ANNALS OF TRANSPLANTATION

REVIEW PAPER

e-ISSN 2329-0358
© Ann Transplant, 2020; 25: e925755
DOI: 10.12659/AOT.925755

Received: 2019.05.07
Accepted: 2020.05.11
Available online: 2020.06.08
Published: 2020.07.24

Kidney Transplantation in the Times of COVID-19 – A Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDEF **Ashraf Imam***
ABCEF **Sadi A. Abukhalaf***
BCD **Riham Imam**
AEF **Samir Abu-Gazala**
ACD **Hadar Merhav****
ABCEF **Abed Khalaileh****

Transplantation Unit, Department of Surgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

* Ashraf Imam and Sadi A. Abukhalaf These authors have contributed equally to the paper and share the first authorship
** Hadar Merhav and Abed Khalaileh equal contribution

Corresponding Author: Ashraf Imam, e-mail: ash_imam04@hotmail.com, ahrafim@hadassah.org.il
Source of support: Departmental sources

Kidney transplantation at the time of the COVID-19 pandemic is challenging. Modifying the immunosuppression protocols is controversial and not evidence based. In this study, we aim to review the published literature of kidney transplant recipients who encountered COVID-19.

A literature review was performed using PubMed, ScienceDirect, and World Health Organization databases to identify relevant English-language articles published up to May 7, 2020.

There were 24 articles that reported 129 kidney transplant recipients who encountered COVID-19. The age mean was 54.2 years with 73.7% as males. The most commonly reported presentations in order were fever (82.3%), cough (58%), shortness of breath (33.2%), and fatigue (30.7%). Acute kidney injury was observed in 34.1% of patients. Kidney transplant patients encountered COVID-19 were maintained on tacrolimus (Tac, 92%), mycophenolate mofetil (MMF, 78.8%), and prednisone (Pred, 77%) and were manage by holding MMF in 79.1% of patients and holding Tac in 34.4% of patients. In all, 20% of patients needed Intensive Care Unit (ICU) admission and 24.6% of patients required mechanical ventilation. In all, 18.8% of patients had died compared to the reported general population COVID-19 mortality of 3.4%.

The clinical presentation of COVID-19 in kidney transplant recipients may be different from the general population with a higher rate of severe disease, complications including renal failure, and mortality.

MeSH Keywords: **COVID-19 • Kidney Transplantation • Organ Transplantation**

Full-text PDF: https://www.annalsoftransplantation.com/abstract/index/idArt/925755

2777 7 1 49

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Background

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV2) [1]. The disease was initially confirmed in China and then rapidly spread worldwide with more than 2 million infected individuals and over 200 000 deaths worldwide [2]. This disease is especially fatal in elderly patients (patients older than 70 years) with comorbidities [3]. Most published data regarding COVID-19 and organ transplant recipients is nonspecific and lacks quality evidence. Data about demographics, characteristics, and clinical presentations of COVID-19 in kidney transplant recipients is scarce [4]. In this study, we aimed to review the published literature regarding kidney transplant patients who encountered COVID-19.

Methods

Literature search

A systematic literature review was performed using PubMed and ScienceDirect databases to identify relevant English-language articles published through May 6, 2020. Search terms included COVID-19, coronavirus, severe acute respiratory syndrome coronavirus 2, 2019-nCoV, SARS-CoV-2, SARS-CoV, MERS-CoV and transplantation. All article types were included: case reports, case series, commentaries, and review articles. A search in the database of the COVID-19 global research on coronavirus disease section of the World Health Organization (WHO) website through May 6, 2020 was performed using the following criteria: transplantation without any additional limits or filters [5]. Additional articles were retrieved by screening the reference lists of the included studies. The search strategy was approved and reviewed by all authors.

Eligibility criteria and study selection

The authors independently reviewed the titles and abstracts for inclusion. Figure 1 displays the flow diagram for this systematic review, based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 [6]. Databases were screened, filtered, and assessed for eligibility. Cases of COVID-19 in kidney transplant patients were included in this study. Articles with unrelated topics and/or with missed information were excluded.

Risk of bias

The National Institutes of Health Quality Assessment Tool for Case Series Studies was used to qualify the reviewed articles [7]. Table 1 shows the results of the 2 reviewers who independently rated the quality of the included studies.

Data extraction and synthesis

Data was independently extracted from reports by 2 reviewers. All reported patients' demographic and clinical characteristics (country, age, sex, time from transplant, donor type, comorbidities, clinical presentation and maximum body temperature, initial complete blood count (CBC), C-reactive protein (CRP), baseline creatinine (Cr), blood urea nitrogen (BUN), renal involvement, baseline immunosuppressant medications, need for intensive care unit (ICU) and mechanical ventilation (MV), duration of illness and outcomes) were extracted, collected and analyzed. Due to the lack of sufficient data, a meta-analysis to assess the association of various patients' findings with demographic data, disease and patient characteristics, or outcomes was not performed. The principal summary measures used were the median, mean, standard deviation, and incidence.

Results

Overview of the included studies

A total of 493 articles were retrieved using the search strategy. After duplication removal, 378 articles were screened; 331 articles were excluded due to unrelated content. The remaining 47 articles were assessed for eligibility through full-text screening. There were 15 articles excluded due to unrelated content or lack of relevant information. There were 32 articles included but only 21 articles reported kidney transplant recipients encountered COVID-19 (Figure 1). For quality assessment, we used the NIH Quality Assessment Tool for Case Series Studies [7]. Five case series and 16 case reports included 58 kidney transplant patients encountered COVID-19. Patients' characteristics and demographics were included in Tables 2–4.

Patients demographics and characteristics

The 21 articles reported 58 kidney transplant patients who encountered COVID-19. There were 20 patients from China, 14 patients from the USA, 9 patients from Spain, 7 patients from the United Kingdom, 5 patients from Italy, 2 patients from Korea, and 1 patient from Turkey. There were 44 male patients (75.9%) and 14 female patients (14 out of 58; 24.1%). The mean age was 52.69 years (range, 24 to 80 years). Transplants were from unknown decreased persons in 16 cases (27.5%), living donors in 9 cases (15.5%), DCD (donor after cardiac death) in 6 cases (10.3%), DBD (donor after brain death) in 2 cases (3.4%), and the remaining 25 cases (43.1%) were from unknown sources. The mean post-transplant period was 7.68 years (range, 0.083 to 31 years). There were 9 patients (15.5%) who were within their first year after transplantation. The most common reported comorbidities were hypertension in 40 patients (68.9%), diabetes mellitus in 21 patients (36.2%), coronary artery/heart

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

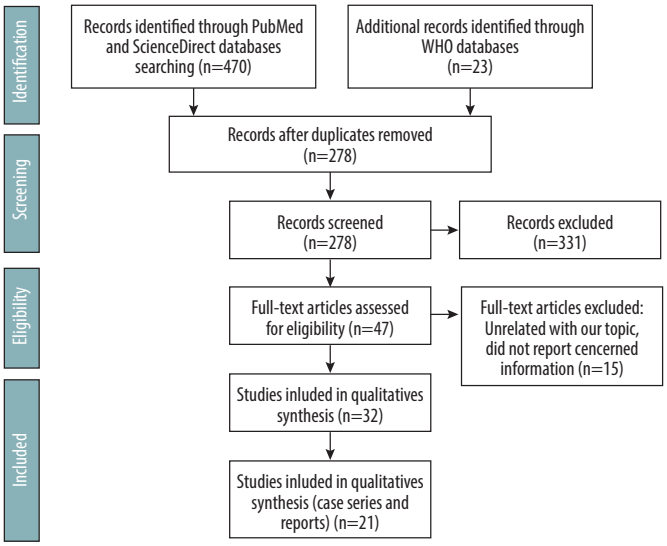

Figure 1. PRISMA flow chart for the present study.

Table 1. Quality ratings of included studies according to NIH quality assessment tool for case series studies.

