	Multiorgan failure
Bhoori *et al*[25] Italy	Liver	3/3 (100%)	>65**	3M	The 3 cases transplanted more than 10 years ago	The 3 had HTN, DM, obesity	3 severe	ND	All three patients their IS regimen had been gradually tapered off, with very low trough concentrations of CI (two patients receiving Cs [28 and 35 ng/mL, respectively] and one receiving tacrolimus [2 1ng/mL]).	3 to 12 days	ARDS in the 3cases

Continued

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
Feng *et al* [26] China	Lung	1/3 (33%)	66	M	Lung transplanted after COVID-19 infection by 42 days	HTN	Severe	ND	ND	ND	Death post operative by 1 day
Alberici *et al* [27] #1 Italy	Kidney	5/20 (25%)	71	M	13 years	IHD	Severe	ND	MMF/CNI/low-dose steroids Dexamethasone		ARDS
Alberici *et al* [27] #2 Italy			57	M	2 years	HCV infection	Severe	ND	MMF/CNI/low-dose steroids, combination of lopinavir and ritonavir, HQ, Dexamethasone Tocilizumab	Overall, patients died after a median of 11 days from admission	ARDS
Alberici *et al* [27] #3 Italy			59	M	5 years	HTN	Severe	ND	MMF/CNI/low-dose steroids, combination of lopinavir and ritonavir, HQ, Dexamethasone		ARDS
Alberici *et al* [27] #4 Italy			70	F	16 years	HTN	Severe	ND	MMF/CNI/low-dose steroids, combination of lopinavir and ritonavir, HQ, Dexamethasone		ARDS
Alberici *et al* [27] #5 Italy			63	M	16 years	HTN	Severe	ND	MMF/CNI combination of lopinavir and ritonavir, HQ, Dexamethasone Tocilizumab		

Continued

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
Maggi *et al* [33] Italy	Liver	1/2 (50%)	69	M	30 days	HIV	Severe	ND	ND	ND	ARDS
Gandolfini *et al* [37] Italy	Kidney	1/2 (50%)	75	M	10 years	COPD, heart disease, HTN, obesity	Severe	Chest CT: 40% lung involvement CRP=180mg/dL Lymphocytes=880	Reduction of MMF and CNI dose lopinavir and ritonavir, HQ Antibiotics	5 days	ARDS
Banerjee *et al* [38] UK	Kidney	1/7 (14%)	76	F	1 year	DM, HTN	Severe (ICU)	CXR: revealed bilateral patchy consolidation Lymphocyts=800 CRP=83mg/dL d-dimer>6000µg/1	MMF stopped, CNI reduced Mechanical ventilator Antibiotics	12 days	ARDS, AKI
Nair *et al* [40] #1 USA	Kidney	3/10 (30%)	56	M	20 years	DM, HTN	Severe (ICU)	CXR: multifocal patchy opacity Lymphocyts=320 CRP=30.6mg/dL Ferritin=2871ng/mL	Cessation of MMF and CNI HQ, azithromycin, ceftriaxone Mechanical vent.	5days	ARDS AKI
Nair *et al* [40] #2 USA			74	F	8 years	HTN, malignancy (not specified)	Severe (ICU)	CXR: multifocal patchy opacity Lymphocyts=440 Ferritin=817ng/mL	Machanical vent. Cessation of CNI, HQ, Azithromycin	21 days	ARDS
Nair *et al* [40] #3 USA			56	F	3 years	DM, HTN	Severe (ICU)	CXR: multifocal patchy opacity Ferritin=994ng/mL CRP=23.5mg/dL	Mechanical vent. Cessation of MMF HQ, azithromycin Levofloxacin, ceftriaxone	8 days	ARDS

Continued

Table 3: Clinical characteristics of deceased transplant recipients infected by COVID-19

