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Short Communication

COVID-19 does not impact HLA antibody profile in a series of waitlisted renal transplant candidates

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ABSTRACT

HLA antibodies are typically produced after exposure to transplanted tissue, pregnancy, and blood products. Sensitization delays access to transplantation and preclude utilization of donor organs. Infections and vaccinations have also been reported to result in HLA antibody formation. It is not known if patients develop HLA antibodies after infection with SARS-CoV-2. Here we analyzed a series of eighteen patients waiting for kidney transplantation who had symptomatic COVID-19 disease and recovered. None of the patients in this initial series developed *de novo* HLA antibodies. Notably, there was no increase in preexisting HLA antibodies in four highly sensitized patients with a CPRA > 80%. These preliminary data suggest that there may not be a need to repeat HLA antibody testing or perform a physical crossmatch on admission serum before kidney transplant for COVID-19 recovered patients. Data from a large number of patients with different demographics needed.

1. Introduction

The presence of Human Leukocyte Antigen (HLA) antibodies delays access to transplantation and is a risk factor for allograft rejection following renal transplantation. Exposure to organ transplantation, pregnancies, and blood transfusions triggers HLA antibody production. Infection and vaccination can activate the immune system, which can induce the production of new HLA antibodies or enhance the level of existing HLA antibodies, which is of particular interest to patients awaiting renal transplantation [1,2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells expressing angiotensin-converting enzyme 2 and Transmembrane Serine Protease 2 surface proteins, and patients awaiting kidney transplantation have a 10.2–15.0% risk of mortality if infected [3,4]. SARS-CoV-2 infection activates both an innate and adaptive immune response, resulting in a profound cytokine storm [5]. Kidney transplant recipients are shown to mount an effective anti-SARS-CoV-2 adaptive immune response, including potent humoral immune activity despite chronic immunosuppression [6]. Importantly, a recent report describes the presence of HLA antibodies in the convalescent serum of male patients without any known allosensitizing events who recovered from coronavirus disease 2019 (COVID-19), suggesting that infection with this virus could result in HLA antibody development [7]. Currently, no studies directly address the question of whether or not patients infected with SARS-CoV-2 develop HLA antibodies. As a result, there is no guidance for transplant providers regarding the need to repeat HLA antibody testing prior to kidney transplantation after COVID-19 infection or vaccination.

2. Materials and methods

2.1. Waitlisted renal transplant candidates

This is a single-center retrospective review of a prospectively maintained database of renal transplant candidates, performed with the approval of our institutional IRB (IRB Number: 20-31396). We routinely perform quarterly HLA antibody testing of all waitlisted patients approaching the top of the deceased donor

Abbreviations: HLA, human leukocyte antigen; ESRD, end-stage renal disease; COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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waiting list and use the virtual crossmatch as the final pretransplant crossmatch in the vast majority of deceased donor kidney transplants (currently >90%) [8]. Eighteen patients near the top of our waiting list were known to have contracted and recovered from COVID-19, one of whom also received a single dose of the COVID vaccine prior to repeating HLA testing.

2.2. SARS-CoV-2 RNA testing

Nasopharyngeal and oropharyngeal samples were collected using swabs immediately placed in a standard viral transport medium. Viral RNA was extracted from 400 μL of respiratory samples and eluted in 50 μL of elution buffer. Detection of SARS-CoV-2 RNA was performed by an adapted previously described real-time RT-PCR assay targeting regions of the virus nucleocapsid (N) gene and also targeting the human RNase P gene for sample quality control [9]. All 18 transplant candidates included in this study were positive for SARS-CoV-2 RNA testing.