Study	Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8	Q 9	Reviewer 1	Reviewer 2
Banerjee	Yes	No	CD	Yes	CD	Yes	No	Yes	Yes	Fair	Fair
Bartiromo	Yes	Yes	NA	NA	Yes	Yes	No	NA	Yes	Fair	Fair
Chen	Yes	Yes	CD	No	Yes	Yes	Yes	NA	Yes	Fair	Fair
Gandolfini	Yes	Yes	CD	Yes	Yes	Yes	Yes	NA	Yes	Fair	Fair
Guillen	Yes	Yes	NA	NA	No	Yes	No	NA	Yes	Fair	Fair
Huang	Yes	No	CD	Yes	Yes	No	Yes	NA	No	Poor	Poor
Ning	Yes	Yes	NA	NA	Yes	Yes	Yes	NA	Yes	Fair	Fair
Seminari	Yes	Yes	NA	NA	Yes	Yes	No	NA	Yes	Fair	Fair
Wang	Yes	No	NA	NA	Yes	Yes	No	NA	Yes	Fair	Fair
Zhang	Yes	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes	Fair	Fair
Zhu	Yes	Yes	NA	NA	Yes	Yes	No	NA	Yes	Fair	Fair
Arpali	Yes	No	CD	NA	CD	Yes	No	Yes	Yes	Fair	Fair
Billah	Yes	No	CD	NA	CD	Yes	No	Yes	Yes	Fair	Fair
Fernández-Ruiz	Yes	Yes	CD	NA	Yes	Yes	Yes	Yes	Yes	Fair	Fair
Fontana	Yes	No	CD	NA	CD	Yes	No	Yes	Yes	Fair	Fair
Hsu	Yes	No	CD	NA	Yes	Yes	No	Yes	Yes	Fair	Fair
Johnson	Yes	Yes	NA	NA	CD	Yes	No	Yes	Yes	Fair	Fair
Kates	Yes	No	CD	Yes	CD	Yes	Yes	Yes	Yes	Fair	Fair
Kim	Yes	Yes	NA	Yes	Yes	Yes	No	Yes	Yes	Fair	Fair
Nair	Yes	No	CD	Yes	Yes	Yes	Yes	Yes	Yes	Fair	Fair
Zhu	Yes	Yes	NA	Yes	CD	Yes	Yes	Yes	Yes	Fair	Fair

NIH – National Institutes of Health; NR – not reported; CD – cannot determine; NA – not applicable. The NIH Quality Assessment Tool for Case Series Studies [7] poses nine questions: 1=Was the study question or objective clearly stated?, 2=Was the study population clearly and fully described, including a case definition?, 3=Were the cases consecutive?, 4=Were the subjects comparable?, 5=Was the intervention clearly described?, 6=Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?, 7=Was the length of follow-up adequate?, 8=Were the statistical methods well-described?, 9=Were the results well-described?

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2. Characteristics of all available reported kidney transplant recipients infected with COVID-19.

Study; Country	Number	Age; Sex	Years post-Tx; Donor	Comorbidities	Clinical presentation; Max Temp	Initial WBCC, NC, LC ($\times 10^9$/L)	Initial CRP (mg/L)	Baseline Cr (mg/dL)^	Initial Cr (mg/dL)
Banerjee; UK [12]	#1	48;M	31; deceased	HTN	Cough, Fever, SOB; N/A	N/A	N/A	3.96	N/A
	#2	67;F	1; DBD	HTN, DM	Cough, Fever, SOB, Hypoxia; N/A	6, N/A, 0.8	83	1.7	2.54; AKI
	#3	54;F	0.25; deceased	DM, CMV infection	SOB, Hypoxia; N/A	11.2, N/A, 0.5	329	1	2.71; AKI
	#4	65;M	1.5; deceased	HTN	SOB, Chest pain; N/A	N/A	N/A	2	N/A
	#5	69;F	0.083; deceased	HTN, DM	SOB, Fever, V/D; 39°C	9.4, N/A, 0.3	N/A	1.9	N/A
	#6	54;M	7; N/A	HTN, HHA	Cough, Fever; 38.5°C	10, N/A, 4	N/A	1.6	2.1; AKI
	#7	45;M	2.5; N/A	HTN	Fever, Flu-like symptoms, Cough, SOB, Hypoxia; N/A	5.5, N/A, 0.3	198	5.1	11; AKI
Bartiromo; Italy [3]	#1	36; F	25; deceased	SLS	Cough, Coryza, Fatigue; 36.3°C	N/A, High, Normal	67	1.5	1.77
Chen; China [24]	#1	49; M	6; DBD	HTN	Hyporexia, Cough, Fever, SOB; 38.6°C	3.4, 2.59, 0.4	74	1.24	1.89
Gandolfini; Italy [25]	#1	75; M	10; deceased	COPD, HTN, Obesity, CAD	Fever, SOB, Flu-like symptoms; 37.5°C	6.5, N/A, 0.8	180	2.1	2.2
	#2	52; F	0.66; DCD	HTN	Fever, SOB, D, Flu-like symptoms; 37.5°C	2.5, N/A, 0.11	158	1.3	2.4; AKI
Guillen; Spain [26]	#1	50; M	4; deceased	HTN, PTLD, SP	Fever, V, Dehydration, Cough, Conjunctivitis, Hypoxia; 38.2°C	10.5, N/A, 1.8 but developed lymphopenia	5	1.3	1.6; AKI
Huang; China [27]	#1	58; M	12; N/A	None	Cough, Fever, SOB, Hypoxia; 37.6°C	N/A but developed lymphopenia	N/A	N/A	N/A
Ning; China [28]	#1	29; M	1.5; Living	HTN	Fever, Fatigue, Chills, Hyporexia, N/V, Chest tightness, nasal stuffiness, Dizziness, Hematuria; 37.7°C	11.4, N/A, 1.5	N/A	N/A	1.1; AKI
Seminari; Italy [29]	#1	50; M	4; N/A	HTN, DM	Cough, Fever; 37.5°C	3.5, 1.8, 1.2 but developed lymphopenia	18.6	N/A	1.7
Wang; China [30]	#1	49; M	2; N/A	HTN, DM	Fever, Respiratory symptoms; N/A	7, 6, 0.6	22.7	N/A	1.4
Zhang; China [31]	#1	38; M	0.5; DCD	None	Cough, Fever; 38.9°C	4.7, 2.6, 0.6	6	N/A	1.1
	#2	64; M	4; DCD	Bladder cancer	Fever, Anuria, Cough,, SOB, Flu-like symptoms; 38.3°C	17.6, 16, 0.5	337	N/A	4.6; AKI
	#3	37; F	0.66; DCD	HTN	Cough, Fever; 39°C	5.6, 3.9, 0.3	9.7	N/A	1.5
	#4	47; M	1.2; DCD	None	Cough, Fever, Flu-like symptoms; 39.8°C	4, 2.3, 0.5	13.3	N/A	1.6
	#5	38; M	3; DCD	HTN, DM	Cough, Fever, Flu-like symptoms; 39.1°C	6.4, 3.2, 0.9	33.7	N/A	1.5
Zhu; China [32]	#1	52; M	12; Living	None	Fatigue, SOB, Chest tightness and pain, N, Hyporexia, Abd.P, Cough, Fever, Headache, Weight loss; 38.9°C	9, 7, 1.13 but developed lymphopenia	30	1.57	1.62

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2 continued. Characteristics of all available reported kidney transplant recipients infected with COVID-19.

