Received: 19 June 2020 | Accepted: 29 June 2020

DOI: 10.1111/tid.13419

LETTER TO THE EDITOR

WILEY

COVID-19 in solid organ transplant recipients

To the Editor,

First identified in December 2019, the novel severe acute respiratory syndrome coronavirus-2 has spread widely.[1,2] Coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020. Post-transplant patients appear to be particularly vulnerable.[3-7]

University of Arkansas for Medical Sciences (UAMS) is the only abdominal transplant institution in the state of Arkansas. Between March 25 and April 20, four transplant recipients with functioning grafts tested positive for COVID-19. Three were African American; one was Hispanic. Median age was 62.5 years (range 49-65). Three patients had received kidney transplant (KT). One had received a simultaneous liver-kidney (SLK). All patients were hypertensive; half were morbidly obese. The SLK recipient was also diabetic with chronic kidney disease. None was a smoker. The median time since transplant was 292 days (range 70-523) (Table 1). All patients had been on tacrolimus and an antimetabolite. All but the SLK patient had been on prednisone.

The most common symptoms were fever, sore throat, and shortness of breath (75% of patients) (Table 2). Half patients reported fatigue, rhinorrhea, headache, cough, and nausea. Altered taste/ smell or diarrhea was reported by one. 75% had contracted COVID-19 by a family member. ¾ patients were hospitalized. At a median follow-up of 41 days (range 26-52), three patients have recovered. One developed acute respiratory distress syndrome (ARDS), was placed on mechanical ventilation, and eventually succumbed.

Three patients were lymphopenic on initial presentation. Inflammatory markers were measured on inpatients. All patients had ferritin levels higher than 1300 ng/mL, c-reactive protein (CRP) above 5 mg/dL, and lactate dehydrogenase (LDH) higher than 200 IU/L. Troponin was above 0.5 ng/mL on the ARDS case (Table 2).

All patients had received immunosuppression induction (Table 3). Half had received antithymocyte globulin. The ARDS patient had received basiliximab; that patient had had a history of monoclonal gammopathy of unknown significance and had received plasma exchange for antibody-mediated rejection.

There is currently no proven COVID-19 treatment.[3,8] With the assumption that T-cell depression poses patients to higher viral infection risk, antimetabolites were discontinued.[9] Tacrolimus was withheld on hospitalized patients.[3,4,10,11] Azithromycin and hydroxychloroquine were administered to all hospitalized patients.[12-15] On the ARDS patient, D-dimer and IL-6 were very high, corroborating reports of high D-dimer and IL-6 association to dismal outcome.[16] The patient received tocilizumab which reversed IL-6 up-trending yet did not alter the outcome.

Despite the small sample, our data resonate reports from the epidemic epicenter[3,4,11]: Disease tends to be more severe among the KT population. Up-to-date, there has not been a single confirmed COVID-19 case on a liver transplant (LT) alone recipient transplanted at the UAMS. If this is a random effect, whether it alludes to comorbidities inherent to the KT population or even a protective immunomodulatory effect on the LT population remains unclear. Notably, international studies have also shown a more indolent COVID-19 course on the LT population.[17,18] It would be interesting to explore whether mild immunosuppression *without T-cell carpet-bombing*

TABLE 1 Patient demographics

Patient	Age	Gender	Race	Type of transplant	Donor type	Time from transplant to infection (days)	Comorbid conditions	Tobacco	F/u (days)
1	49	F	AA	DDKT	DBD	314	HTN, morbid obesity, hyperthyroidism	No	52
2	64	F	AA	DDKT	DBD	523	HTN, morbid obesity, MGUS, SVC stenosis, AMR	No	39
3	61	M	Hispanic	SLK	DBD	70	HTN, DM, CKD, hypothyroidism	No	43
4	65	F	AA	DDKT	DBD	270	HTN, renal cell carcinoma	No	26

Abbreviations: AA, African American; AMR, antibody-mediated rejection; CKD, chronic kidney disease; DBD, donation after brain death; DDKT, deceased donor kidney transplant; DM, diabetes mellitus; F, female; f/u, follow-up; HTN, hypertension; M, male; MGUS, monoclonal gammopathy of unknown significance; SLK, simultaneous liver-kidney transplant; SVC, superior vena cava.

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; IL-6, interleukin-6; KT, kidney transplant; LDH, lactate dehydrogenase; SLK, simultaneous liver-kidney transplant.

TABLE 2 Initial presentation, course, and laboratory findings

Pt	Exposure	Presenting symptom	Fever	CXR findings	CT findings	WBC initial/nadir (K/μL)	L (%)[a]
1	Husband (first responder)	Sore throat, SOB, fatigue, headache, rhinorrhea	No	N/A	N/A	4.5/3.8	32.1/ 36.6/ 36.6
2	Unknown	Fever, sore throat, SOB, cough	Yes	Diffuse b/l air-space disease	RLL consolidation, focal mass-like consolidation in posterior segment of RUL, diffuse consolidation of LLL	4.0/0.82	0.7/ 0.66/ 0.29
3	Wife	Fever, sore throat, cough, fatigue, rhinorrhea, headache, nausea, diarrhea, altered taste & smell	Yes	Subtle air-space disease in the LLL	N/A	1.67/ 0.76	0.43/ 1.26/ 1.26
4	Daughter, (grandson had exposure at daycare)	Fever, SOB, Fatigue, cough, nausea, diarrhea, poor appetite	Yes	Min bibasilar atelectatic change	N/A	3.91/ 2.83	0.53/ 1.4/ 1.4

Abbreviations: b/l, bilateral; CRP, C-reactive protein; CXR, chest x-ray; Disp; disposition; ICU, intensive care unit; IL-6, interleukin-6; L, lymphocyte count; LDH, lactate dehydrogenase; MV, mechanical ventilation; N/A, non-applicable; NC, nasal cannula; PCT, procalcitonin; RLL, right lower lobe; RUL, right upper lobe; SOB, shortness of breath; WBC, white blood cell count.