2.3. HLA antibody testing

The HLA class I and class II antibodies were measured using the Luminex-based single antigen bead assay as previously described (One Lambda Inc., Canoga Park, CA) [8]. Serum samples are pretreated with dithiothreitol (DTT) to prevent aggregation of high titer antibodies (termed prozone effect) and to increase the sensitivity of antibody detection. Moreover, we have re-tested pre- and post-COVID sera obtained from the highly sensitized patients with a CPRA value of >80% to confirm that no HLA antibody specificity was missed due to inhibitory effects commonly observed in sera of high cPRA patients. Based on the recommendation by Tambur et al. and baseline neat mean fluorescence intensity (MFI) values of four patients, we chose 1:16 dilution (with Phosphate buffered saline) for all >80% CPRA sera samples [10]. Antibody specificity is determined based on the known amino acid homologies and cross-reactivity patterns among core HLA allotypes. The MFI is used as an arbitrary unit of antibody quantity. If multiple beads have allelic variants of the same antigen (e.g., HLA-A*68:01, *68:02, – variants of HLA-A68 antigen), then the average MFI of all reactive beads are used to quantify HLA-A68 antibody MFI. LABXpress Pipettor (One Lambda), a high throughput liquid handling system to aspirate and dispense precise volumes into test wells of a 96-well reaction plate, is used to minimize inter-assay variations. We compared the HLA antibody results before and after COVID-19 for each patient to assess HLA antibody formation.

3. Results

The patient characteristics are presented in Table 1. The average age was 51.5 years old at the time of COVID-19 diagnosis, and one patient was on immunosuppression (Prednisone 5 mg daily). Most patients were male (72%, n = 13). The majority of the patients (72%, n = 13) were Hispanic; 4 were Asians, and 1 was African American. Fourteen patients were unsensitized, and four were highly sensitized (2 with 100% CPRA, 1 with 89% CPRA, and 1 with 98% CPRA). Ten of the eighteen patients with a history of SARS-CoV-2 infection required hospitalization due to COVID-19, and the average length of hospital stay was 5.4 days. One patient required mechanical ventilation in the intensive care unit. Routine quarterly single antigen testing has been repeated an average of 53.2 days after the diagnosis of infection.

Table 2 depicts the pre-COIVID and post-COVID single antigen test results for four highly sensitized patients. The HLA antibody specificities and MFI remain unchanged in post-COVID samples compared to respective pre-COVID samples. The cPRA was

Table 1
Characteristics of 18 kidney transplant waitlist candidates who recovered from COVID-19.

	Pt-1	Pt-2	Pt-3	Pt-4	Pt-5	Pt-6	Pt-7	Pt-8	Pt-9	Pt-10	Pt-11	Pt-12	Pt-13	Pt-14	Pt-15	Pt-16	Pt-17	Pt-18
Age (years)	36	39	57	71	27	41	52	37	73	43	41	59	55	74	59	49	65	49
Gender	M	F	F	F	M	M	M	M	F	M	M	M	F	M	M	M	M	M
Ethnicity	H	H	H	H	A	A	H	H	H	AA	H	H	A	H	A	H	H	H
Etiology of renal failure	CAN	GN (ANCA +)	OU	HTN/DM	AIN	HTN	HTN/DM	HTN	DM	HTN	DM	PCK	HTN/DM	DM	HTN	DM/HTN	PCKD	PCKD
HTN (yes/no)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
DM (yes/no)	No	No	No	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	No	Yes	No	No
BMI	31.3	27.9	32.2	27.2	23.5	27.5	30.1	23.3	30	28.02	25.76	28.19	32.42	22.7	24.3	25.7	33.3	23.9
Method of diaylsis	HD	HD	HD	HD	HD	HD	HD	HD	HD	HD	HD	Predialyis	HD	HD	PD	HD	HD	HD
History of blood transfusions	3	UK	Yes	UK	2	No	UK	UK	22	No	UK	UK	UK	Yes	No	No	No	No
Previous transplants	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Multiparous (yes/no)	NA	Yes	Yes	Yes	NA	NA	NA	NA	Yes	NA	NA	NA	No	NA	NA	NA	NA	NA
SARS-CoV-2 mRNA test positive date (mo.yr)	01.21	04.20	06.20	11.20	01.21	08.20	08.20	04.20	09.20	11.20	07.20	09.20	01.21	08.20	11.21	12.20	12.20	11.20
Immunosuppressed at time of infection	No	No	No	No	Pre	No	No	No	No	No	No	No	No	No	No	No	No	No
cPRA prior to COVID	100%	100%	98%	89%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
cPRA after COVID	100%	100%	98%	89%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
Required hospitalization (yes/no)	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Mo	Yes
Length of hospital stay (days)	NA	17	NA	3	NA	4	11	3	1	NA	NA	5	1	NA	NA	6	NA	3
Length of ICU stay	NA	UK	NA	0	NA	0	3	0	0	NA	NA	NA	NA	NA	NA	0	NA	0
Required oxygen supplimentation	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	Yes	No	No
Required mechanical ventilation (yes/no)	NA	No	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	NA	NA
Day of mechanical ventilation	NA	NA	NA	NA	NA	NA	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COVID treatments	None	None	None	Dex	mAb	None	CP	None	None	None	None	None	None	None	mAb	Dex	None	None
COVID Vaccine (yes/no)	No	No	No	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No