Study; Country	Number	Age; Sex	Years post-Tx; Donor	Comorbidities	Clinical presentation; Max Temp	Initial WBCC, NC, LC (×10⁹/L)	Initial CRP (mg/L)	Baseline Cr (mg/dL)^	Initial Cr (mg/dL)
Arpali; Turkey [37]	#1	28; F	0.5; Living	LLS	Fever, Fatigue, Sore throat, Rhinorrhea; 38°C	3.1, N/A, 0.3	5.7		0.92
Billa; USA [38]	#1	44; M	7; deceased	None	SOB; N/A			2.3	2.3; AKI
Fontana; Italy [39]	#1	61; M	15; deceased	NMZL, PD, NB	Fever, Chills; 38°C	5.4, 4.2, 1.2 but developed lymphopenia	41	1.5	1.9
Hsu; USA [40]	#1	39; M	3;	DCM, DM, HTN, Obesity	Fever, Headache, Sore throat, Cough, SOB, Fatigue, Myalgia, Dizziness, Chills; 38.8°C	2.5, N/A, 0.2	67	1	0.85
Kates, USA [41]	#1	54; M	20; deceased	HTN, DM,	Fever, Chills, Fatigue, Cough, SOB, N/V/D; 40°C	6.2, N/A, 2 but developed lymphopenia		1.9	3.4; AKI
Johnson; USA [42]	#1	57; M	0.66; deceased	None	Fever, Chills, Hyporexia, Abd. bloating, Back pain, Fatigue, Myalgia, SOB, Anorexia, D, Oliguria; 38.2°C	1.4, 0.7, 0.3		2	3.2;
Kim; Korea [43]	#1	36; M	4; Living	None	Fever, Cough, Rhinorrhea, D, Oliguria, Chest discomfort; 38.5°C	6.6, 5.4, 0.6	46	1.47	2
	#2	46; M	9; deceased	DM	Cough; N/A	4, 2, 1.3	27	2	1.85
Fernández-Ruiz; Spain [44]	#1	78; M	8.3; N/A	HTN, Prostate CA	Fever, SOB				
	#2	73; M	1.8; N/A	HTN, DM	Fever, SOB, Cough,				
	#3	80; M	3.8; N/A	HTN, DM	SOB, Cough, Myalgia, Hyporexia				
	#4	71; F	6; N/A	HTN	Fever, SOB, Cough, Sore throat				
	#5	71; M	30; N/A	HTN, DM, CAD	Fever, Abd.P				
	#6	76; M	14.8; N/A	HTN, Obesity	Fever, Rhinorrhea				
	#7	39; M	16.8; N/A	HTN	Fever, Myalgia				
	#8	65: M	6.5; N/A	HTN, DM, OSA	Fever, SOB, Cough				
Nair; USA [45]	#1	51; M	0.42; deceased	HTN, DM, CAD	Fever, Chills, Cough	9.2, N/A, 1.1			0.88
	#2	37; M	7; living	HTN, DM	Cough, Chills, Nasal congestion, Myalgia	5, N/A, 2.4	180		1.93
	#3	63; F	11.6; living	HTN	Fever, Chills, Cough, Myalgia, Headache;	9, N/A, 1.2	34		1.2
	#4	30; F	3.7; living	HTN, DM	Fever, Myalgia, Headache, V	3.7, N/A, 1.2			1.5
	#5	56; M	20; deceased	HTN, DM	Fever, Cough, Fatigue	4, N/A, 0.3	306		4.8; AKI
	#6	80; M	13.8; living	HTN, DM, CAD	Fever, Chills, Fatigue, Myalgia, D	5, N/A, 0.2	87		1.9
	#7	45; M	3.4; deceased	HTN, DM	Fever, Cough, Myalgia, D	5.2, N/A, 1.1	38		1.74
	#8	68; M	11.6; N/A	HTN, DM	Fever, Cough, SOB	6.7, N/A, 0.5	240		1.46; AKI

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2 continued. Characteristics of all available reported kidney transplant recipients infected with COVID-19.

Study; Country	Number	Age; Sex	Years post-Tx; Donor	Comorbidities	Clinical presentation; Max Temp	Initial WBCC, NC, LC ($\times 10^9$/L)	Initial CRP (mg/L)	Baseline Cr (mg/dL)^	Initial Cr (mg/dL)
Nair; USA [45] [continued]	#9	75; F	8.6; living	HTN, CA	Fever, Cough, SOB, Fatigue	6.3, N/A, 0.4	50		1.3
	#10	57; F	11.6; deceased	HTN, DM	Cough, SOB, Chills, Fatigue	11, N/N, 1.4	230		1.6; AKI
Zhu; China [46]	#1	24; M		None	Fever; 38°C	N/A	30		2.24
	#2	55; M		CAD	Cough, SOB, Fatigu	N/A, N/A, 0.3	80		3.48
	#3	29; M		None	Fever, Cough, SOB, Fatigue, D; 38.8°C	N/A, N/A, 0.47	118		2.84
	#4	30; M		HTN	Fever, Cough, SOB, Fatigue; 39°C	N/A, N/A, 0.6	42		2.36
	#5	50; M		HTN	Fever, Cough, SOB, Fatigue; 38.6°C	N/A, N/A, 0.4	40		N
	#6	65; F		None	Fever, Cough, SOB, Fatigue, D; 38°C	N/A, N/A, 0.7	40		N
	#7	52; M		HTN, CAD	Fever, Cough, SOB, Fatigue; 38.9°C	N/A, N/A, 1	54		N
	#8	49; M		None	Fever, Cough, SOB, Fatigue, D; 39.2°C	N/A	49		N
	#9	59; M		HTN, COPD	Fever, Cough, SOB, Fatigue; 38.4°C	N/A, N/A, 0.4	100		5.2; AKI
	#10	37; F		HTN	Fever, Cough, SOB, Fatigue; 40°C	N/A, N/A, 0.2	34		2.14

Study; Country	Initial D-dimer, (µg/L)	Initial ALT/AST (U/L)	Initial LDH (U/L)	Baseline ISMs	Management	ICU & MV	Outcomes*
Banerjee; UK [12]	N/A	N/A	N/A	Aza, Pred	No change in ISMs	None	Recovered, N/A
	2032	N/A	1226	Tac, MMF, Pred	Tac, MMF stopped, Abx	Both	Died after 12d
	N/A	N/A	N/A	Tac, MMF, Pred	Tac, MMF stopped, Abx, oseltamivir	MV	Alive but suffers, 7d
	N/A	N/A	N/A	Tac, MMF, Pred	MMF stopped	Both	Alive but suffers
	N/A	N/A	N/A	Tac, MMF, Pred	MMF stopped, Abx, PC, furosemide, Blood transfusion	ICU	Alive but suffers, 7d
	N/A	N/A	N/A	Tac, MMF	MMF stopped, PC	None	Alive but suffers, 11d
	1907	N/A	502	Tac, Aza, Pred	Aza stopped, Tac reduced, Pred increased, HD	None	Recovered, 13d
Bartiromo; Italy [3]	N/A	N/A	N/A	Tac, Pred	Tac stopped, hydroxychloroquine, Abx, lopinavir/ritonavir (for 2 days), darunavir/cobicistat	None	Recovered, 14d
Chen; China [24]	N/A	57/50	N/A	Tac, MMF, Pred	ISMs stopped, Ribavirin, Abx, IVIG, IVMP	ICU	Recovered, 32d
Gandolfini; Italy [25]	N/A	25/45	301	Tac, MMF, Pred	Tac, MMF, stopped, Hydroxychloroquine, Abx, Lopinavir/ritonavir	None	Died, 5d
	832	26/62	718	Tac, MMF, Pred	Tac, MMF, stopped, Abx, Hydroxychloroquine, Darunavir/cobicistat	None	Recovered, 8d

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2 continued. Characteristics of all available reported kidney transplant recipients infected with COVID-19.