Reference	Organ	No	Age	Sex	Time since Tx	Comorbities	COVID-19 severity	Radiologic features and relevant labs	Therapeutic approach	Length of hospital stay	Cause of death
Abrishami *et al* [47] Iran	Kidney	8/12 (67%)	32-66 (median 56)	7M/ 1F	3-18 years (median 14.5)	1 HTN, IHD 7 none	8 Severe (ICU)	Lymphopenia (6/8), Elevated CRP (6/8), elevated creatinine (3/8)	ND	ND	8 ARDS
Malard *et al* [48] France	HSCT	1/7 (14%)	65	M	ND	HTN	Severe	ND	ND	17 days	ARDS
Montagud-Marrahi *et al* [49] Spain	31 Kidney 2 Dual	2/33 (6%)	87 72	F M	ND	ND	Both severe (ICU)	ND	ND	13 days 22 days	ARDS
Holzhauser *et al* [50] USA	Heart	1/2 (50%)	59	F	8 years	DM, HTN, CKD	Severe	CXR: bilateral diffuse bronchial wall thickening and patchy peribronchial ground-glass opacities CRP=110 mg/dL Ferritin 4342ng/mL (day 6)	HQ, doxycyclin, IVIG, lopinavir/ritonavir CVVHD Heparin drip	10 days	ARDS AKI

*Only two from ten patients were reported in details

**This is the age reported in this article

AKI: acute kidney injury; ARDS: acute respiratory distress syndrome; CKD: chronic kidney disease; CNI: calcineurin inhibitor; COPD: chronic obstructive pulmonary disease; CRP: C reactive protein; Cs: cyclosporine; CVVHD: continuous veno-venous hemodialysis ; CXR: chest x ray; ECMO: extracorporeal membrane oxygenation; F: female; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HHD: hypertensive heart disease; HSCT: Haematopoeitic Stem cell Transplant; HFOT: high flow O therapy; HIV: human immunodeficiency virus; HQ: hydroxychloroquine; HTN: hypertension; ICU: intensive care unit; IHD: ischemic heart disease;IS: immunosuppressive; LPV/r: lopinavir/ritonavir; M: male; MMF: mycophenolate mofetil; MP: methylprednisolone; MPA: mycophenolic acid; ND: not determined; Ps: pseudomonas; TCUKTP: The Columbia University Kidney Transplant Program; Tx: transplant

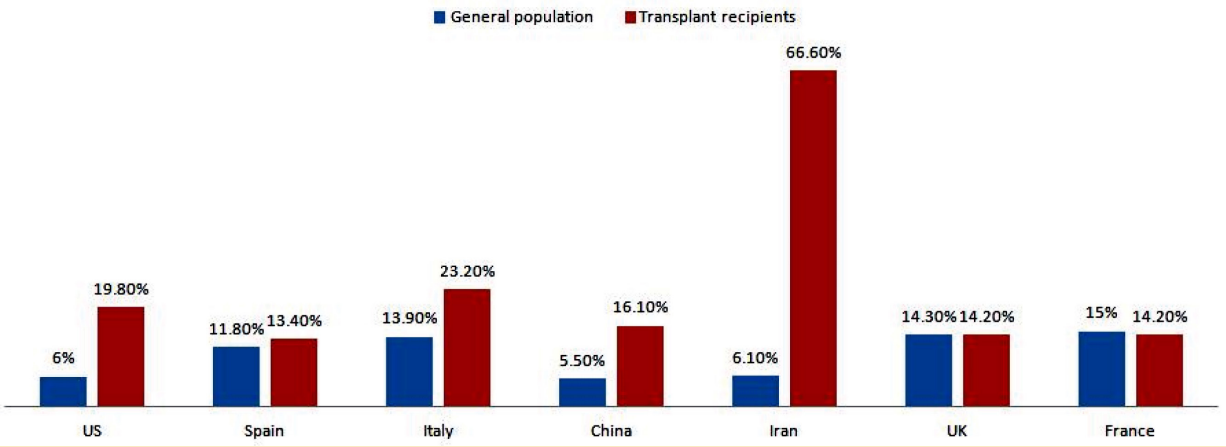

Figure 2: Mortality rates in transplant recipients infected with COVID-19 in selected countries compared to the corresponding mortalities in general population. Data of general population adapted from Dong, *et al* [1]

mortality at the same country (Fig 2).

DISCUSSION

In this review, we studied the cases of SARS-CoV-2 infection in solid organ transplant recipients. All reported patients received various regimens of immunosuppression which theoretically would lead to more severe infections or increased mortality.