[a]Admit, peak, terminal.

TABLE 3 Immunosuppression, antiviral, and antimicrobial treatments

Patient	Organ type	Time from transplant to infection (days)	Induction	CNI	Antimetabolite	Total daily dose (mg)	mTOR	Prednisone (mg)	Immunosuppression changes	COVID19 directed therapy	Antimicrobial agents
1	DDKT	314	ATG	FK	MPA	720	N/A	5	d/c MPA	Azithro	
2	DDKT	523	Basiliximab	FK	MMF	500	N/A	5	d/c FK, MMF	Tocilizumab, azithro, HQC	Cefepime, linezolid, levofloxacin, vancomycin, meropenem, fluconazole, micafungin, amikacin, zosyn,
3[a]	SLK	70	Basiliximab	FK	MPA	1440	N/A	N/A	d/c MPA, decrease FK	HQC, azithro	Cefazolin, vanc, cefepime, metronidazole, nystatin
4	DDKT	270	ATG	FK	MMF	1000	SRL	5	d/c FK, MMF and SRL; SRL was resumed while inpatient	HQC, azithro	Levofloxacin, metronidazole, fluconazole, cefepime, vanc

Abbreviations: ATG, antithymocyte globulin; azithro, azithromycin; d/c, discontinue; FK, tacrolimus; HCAP, healthcare-associated pneumonia; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MPA, mycophenolic Acid; mTOR, mammalian target of rapamycin inhibitor; PNA, pneumonia; SRL, sirolimus; UTI, urinary tract infection; vanc, vancomycin; zosyn, piperacillin-tazobactam.

[a]Patient had received plasma exchange × 6 in 11/2018 for the treatment of antibody-mediated rejection.

D-dimer (ng/mL)[a]	Ferritin (ng/mL)[a]	Troponin (ng/mL)[a]	CRP (mg/dL)[a]	IL-6 (pg/mL)[a]	LDH (IU/L)[a]	PCT (ng/mL)[a]	O_2	Disp.
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Remained home
1600/ 25 671/ 14, 975	1314/ >15 000/ >1500	0.66/ 0.66/ 0.12	164.3/ 371/ 116.1	7779.8/ 49 517.0/ 499.3	211/ 3627/ 3627	3.69/ 37.02/ 37.02	MV, trach	ICU/Death
732	1125/ 1914/ 1914	<0.03/ 0.07/ <0.03	146.6/ 152.4/ 87.3	N/A	455/ 508/ 332	0.14/ 0.17/ 0.10	No	D/c home
14 470	2164/ 4318/ 1976	0.03/ 0.04/ 0.04	18.3/ 78.3/ 14.4	N/A	331/ 448/ 367	0.13/ 0.35/ 0.35	NC	D/c home

confers a shield against severe COVID-19 elicited cytokine storm.[19] To be determined.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose as described by *Transplant Infectious Disease*.

AUTHOR CONTRIBUTIONS

EG was responsible for conception, design, analysis and writing of the study; SZ, AS, SB, and LB were involved with the collection and interpretation of data, review and editing of the manuscript.

Emmanouil Giorgakis[1]
Shannon P. Zehtaban[1]
Amanda E. Stevens[1]
Sushma Bhusal[2]
Lyle Burdine[1]

[1]*Division of Solid Organ Transplantation, Department of Surgery, University of Arkansas for Medical Sciences, Little Rock, AR, USA*
[2]*Division of Nephrology, Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, AR, USA*

Correspondence
Emmanouil Giorgakis, UAMS Medical Center, 4301 W Markham St, Little Rock, AR 72205, USA.
Email: EGiorgakis@uams.edu

ORCID

Emmanouil Giorgakis https://orcid.org/0000-0002-5019-5497

REFERENCES

1. WHO. Coronavirus disease 2019 (COVID-19) situation report 2020.
2. 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;20(7):1859-1863.
3. Nair V, Jandovitz N, Hirsch JS, et al. COVID-19 in kidney transplant recipients. *Am J Transplant*. 2020;20(7):1819-1825.
4. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med*. 2020;382(25):2475-2477.
5. 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):1083-1088.
6. 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;20(7):1875-1878.
7. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.

8. Fauci AS, Lane HC, Redfield RR. Covid-19 — Navigating the uncharted. *N Engl J Med*. 2020;382(13):1268-1269.
9. Uematsu J, Sakai-Sugino K, Kihira-Nakanishi S, et al. Inhibitions of human parainfluenza virus type 2 replication by ribavirin and mycophenolate mofetil are restored by guanosine and S-(4-nitrobenzyl)-6-thioinosine. *Drug Discov Ther*. 2019;13(6):314-321.
10. D'Antiga L. Coronaviruses and immunosuppressed patients: the facts during the third epidemic. *Liver Transplant*. 2020;26(6):832-834.
11. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800-1808.
12. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother*. 2020;75(7):1667-1670.
13. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;e105949.
14. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020;55(5):e105938.
15. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020.
16. Gao Y, Li T, Han M, et al. Diagnostic utility of clinical laboratory data determinations for patients with the severe COVID-19. *J Med Virol*. 2020;92(7):791-796.
17. Bhoori S, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol*. 2020;5(6):523-533.
18. Verma A, Khorsandi SE, Dolcet A, et al. Low prevalence and disease severity of COVID-19 in post-liver transplant recipients-A single centre experience. *Liver Int*. 2020;40(8):1972-1976.
19. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.