Study; Country	Initial D-dimer, (μg/L)	Initial ALT/AST (U/L)	Initial LDH (U/L)	Baseline ISMs	Management	ICU & MV	Outcomes*
Guillen; Spain [26]	8900	N/A	N/A	Tac, Pred, Eve	Tac, Eve stopped, Abx, hydroxychloroquine, Lopinavir/ Ritonavir, INF-β	Both	Alive but suffers, 12d
Huang; China [27]	N/A	N/A	N/A	MMF, Pred	MMF, Pred stopped, Abx, oseltamivir, Lopinavir/ritonavir, IVMP	MV	Died, 40d
Ning; China [28]	N/A	20/23 but elevated later	N/A	MMF, Pred, CsA	No change in ISMs, Abx, lopinavir/ ritonavir, IVIG	None	Recovered, 12d
Seminari; Italy [29]	N/A	14/22	167 then 277	Tac, MMF	No change in ISMs, Abx	None	Recovered, 13d
Wang; China [30]	N/A	N/A	N/A	MMF, Pred, CsA	No change in ISMs, INF-α, ribavirin, lopinavir/ritonavir IVMP	None	Recovered, 12d
Zhang; China [31]	185	66/41	193	Tac, MMF, Pred	MMF stopped, Tac reduced, oseltamivir	None	Recovered, 16d
	630	21/31	180	MMF, Pred	ISMs stopped, Abx, oseltamivir	None	Alive but suffers, 7d
	1015	70/49	160	Tac, MMF, Pred	Tac, MMF stopped, oseltamivir, IVIG	None	Recovered, 11d
	225	7/26	235	Tac, MMF, Pred	ISMs stopped, oseltamivir	None	Recovered, 19d
	195	20/21	248	Tac, MMF, Pred	No change in ISMs, oseltamivir	None	Recovered, 7d
Zhu; China [32]	N/A	30/29 but elevated later	N/A	Tac, MMF, Pred	ISMs stopped, Abx, IVMP, IVIG, INF-α, GAD	None	Recovered, 18d
Arpali; Turkey [37]				Tac, Pred	No change in ISMs, oseltamivir	None	Recovered, 7d
Billa; USA [38]	1100		285	Tac, MMF, Pred	Tac reduced, IVMP,	MV	Alive but suffers, 31d
Fontana; Italy [39]	N		N	Pred, CsA	CsA stopped, Pred increased, Abx, Hydroxycloroquine, Tocilizumab, IVIG,	None	Recovered, 22d
Hsu; USA [40]	1124	54/44	361	Tac, MMF, Pred	MMF stopped, hydroxychloroquine, remdesivir	ICU	Recovered, 15d
Kates, USA [41]		34/48		Tac, MMF,	MMF stopped, Tac reduced, Pred, Abx, chloroquine, hydroxychloroquine,	None	Recovered, 16d
Johnson; USA [42]				Tac, MMF,	Tac, MMF reduced, Abx, hydroxychloroquine,	None	Recovered, 23d
Kim; Korea [43]		35/32		Tac, MMF, Pred	Tac, MMF stopped, lopinavir/ritonavir, IVMP, hydroxychloroquine	None	Recovered, 23d
		10/14		Tac, MMF, Pred	MMF stopped, hydroxychloroquine, Abx,	None	Recovered, 17d
Fernández-Ruiz; Spain [44]				Tac, Pred	Tac reduced, lopinavir/ritonavir	None	Died, 5d
				Tac, MMF, Pred	Tac reduced, MMF, Pred stopped, lopinavir/ritonavir, hydroxychloroquine, IVIG	None	Alive but suffers, 23d
				Tac, MMF, Pred	Tac reduced, MMF stopped, lopinavir/ritonavir, hydroxychloroquine	None	Alive but suffers, 28d

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2 continued. Characteristics of all available reported kidney transplant recipients infected with COVID-19. 5

Study; Country	Initial D-dimer, (µg/L)	Initial ALT/AST (U/L)	Initial LDH (U/L)	Baseline ISMs	Management	ICU & MV	Outcomes*
Fernández-Ruiz; Spain [44] [continued]				Tac, MMF, Pred	Tac reduced, MMF, Pred stopped, lopinavir/ritonavir, hydroxychloroquine, IVIG, IVMP	None	Died, 16d
				Tac	Tac reduced, hydroxychloroquine, IVIG,	None	Alive but suffers, 9d
				MMF, Pred, Srl	MMF stopped, hydroxychloroquine, IVMP	None	Recovered, 13d
				Tac, Pred, Eve	Tac, Eve stopped, hydroxychloroquine, IVMP, Tocilizumab,	None	Alive but suffers, 16d
				Tac, MMF, Pred	Tac, MMF reduced, lopinavir/ ritonavir, hydroxychloroquine	None	Alive but suffers, 17d
Nair; USA [45]				Tac, MMF, Pred, Eve	No change in ISMs	None	Recovered
				Tac, MMF, Pred	MMF stopped, hydroxychloroquine, azithromycin	None	Recovered
				Tac, MMF	MMF stopped, hydroxychloroquine, azithromycin, Abx	None	Recovered
				Tac, MMF, Pred	MMF stopped, hydroxychloroquine, azithromycin, Abx	None	Recovered
				Tac, MMF, Pred	Tac, MMF stopped, hydroxychloroquine, azithromycin, Abx	Both	Died
				Tac, MMF	Tac, MMF stopped, hydroxychloroquine, azithromycin, Abx, IVMP	Both	Recovered
				Tac, MMF, Pred	MMF stopped, hydroxychloroquine, azithromycin, Abx, IVMP	None	Recovered
				Tac, MMF, Pred	MMF stopped, hydroxychloroquine, azithromycin, Abx	ICU	Recovered
Nair; USA [45] [continued]				Pred, Srl	Srl stopped, hydroxychloroquine, azithromycin	Both	Died
				Tac, MMF	MMF stopped, hydroxychloroquine, azithromycin, Abx, Pred	Both	Died
Zhu; China [46]		N		Tac, MMF, Pred	No change in ISMs, Avx	None	Recovered, 43d
		N		Tac, MMF, Pred	MMF stopped, Tac reduced, IVIG, Avx	MV	Recovered, 48d
		N		Tac, MMF, Pred	MMF stopped, IVMP, Avx	None	Recovered, 37d
		N		Tac, MMF, Pred	Tac, MMF stopped, IVIG, IVMP, Avx	None	Recovered, 37d
		104; N/A		Tac, MMF, Pred	Tac, MMF stopped, IVIG, IVMP, Avx	None	Recovered, 34d
		N		Tac, MMF	Tac, MMF stopped, IVIG, IVMP, Avx	MV	Alive but suffers, 49d
		94; N/N		Tac, MMF, Pred	Tac, MMF stopped, IVIG, IVMP, Avx	None	Recovered, 20d

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 2 continued. Characteristics of all available reported kidney transplant recipients infected with COVID-19.

Study; Country	Initial D-dimer, (µg/L)	Initial ALT/AST (U/L)	Initial LDH (U/L)	Baseline ISMs	Management	ICU & MV	Outcomes*
Zhu; China [46] [continued]		97; N/A		Tac, MMF	Tac, MMF stopped, IVMP, Avx	None	Recovered, 34d
		61; N/A		CsA, mizoribine	ISMs stopped, IVIG, IVMP, Avx	MV	Died, 6d
		163; N/A		Tac, MMF, Pred	Tac, MMF stopped, IVIG, IVMP, Avx	None	Recovered, 31d

* Recovered indicates recovery of clinical symptoms and signs not negative COVID-19 testing; ^ Initial Creatinine (Cr) indicates Cr serum level in mg/dL unit before encountering COVID-19.
ISMs – immunosuppressant medications; Max Temp – maximum temperature; DOI – duration of illness: ; ICU – Intensive Care Unit; MV – mechanical ventilation; CRP – C-reactive protein; WBCC – white blood cell count; normal is 3.5–10 (×10^9/L); NC – neutrophil count, normal is 1.5–8 (×10^9/L); LC – lymphocyte count, normal is 1–3.5 (×10^9/L); AKI – acute kidney injury; Aza – azathioprine; MMF – mycophenolate mofetil; Tac – tacrolimus; Pred – prednisone; N/A – not available; DCD – donor after cardiac death; DBD – donor after brain death; Abx – antibiotics; Avx – antivirals; V/D – vomiting/diarrhea; PC – Paracetamol; SLS – Senior-Loken syndrome; LOS – loss of appetite; IVMP – intravenous methylprednisolone; IVIG – intravenous immunoglobin; D – Diarrhea; PTLD – post-transplant lymphoproliferative disease; SP – splenectomy; V – vomiting; Eve – everolimus: ; INF-β – interferon beta; CsA – ciclosporin; N/V – nausea/vomiting; INF-α – interferon α; Abd.P – abdominal pain; GAD – glycyrrhizic acid diamine; CMV – cytomegalovirus; HHA – hereditary haemolytic anaemia; HD – hemodialysis; LDH – lactate dehydrogenase; ALT – alanine aminotransferase; AST – aspartate aminotransferase; LLS – lupus-like syndrome; NMZL – nodal marginal zone lymphoma; PD – Parkinson disease; NB – neurogenic bladder; DCM – dilated cardiomyopathy; CAD – coronary artery disease; OSA – obstructive sleep apnea; CA – cancer; Srl – Sirolimus.

disease in 6 patients (10.3%), COPD in 2 patients (3.4%), and obesity in 3 patients (5.2%). In 11 patients (18.9%) there was no comorbidities reported. These variables are presented in the Table 3.