The percentage of patients with asymptomatic or mild disease was 21.7%; 38.7% had moderate severity and 39.6% had severe disease. The total mortality was 20%; 35.7% of the recipients who had severe infection died. We can thus conclude that solid organ transplant recipients who receive immunosuppressive are at greater risk for presenting with severe manifestations of COVID-19 and subsequent mortality.

There is over-activation of the complement system and prolonged inflammatory response due to discordant expression of type I and type II cytokines resulting in cytokine storm and unfavorable outcome in SARS-CoV-2 infection [52].

Corticosteroids have a role in reducing systemic symptoms and decreasing alveolar exudation that results from cytokine storm [53].

Calcineurin inhibitors (CNIs) could inhibit the viral replication in vitro [54]. Cyclosporin could also inhibit replication of several coronaviruses in vitro independent of its immunosuppressive effect and at noncytotoxic concentrations [55].

These findings may support continuing the use of immunosuppressive therapy in selected transplant recipients with SARS-CoV-2 infection.

Alberici, *et al* [27], described their experience with managing patients with kidney disease including patients with renal transplantation during the current COVID-19 pandemic in Brescia city in the Lombardy region of Italy and provided preliminary outcome data on 20 kidney transplant recipients. Among them, 5 (25%) patients died. Their treatment approach included two phases: the first phase considered antiviral drugs (e.g., lopinavir/ritonavir, darunavir/cobicistat darunavir/ritonavir, and chloroquine-hydroxychloroquine,) that could manage the first phase of the disease, which is associated with viral replication and cytopathic effect. In the second phase of the disease, which begins 7–10 days after the onset of symptoms, they have considered immunosuppressive and immunomodulatory drugs that may be of benefit during this phase, which is characterized by hyperinflammatory and cytokine release syndromes that ultimately leads to increased risk of death with the progressive lung involvement and escalating needs of oxygen supplementation and ventilatory support. They postulated that use of

glucocorticoid and the interleukin-6 inhibitor, tocilizumab, in this phase could be beneficiary [27].

Akalin, *et al* [11], described 36 consecutive adult kidney-transplant recipients; 97% of patients were receiving tacrolimus, 94% prednisone, and 86% mycophenolate mofetil or mycophenolic acid; 78% of patients were hospitalized, 39% of whom required intubation. The total fatality rate was 28% (n=10). They managed the kidney transplant recipients infected by SARS-CoV-2 by withdrawal of an antimetabolite in 86% of patients. In addition, tacrolimus was withheld in 21% of severely ill patients. They administered hydroxychloroquine to 86% of patients and apixaban to patients with D-dimer levels >3.0 μg/mL; two patients received tocilizumab.

The Columbia University Kidney Transplant Program reported a series of 15 kidney transplant recipients infected with SARS CoV-2 [19]. At time of diagnosis, all but one were taking tacrolimus; 80% were also taking either mycophenolate mofetil or mycophenolic acid; 67% were taking prednisone.

They have managed the immunosuppressive therapy in infected patients by complete cessation of antimetabolites or leflunomide in 10 out of 14 (71%) patients while continuing the tacrolimus and the baseline prednisone in those who were on maintenance prednisone. Two (13%) patients died in this series.

Fernández-Ruiz, *et al* [23], reported a cohort of 18 solid organ transplant recipients infected with SARS-CoV-2 (8 kidneys [44%], 6 livers [33%], and 3 hearts [22%]) at a tertiary-care center in Madrid. They managed the patients by administering lopinavir/ritonavir (usually associated with hydroxychloroquine in 50% of patients, hydroxylchloroquine as monotherapy in 27.8% of patients, and interferon-β in 16.7% of recipients. None of the patients described stopped their immunosuppressive therapy. The case fatality rate was 28% (5 of 18).

Pereira, *et al* [22], reported the largest cohort in this review. It included 90 patients with a median age of 57 years; 46 were kidney recipients, 17 lung, 13 liver, 9 heart, and 5 dual-organ transplants; 24% of patients had mild disease, 46% had moderate and 30% had severe disease. In accordance with our results, most of the organ transplant recipients had moderate-to-severe disease. However, in the cohort of Pereira, *et al* (n=68), 12% required non-rebreather and only 35% required intubation. Fatality of SARS-CoV-2 infection reported in this cohort was 18% (24% of hospitalized patients and 52% of patients admitted to the ICU). Yet, details regarding mortality with each organ transplant were not mentioned in the study. The treatment approach in this cohort was based upon expert opinion. They decreased or held the antimetabolite while dosing of other agents was less uniformly decreased [22].