Clinical presentation

The most frequently reported clinical presentation was fever; it was reported in 49 patients (84.5%) with a mean maximum temperature of 38.47°C (±0.79°C). Other reported clinical symptoms were cough (70%), shortness of breath (SOB) (56.9%), flu-like symptoms including myalgia and fatigue (60%), gastrointestinal symptoms including vomiting, diarrhea, nausea, abdominal pain/bloating and hyporexia/anorexia (44.8%), chills (17.2%), and chest pain/tightness/discomfort (6.9%). Less frequently reported symptoms included headache, dizziness, sore throat, rhinorrhea, nasal congestion, and stuffiness, coryza, dehydration, conjunctivitis, hematuria, and oliguria. These variables are presented in the Table 3.

Laboratory results

The initial white blood cell count median was 6×10^9 (±3.4×10^9). The initial median lymphocyte cell count was 0.6×10^9 (±0.72×10^9). Initial leukopenia and lymphopenia were reported in 22.8% and 63%, respectively. However, lymphopenia was eventually developed in 79% of patients. Median of the initial CRP was 49 mg/L (±92.4 mg/L) and high CRP (>5 mg/dL) levels were noted in 97.2% of cases. Median of the baseline serum Cr was 1.65 mg/dL (±0.96 mg/dL) and 85% of patients had baseline serum Cr >1.2 mg/dL. Median initial (post infection) serum Cr was 1.9 mg/dL (±1.7 mg/dL) and acute kidney injury (AKI) was observed in 28.2% of patients. High D-dimer (>500 µg/L), ALT (>50 U/L), AST (>54 U/L), and LDH (>225 U/L) levels were observed in 72.7%, 44%, 15%, and 69.2%, respectively. These variables are presented in the Table 3.

Immunosuppression management

Patients were treated with different immunosuppressive regimens though the most frequently reported regimen included tacrolimus (Tac), mycophenolate mofetil (MMF), and prednisone (Pred) which was reported in 33 patients (56.9%).

Pred was prescribed in 81% of patients and discontinued in 14.8%, increased in 4.2% and not changed in 80.8%. MMF was prescribed in 79.3% of patients and discontinued in 72%, reduced in 4.3%, and not changed in 15.2%. Tac was prescribed in 82.7% of patients and discontinued in 47.9%, reduced in 20.8%, and not changed in 25.8%. Other baseline immunosuppression medications were azathioprine, everolimus, ciclosporin, sirolimus, and mizoribine. These medications were held in some patients and not changed in others; 13.8% of patients recovered with no change in immunosuppression medications. These variables are presented in the Table 4.

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 3. Clinical Characteristics for the 58 Reported Kidney Transplant Patients Who Encountered COVID-19.

Variable (n=58)	Value
Age (mean, range)	52.69 (24–80)
Sex	
Male	44/58 (75.9%)
Female	14/58 (24.1%)
Kidney transplant years age (mean, range)	7.68 (0.083–31)
Within 1 year	9/58 (15.5%)
Beyond 1 year	49/58 (84.5%)
Type of donor	
DCD	6/58 (10.3%)
DBD	2/58 (3.4%)
Deceased, unknown	16/58 (27.5%)
Living	9/58 (15.5%)
Not available	25/58 (43.1%)
Comorbidities	
HTN	40/58 (68.9%)
DM	21/58 (36.2%)
CAD	6/58 (10.3%)
COPD	2/58 (3.4%)
Obesity	3/58 (5.2%)
None	11/58 (18.9%)
Clinical presentation	
Fever	49/58 (84.5%)
Max. temp (average, SD)	38.47 (±0.79)
Chills	10/58 (17.2%)
Cough	40/58 (70%)
SOB	33/58 (56.9%)
Chest pain/discomfort/tightness	4/58 (6.9%)
Flu-like symptoms	6/58 (10.3%)
Fatigue	20/58 (34.5%)
Myalgia	9/58 (15.5%)
Vomiting	4/58 (6.9%)
Diarrhea	10/58 (17.2%)
Abdominal pain/bloating	3/58 (5.2%)
Nausea	3/58 (5.2%)
Hyporexia/anorexia	6/58 (10.3%)
Headache	4/58 (6.9%)
Dizziness	2/58 (3.4%)
Sore throat	3/58 (5.2%)
Rhinorrhea/nasal congestion/ stuffiness	5/58 (8.6%)
Oliguria	2/58 (3.4%)
Laboratory	
White Cell Count	
Median (SD) per l	6×10^9 ($\pm3.4\times10^9$)
Leukopenia (<4×10^9/l)	8/35 (22.8%)
Neutrophils count	
Median (SD) per l	3.2×10^9 ($\pm3.9\times10^9$)
Neutropenia (<1.5×10^9/l)	1/13 (7.6%)
Lymphocyte count	
Median (SD) per l	$0.6^*\times10^9$ ($\pm0.72\times10^9$)
Lymphopenia (<1×10^9/l)	34/43 (79%)
Initial C-reactive protein (CRP)	
Median (SD)	49 (±92.4)
High CRP (>5 mg/dl)	36/37 (97.2%)
Baseline serum creatinine (Cr)	
Median (SD)	1.65 (±0.96)
High Cr (>1.2 mg/dL)	17/20 (85%)
Initial serum Creatinine (Cr)	
Median (SD)	1.9 (±1.7)
AKI	13/46 (28.2%)
Initial D-dimer	
Median (SD)	1015 (±2485)
High D-dimer (>500 µg/L)	8/11 (72.7%)
Initial ALT	
Median (SD)	34 (±39.8)
High ALT (>50 U/l)	11/25 (44%)
Initial AST	
Median (SD)	32 (±13.6)
High AST (>54 U/l)	3/20 (15%)
Initial lactate dehydrogenase (LDH)	
Median (SD)	266.5 (±311)
High LDH (>225 U/l)	9/13 (69.2%)

Patients who died had their immunosuppression medications held (Tac 50%, MMF 100%, Pred 28.5%, ciclosporin 100%, sirolimus 100%, mizoribine100%), reduced (Tac 33.3%) or continued unchanged (Tac 16.6%, Pred 71.4%). These variables are presented in the Table 5.

Overall, patients had their immunosuppression medications held (Tac 47.9%, MMF 80.4%, Pred 14.8%, ciclosporin 50%, sirolimus 50%, mizoribine100%, azathioprine 50%), reduced (Tac 33.3%, MMF 4.3%) or continued unchanged (Tac 25.8%, MMF 15.2%, Pred 80.8%). Overall, 4.2% of patients were managed

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 4. Management and Outcomes of the 58 Reported Kidney Transplant Patients Who Encountered COVID-19.

Variable	Value	
Baseline Immunosuppression		
Tacrolimus	48/58	(82.7%)
Mycophenolate mofetil	46/58	(79.3%)
Prednisone	47/58	(81%)
Azathioprine	2/58	(3.4%)
Everolimus	3/58	(5.2%)
Ciclosporin	4/58	(6.8%)
Sirolimus	2/58	(3.4%)
Mizoribine	1/58	(1.7%)
Management		
Immunosuppression		
Held tacrolimus	23/48	(47.9%)
Reduced tacrolimus	10/48	(20.8%)
No change tacrolimus	15/48	(25.8%)
Held mycophenolate mofetil	37/46	(80.4%)
Reduced mycophenolate mofetil	2/46	(4.3%)
No change mycophenolate mofetil	7/46	(15.2%)
Held prednisone	7/47	(14.8%)
Increased prednisone	2/47	(4.2%)
No change prednisone	38/47	(80.8%)
Azathioprine	Held 1; No change 1	
Everolimus	Held 2; No change 1	
Ciclosporin	Held 2; No change 2	
Sirolimus	Held 1; No change 1	
Mizoribine	Held 1	
Other Tx		
Lopinavir/Ritonavir	12/58	(20.6%)
Hydroxychloroquine	25/58	(43.1%)
Azithromycin	9/58	(15.5%)
Oseltamivir	8/58	(13.8%)
Antibiotics	24/58	(41.3%)
Intravenous methylprednisolone	19/58	(32.7%)
Intravenous immunoglobulin	15/58	(25.8%)
Unspecified antivirals	10/58	(17.2%)
Interferon α, β	3/58	(5.2%)
Tocilizumab	2/58	(3.4%)
Remdesivir	1/58	(1.7%)
ICU admission	11/58	(19%)
MV requirement	13/58	(22.4%)
Outcomes		
Clinically recovered/Discharged	36/58	(62%)
Illness days duration (median, Range)	17.5	(7–48)
Alive but suffers/In hospital	13/58	(22.4%)
Illness days duration (median, range)	14	(7–49)
Death	9/58	(15.5%)
Illness days duration (median, range)	9	(5–40)

by increasing the dose of prednisone. These variables are presented in the Table 4.

COVID-19 directed management

Treatment targeted COVID-19 included antibiotics (41.3%), hydroxychloroquine (43.1%), intravenous methylprednisolone (32.7%), intravenous immunoglobulin (25.8%), lopinavir/ritonavir (20.6%), unspecified antivirals (17.2%), azithromycin (15.5%), oseltamivir (13.8%), interferon a,b (5.2%), tocilizumab (3.4%), and remdesivir (1.7%). These variables are presented in the Table 4.

COVID-10 targeting treatment used in patient who died included antibiotics (55.5%), hydroxychloroquine (55.5%), lopinavir/ritonavir (44.4%), intravenous methylprednisolone (33.3%), and intravenous immunoglobulin (22.2%).

Patients outcomes

Overall, 19% of patients needed intensive care unit (ICU) admission and 22.4% of patients required mechanical ventilation (MV). Overall, 62% of patients recovered and were discharged with median of the illness duration of 17.5 days (range, 7 to 48 days). At the time of report publication, 22.4% of patients were alive and hospitalized, with median of the illness duration of 14 days (range, 7 to 49 days). Overall, 15.5% of patients had died with median of the illness duration of 9 days (range, 5 to 40 days).

Characteristics of patients who died

The mean age was 66.2 years with 55.5% of patients older than 65 years; 55.5% of patients were male and the mean of the transplant age was 9.7 years. Hypertension, diabetes mellitus, and COPD were reported in 88.8%, 33.3%, and 100% of patients, respectively. In addition, 66.6% of patients had lymphopenia and 66.6% had high CRP serum levels. Acute kidney injury (AKI) was reported in 44.4% of patients (Table 5).

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 5. Characteristics and management of the COVID-19 kidney transplant patients with death as the outcome.

Variable (n=9)	Value
Age in years (mean)	66.2
>65y	55.5%
<65y	44.5%
Sex, Male	55.5%
Kidney transplant years age (Mean)	9.7
Comorbidities	
HTN	88.8%
DM	33.3%
COPD	100%
Laboratories	
Lymphopenia (<1*10^9/l)	66.6%
High CRP (>5 mg/dl)	66.6%
Acute kidney injury	44.4%
Baseline Immunosuppression regimen	
Tac, MMF, Pred	44.4%
Management	
Immunosuppression	
Held tacrolimus	3/6 (50%)
Reduced tacrolimus	2/6 (33.3%)
No change tacrolimus	1/6 (16.6%)
Held mycophenolate mofetil	6/6 (100%)
Held prednisone	2/7 (28.5%)
No change prednisone	5/7 (71.4%)
Held ciclosporin	1/1 (100%)
Held sirolimus	1/1 (100%)
Held mizoribine	1/1 (100%)
Tx targets COVID-19	
Lopinavir/Ritonavir	44.4%
Hydroxychloroquine	55.5%
Oseltamivir	11.1%
Antibiotics	55.5%
Intravenous methylprednisolone	33.3%
Intravenous immunoglobulin	22.2%
ICU admission	33.3%
MV requirement	55.5%
Disease days duration (median, range)	9 (5–40)

Pooled results

Three studies reported 36, 20, and 15 patients, respectively. These studies reported results without demographics and characteristics for each patient and thus were not included in our tabulated results. However, these 3 studies were used to draw pooled measures for all reported kidney transplant patients who encountered COVID-19, found in the literature. The total number of kidney transplant patients who encountered COVID-19 reported in the literature was 129 cases. The age mean was 54.2 years with 73.7% of the patients were males. The transplant age mean was 8.2 years with 65.4% of the transplants from a deceased source. Hypertension, diabetes mellitus, and coronary artery disease were reported in 82.6%, 40%, and 14% of cases, respectively. The most commonly reported presentations in order were fever (82.3%), cough (58%), SOB (33.2%), fatigue (30.7%), diarrhea (19.7%), myalgia (17.3%), sore throat (7.6%), and vomiting (6.9%) (Table 6).

The initial white blood cell count mean was 5.37×10^9. The initial mean lymphocyte cell count was 0.77×10^9. Leukopenia and lymphopenia were reported in 21.9% and 79% of patients, respectively. Mean initial CRP was 52.4 mg/L and high CRP (>5 mg/dL) levels were noted in 71.6% of cases. Mean initial (post infection) serum Cr was 1.85 mg/dL and AKI was observed in 34.1% of patients. High D-dimer (>500 µg/L) and lactate dehydrogenase (LDH, >225 U/L) levels were observed in 64.8% and 52.6%, respectively. Kidney transplant patients encountered COVID-19 were maintained on Tac (92%), MMF (78.8%), Pred (77%), and azathioprine (5.2%) and were manage by holding MMF in 79.1% of patients and holding Tac in 34.4% of patients. These patients received treatments targeted for COVID-19 which included hydroxychloroquine (77.6%), lopinavir/ritonavir (49.8%), antibiotics (48%), azithromycin (40.5%), and tocilizumab (11.8%). Overall, 20% of patients needed ICU admission, 24.6% of patients required MV, 42% of patients recovered and were discharged, 41.3% of patients were alive and hospitalized at the time of the study publication, and 18.8% of patients had died (Tables 6, 7).

Discussion

Fever in COVID-19 has been reported in 99% of patients [18,19]. Our study has found that 15% of the kidney transplant patients had no fever on presentation or during their hospitalization. On the other hand, cough, shortness of breath, myalgia, headache, sore throat, and gastrointestinal symptoms were more common than the typical COVID-19 presentation [18–21].

Additionally, this review found that there were several unreported symptoms that appeared in the COVID-19 positive kidney transplant patients, like chest tightness and pain, coryza, dehydration, conjunctivitis, dizziness, and weight loss [20].

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 6. Clinical characteristics of the 58 reported kidney transplant patients who encountered covid-19 compared with previous published studies.