Montagud-Marrahi, *et al* [49], had 33 kidney transplant recipients in Spain; two of them also had a pancreatic transplantation. They had a favorable outcome; only two patients died, 31(94%) survived. Their policy for immune suppression was to discontinue mycophenolate and/or mTOR-i in all patients; if patients were on CNIs, it would also be stopped if lopinavir/ritonavir is prescribed (due to interactions); steroids were maintained as in many programs; 78.8% of their patients had ≥1 immunosuppressants withdrawn.

Malard, *et al* [48], studied patients with hematological diseases. In their cohort, they had seven patients who received HSCT. None of these patients was on immunesuppression with CNIs or antimetabolites; they had a favorable outcome; only one patient died, six survived.

Abrishami, *et al* [47], described a case series of 12 kidney transplant recipients. All patients included in this series were on steroids, calcineurin inhibitors/sirolimus, and mycophenolate mofetil/azathioprine at the time of admission. They have changed the regimen of immunosuppressive therapy by reducing the dose of immunosuppressive agents and changing the oral to intravenous steroid. However, only four patients survived, a fatality rate of 75%.

Calculating the number of patients who died among those who stopped or continued immunosuppressive therapy was not easy, as this was not detailed in all articles.

Chen, *et al* [26], had reported three lung transplant recipients following COVID-19 infection with extreme high sequential organ failure assessment scores. They have postulated that performing lung transplantation in end-stage patients with respiratory failure due to COVID-19-related pulmonary fibrosis could help in reducing mortality rate in such patients. Two of the three recipients survived post-lung transplantation.

We did not include study of Agnes, *et al* [56], as their results reported in Italian registry might have been included in other studies. In their report, they had 24 liver transplant recipients with COVID-19 of whom 19 were survived (79%), which is similar to other studies.

The concern that immunosuppression may be associated with poor virologic control is present, increasing the risk of developing a more severe disease and more prolonged viral shedding than the general population. On the other hand, reducing immunosuppression may lead to acute rejection and may cause an immune reconstitution-like reaction with a paradoxical worsening of the disease.

In the described cohorts in this review, transplant recipients with SARS-CoV-2 infection appeared to have mostly a moderate-to-severe disease, although testing limitations and reporting bias could likely make undercounting of mild/asymptomatic cases.

Our results showed a higher mortality among organ transplant recipients with SARS-Cov-2 infection (20%) if compared to the reported 4%–14% mortality rate among patients with COVID-19 in the general population [1]. The median age for our transplant cohort was 52 years; when the mortality was compared to the cohort from New York, it was clear that younger ages had lower mortality and older ages had higher mortality (Fig 1). We hypothesize that at younger ages immunosuppression may offer survival benefit given that the pathogenesis of COVID-19 is the development of cytokine storm. Yet, with advancing age transplant recipients would have more comorbidities which may lead to increased mortality.

Variation in mortality among different countries (Fig 2) was also noted which could be related to the overwhelming nature of this disease to the health care systems that could affect mortality; for certain countries, the mortality was similar to the general population. Some countries had few cases, hence, we excluded them from the analyses.

Many of the included studies were case-reports and it would be reasonable to assume that there might be some reporting bias due to reporting cases with favorable outcomes—most of these case reports showed no mortalities. Cohorts may have shown better representation of the true mortality. However, another confounder was that most of these cohorts were from areas where the health care system was overwhelmed (e.g., New York and Iran). These might overestimate the mortality.

In conclusion, our results showed a higher mortality rate among organ transplant recipients with SARS-CoV-2 infection compared with COVID-19 patients in the general population. Most of the studies documented similar presentation to the general population and outcomes were different in various countries based on outbreak settings and if the country's health care system was overwhelmed. Further research is needed to guide immunosuppression regimens and understand long-term complications of COVID-19 in transplant recipients and on transplanted organs.

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