Variable	This study	Akalin et al. [47]	Alberici et al. [48]	CUKTP [49]	Pooled (mean)
Number of patients	58	36	20	15	129
Age (mean)	52.69		59	51	54.2
Sex					
Male	75.9%	72%	80%	67%	73.7%
Female	24.1%	28%	20%	33%	26.2%
Kidney transplant years age (mean)	7.68		13	4	8.2
Type of donor					
Deceased	41.2%	75%		80%	65.4%
Comorbidities					
HTN	68.9%	94%	85%		82.6%
DM	36.2%	69%	15%		40%
CAD	10.3%	17%	15%		14%
Clinical presentation					
Fever	84.5%	58%	100%	87%	82.3%
Cough	70%	53%	50%	60%	58%
SOB	56.9%	44%	5%	27%	33.2%
Fatigue	34.5%			27%	30.7%
Myalgia	15.5%	36%	5%	13%	17.3%
Vomiting	6.9%			7%	6.9%
Diarrhea	17.2%	22%		20%	19.7%
Sore throat	5.2%		10%		7.6%
Laboratory					
White cell count					
Mean per l ($\times 10^9$)	6	5.3	5.4	4.8	5.37
Leukopenia ($<4\times 10^9$/l)	22.8%	21%			21.9%
Lymphocyte count					
Mean per l ($\times 10^9$)	0.6	0.6	1.1	0.8	0.77
Lymphopenia ($<1\times 10^9$/l)	79%	79%			79%
Initial C-reactive protein (CRP)					
Mean	49	7.9	49	104	52.4
High CRP (>5 mg/dl)	97.2%	46%			71.6%
Initial serum Creatinine (Cr)					
Mean	1.9		1.8		1.85
AKI	28.2%			40%	34.1%
Initial D-dimer					
Mean	1015	1020	279		771.3
High D-dimer (>500 µg/L)	72.7%	57%			64.8%
Initial lactate dehydrogenase (LDH)					
Mean	266.5	336	231	275	277
High LDH (>225 U/l)	69.2%	36%			52.6%

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

Table 7. Management and outcomes of the 58 reported kidney transplant patients who encountered COVID-19 compared with previous published studies.

Variable	This study	Akalin et al. [47]	Alberici et al. [48]	CUKTP [49]	Pooled (mean)
Baseline Immunosuppression					
Tacrolimus	82.7%	97%	95%	93%	91.9%
Mycophenolate mofetil	79.3%	86%	70%	80%	78.8%
Prednisone	81%	94%	65%	67%	77%
Azathioprine	3.4%			7%	5.2%
Management					
Immunosuppression					
Held tacrolimus	47.9%	21%			34.4%
Held mycophenolate mofetil	80.4%	86%		71%	79.1%
Other Tx					
Lopinavir/Ritonavir	20.6%		79%		49.8%
Hydroxychloroquine	43.1%	86%	95%	86.6%	77.6%
Azithromycin	15.5%	46%		60%	40.5%
Antibiotics	41.3%		55%		48.1%
Tocilizumab	3.4%	7%	30%	7%	11.8%
ICU admission	19%		20%		20%
MV requirement	22.4%	39%	10%	27%	24.6%
Outcomes					
Clinically recovered/Discharged	62%	36%	15%	53%	42%
Alive but suffers/In hospital	22.4%	43%	60%	40%	41.3%
Death	15.5%	28%	25%	7%	18.8%

Interestingly, the previously unreported chest tightness and pain symptoms in other cohorts had an incidence of 7% in this cohort.

COVID-19 causes of pneumonia can be severe enough to be lethal, especially in patients with advanced age or underlying medical comorbidities [22]. Those comorbidities include cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, chronic kidney disease, and obesity (body mass index ≥30 kg/m^2) [3,22]. Kidney transplant patients infected with COVID-19 are a fragile and high-risk group due to immunosuppressant medications (ISMs), kidney disease, and common comorbidities. In this review, 81% of patients had comorbidities, with diabetes mellitus and hypertension as the most common reported comorbidities. This fact exposes those patients to a more severe COVID-19 infection, not to mention the additional unclear risk of the immunosuppression. Kidney transplant recipients and candidates are as a rule in a high-risk group due to the high incidence and prevalence of hypertension, diabetes, obesity, and advanced age in this group.

It was previously reported that a progressive decline in lymphocyte count was observed in non-survivors compared to more stable levels in survivors [18]. In the present study, 66.6% of patients who died had lymphopenia. Given the fact that ISMs can induce lymphopenia, many kidney transplant patients can have a baseline lymphopenia that might further deteriorate and worsen the prognosis [8].

AKI, proteinuria, and hematuria have all been reported in COVID-19 patients. AKI has been reported to have occurred in 25% to 29% of critically ill COVID-19 patients in Wuhan, China [23,24]. The incidence of AKI among patients who are less severely ill is unknown. In our cohort, AKI was reported in 28.2% of patients. However, the pooled AKI prevalence was 34.1% (see Table 6). This may indicate that kidney transplant patients infected with COVID-19 are more likely to have AKI than other cohorts. AKI has been associated with worse outcomes [25] and subsequently, kidney transplant patients infected with COVID-19 may have worse outcomes and mortality.

Several studies and a report from the Chinese Center for Disease Control and Prevention have classified COVID-19 severity [23,26] as mild, severe, and critical disease that were reported in 81%, 14%, and 5% of patients. However, in our

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

cohort, mild disease was only reported in 43% of patients while severe disease that presents with SOB or hypoxia was reported in 57% of patients.

The WHO reported that recovery time appears to be around 2 weeks for mild infections and 3 to 6 weeks for severe disease [27]. In this report, it appears that 62% of patients recovered clinically from the COVID-19 with a median duration of illness of 17.5 days (range, 7 to 48 days). Rates of ICU admission were reported to range between 5% to 12% while the rate of MV was 2.3% in the general population [28,29]. In our cohort, 19% of patients were admitted to the ICU and 22.4% of patients required MV.

The most recently reported mortality rate of COVID-19 was 3.77% [30]. The mortality rate of kidney transplant patients infected with COVID-19 in this cohort was 15.5% (9 out of 58 patients) and the pooled mean was 18.8%. Despite the small number of patients included in the present study, this high mortality rate indicates that COVID-19 in kidney transplant patients may portend an ominous outcome. We found that 11.1% of the 1-year transplant age patients had died while 16.3% mortality was found for patients with transplant age more than 1 year.

It has been reported that 81% of COVID-19 patients present with mild disease and can be managed at home, while severe and critical COVID-19 disease should be managed with prompt hospitalization while ensuring appropriate infection control and supportive care [23,31,32]. The hospitalized patients should be managed with empiric treatment for bacterial pneumonia in selected patients, prevention of venous thromboembolism, and avoiding nebulized medications. The WHO and CDC recommend against systemic glucocorticoids in COVID-19 patients unless there are other indications [31,32]. To date, all suggested medications are under investigation with no proven efficacy against COVID-19. These medications include remdesivir, hydroxychloroquine/chloroquine, azithromycin and hydroxychloroquine, convalescent plasma, tocilizumab, favipiravir, interferon beta, and lopinavir/ritonavir. A registry of international clinical trial can be found at *https://www.clinicaltrials.gov/ct2/results?cond=covid19&term=&cntry=&state=&city=&dist*. Most of our cohort had been hospitalized and could not be managed at home due to the severity of the disease. They had been managed with antibiotics (41.3%), hydroxychloroquine (43.1%), intravenous methylprednisolone (32.7%), intravenous immunoglobulin (25.8%), lopinavir/ritonavir (20.6%), unspecified antivirals (17.2%), azithromycin (15.5%), oseltamivir (13.8%), interferon a,b (5.2%), tocilizumab (3.4%), and remdesivir (1.7%).

The effect of immunosuppression on the progression of COVID-19 is not clear yet. There are 2 aspects that cannot be ignored when dealing with immunosuppression and COVID-19. Firstly, it was proven that COVID-19 patients have a high prevalence of lymphopenia [33] but it is not clear yet whether lymphopenia is a risk factor for COVID-19 or a result of it. Secondly, it is thought that the severity of COVID-19 may be the result of a hyperinflammatory response (cytokine storm). Thus, many have questioned the role of immunomodulation in the treatment of severe cases [34,35].

Interestingly, D'Antiga from Italy recently published a study that concluded that immunocompromised patients do not have an increased risk of developing severe pulmonary disease compared to the general population [36].

Conclusions

Kidney transplant patients may present with atypical clinical picture of the COVID-19. Fever may be absent while other atypical symptoms may prevail. Therefore, a high index of suspicion for COVID-19 and perhaps even surveillance in this population may help in early diagnosis and prevention of further transmission. The role of immunosuppression therapy should be assessed in every case individually.

Conflicts of interest

None.

References:

1. World Health Organization (WHO): Novel coronavirus (2019 nCoV), 2020; available from: *https://www.who.int/health-topics/coronavirus#tab=tab_1*
2. World Health Organization (WHO): Coronavirus disease 2019 (COVID-19) Situation Report – 88, 2020; available from *https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/*
3. Zhou F, Yu T, Du R et al: Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study [published correction appears in Lancet, 2020; 395(10229): 1038. [published correction appears in Lancet, 2020; 395(10229): 1038]. Lancet 2020; 395(10229): 1054–62
4. Bartiromo M, Borchi B, Botta A et al: Threatening drug-drug interaction in a kidney transplant patient with coronavirus disease 2019 (COVID-19). Transpl Infect Dis, 2020 [Online ahead of print]
5. World Health Organization (WHO): COVID-19 global literature on coronavirus disease, in, 2020; available from *https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/*
6. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med, 2009; 6(7): e1000097
7. National Heart, and Blood Institute: Study quality assessment tools. 2020; available from: *https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools*

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

8. Banerjee D, Popoola J, Shah S et al: COVID-19 infection in kidney transplant recipients. Kidney Int, 2020; 97(6): 1076–82
9. Chen S, Yin Q, Shi H et al: A familial cluster, including a kidney transplant recipient, of Coronavirus Disease 2019 (COVID-19) in Wuhan, China. Am J Transplant, 2020 [Online ahead of print]
10. Gandolfini I, Delsante M, Fiaccadori E et al: COVID-19 in kidney transplant recipients. Am J Transplant, 2020 [Online ahead of print]
11. Guillen E, Pineiro GJ, Revuelta I et al: Case report of COVID-19 in a kidney transplant recipient: Does immunosuppression alter the clinical presentation? Am J Transplant, 2020 [Online ahead of print]
12. Huang J, Lin H, Wu Y et al: COVID-19 in posttransplant patients-report of 2 cases. Am J Transplant 2020 [Online ahead of print]
13. Ning L, Liu L, Li W et al: Novel coronavirus (SARS-CoV-2) infection in a renal transplant recipient: Case report. Am J Transplant, 2020 [Online ahead of print]
14. Seminari E, Colaneri M, Sambo M, et al: SARS Cov-2 infection in a renal-transplanted patient: A case report. Am J Transplant, 2020 [Online ahead of print]
15. Wang J, Li X, Cao G et al: COVID-19 in a kidney transplant patient. Eur Urol, 2020; 77(6): 769–70
16. Zhang H, Chen Y, Yuan Q et al: Identification of kidney transplant recipients with coronavirus disease 2019. Eur Urol, 2020; 77(6): 742–47
17. Zhu L, Xu X, Ma K et al: Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant, 2020 [Online ahead of print]
18. Wang D, Hu B, Hu C et al: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA, 2020; 323(11): 1061–69
19. Huang C, Wang Y, Li X et al: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet, 2020; 395(10223): 497–506
20. World Health Organization (WHO): Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19), (2020), in, 2020; available from: *https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf*
21. Cheung KS, Hung IF, Chan PP et al: Gastrointestinal manifestations of SARS-CoV-2 infection and virus load in fecal samples from the Hong Kong cohort and systematic review and meta-analysis. Gastroenterology, 2020 [Online ahead of print]
22. Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the chinese center for disease control and prevention. JAMA, 2020 [Online ahead of print]
23. Yang X, Yu Y, Xu J et al: Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study [published correction appears in Lancet Respir Med. 2020 Apr;8(4): e26]. Lancet Respir Med, 2020; 8(5): 475–81
24. Chen T, Wu D, Chen H et al: Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study [published correction appears in BMJ, 2020;3 68: m1295]. BMJ, 2020; 368: m1091
25. Shi S, Qin M, Shen B et al: Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol, 2020 [Online ahead of print]
26. Kujawski S, Wong K, Collins J et al., COVID-19 Investigation Team: Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. Nat Med, 2020 [Online ahead of print]
27. World Health Organization Director-General's opening remarks at the media briefing on COVID-19 – 24 February 2020; available from: *https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---24-february-2020*
28. Grasselli G, Pesenti A, Cecconi M: Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: Early experience and forecast during an emergency response. JAMA, 2020 [Online ahead of print]
29. Guan WJ, Ni ZY, Hu Y et al: Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med, 2020; 382(18): 1708–20
30. Zhang J, Wang X, Jia X et al: Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. Clin Microbiol Infect, 2020; 26(6): 767–72
31. Prevention, Centers for Disease Control and Prevention: Interim clinical guidance for management of patients with confirmed 2019 novel coronavirus (2019-nCoV) infection. 2020
32. World Health Organization: Home care for patients with suspected novel coronavirus (nCoV) infection presenting with mild symptoms and management of contacts. 2020
33. Guan W-J, Ni Z-Y, Hu Y et al: Clinical characteristics of 2019 novel coronavirus infection in China. MedRxiv, 2020; 2002.2006.20020974
34. Ritchie AI, Singanayagam A: Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? Lancet, 2020; 395: 1111
35. Booth CM, Matukas LM, Tomlinson GA et al: Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area [published correction appears in JAMA. 2003 Jul 16;290(3): 334]. JAMA, 2003; 289(21): 2801–9
36. D'Antiga L: Coronaviruses and immunosuppressed patients: The facts during the third epidemic. Liver Transpl, 2020; 26(6): 832–34
37. Arpali E, Akyollu B, Yelken B et al: Case report: A kidney transplant patient with mild COVID-19. Transpl Infect Dis 2020;e13296. doi: 10.1111/tid.13296.
38. Billah M, Santeusanio A, Delaney V, Cravedi P, Farouk SS. A catabolic state in a kidney transplant recipient with COVID-19. Transpl Int, 2020 [Online ahead of print]
39. Fontan Fontana F, Alfano G, Mori G et al: COVID-19 pneumonia in a kidney transplant recipient successfully treated with tocilizumab and hydroxychloroquine. Am J Transplant, 2020 [Online ahead of print]
40. Hsu JJ, Gaynor P, Kamath M et al: COVID-19 in a high-risk dual heart and kidney transplant recipient. Am J Transplant, 2020 [Online ahead of print]
41. Kates OS, Fisher CE, Stankiewicz-Karita HC et al: Earliest cases of coronavirus disease 2019 (COVID-19) identified in solid organ transplant recipients in the United States. Am J Transplant, 2020 [Online ahead of print]
42. Johnson KM, Belfer JJ, Peterson GR et al: Managing COVID-19 in renal transplant recipients: A review of recent literature and case supporting corticosteroid-sparing immunosuppression. Pharmacotherapy, 2020 [Online ahead of print]
43. Kim Y, Kwon O, Paek JH et al: Two distinct cases with COVID-19 in kidney transplant recipients. Am J Transplant, 2020 [Online ahead of print]
44. Fernández-Ruiz M, Andrés A, Loinaz C et al: COVID-19 in solid organ transplant recipients: A single-center case series from Spain. Am J Transplant, 2020 [Online ahead of print]
45. Gandolfini I, Delsante M, Fiaccadori E et al: COVID-19 in kidney transplant recipients. Am J Transplant, 2020 [Online ahead of print]
46. Zhu L, Gong N, Liu B et al: Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: A summary of 10 confirmed cases in Wuhan, China. Eur Urol, 2020; 77(6): 748–54
47. Akalin E, Azzi Y, Bartash R et al: Covid-19 and kidney transplantation. N Engl J Med, 2020 [Online ahead of print]
48. Alberici F, Delbarba E, Manenti C et al: A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int, 2020; 97(6): 1083–88
49. Columbia University Kidney Transplant Program: Early description of coronavirus 2019 disease in kidney transplant recipients in New York. J Am Soc Nephrol, 2020; 31(6): 1150–56

Indexed in: [Science Citation Index Expanded] [Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]