Acute interstial nephritis (AIN), African American (AA), Antineutrophil cytoplasmic antibodies (ANCA), Asian (A), Convalescant plasma (CP), Chronic allograft nephropathy (CAN), Dexamethasone (Dex), Diabetes mellitus (DM), Diffuse proliferative glomerulonephritis (DPGN), Glomerulonephrosis (GN), Hispanic (H), Hypertension (HTN), Monoclonal antibody (mAb), Not applicable (NA), Obstructive uropathy (OU), Polycystic kidney disease (PCKD), Prednisone (Pred), Systemic lupus erythematosus (SLE), Unknown (UK).

Table 2
Specificity and mean fluorescence intensity (MFI) of HLA antibodies in four highly sensitized patients with a CPRA value of over 80%.

Pt-1: CPRA 100%					**Pt-2:** CPRA 100%					**Pt-3:** CPRA 98%					**Pt-4:** CPRA 89%				
	Neat Serum		1:16 dilution			Neat Serum		1:16 dilution			Neat Serum		1:16 dilution			Neat Serum		1:16 dilution	
Specificity	Pre-COVID (11/2020)	Post-COVID (02/2021)	Pre-COVID (11/2020)	Post-COVID (02/2021)	**Specificity**	Pre-COVID (05/2019)	Post-COVID (06/2020)	Pre-COVID (05/2019)	Post-COVID (06/2020)	**Specificity**	Pre-COVID (06/2020)	Post-COVID (09/2020)	Pre-COVID (06/2020)	Post-COVID (09/2020)	**Specificity**	Pre-COVID (07/2019)	Post-COVID (12/2020)	Pre-COVID (07/2019)	Post-COVID (12/2020)
Cw15	19,716	16,588	4328	4028	**A68**	22,279	21,366	4370	1533	**B7**	22,595	17,049	4049	4300	**A32**	5908	7629	*	*
A33	19,331	19,482	9228	6981	**A2**	21,866	21,786	4324	1687	**B60**	21,315	19,231	3864	3928	**A25**	5509	6795	*	*
A31	18,810	18,431	9925	7620	**A69**	20,149	19,772	4418	1578	**B8**	20,743	18,742	3609	3714	**B49**	4304	7209	*	*
A29	18,736	18,325	11,083	8587	**B76**	19,319	18,143	4468	1190	**B67**	20,712	18,240	3676	3822	**B51**	3994	6397	*	*
A80	18,627	18,045	14,259	11,264	**B50**	18,927	17,109	7142	2707	**B39**	20,605	18,508	3302	3405	**B59**	3581	5090	*	*
A11	18,221	17,215	11,058	8744	**B72**	18,255	17,967	8617	3585	**B61**	20,287	18,375	3411	3671	**B38**	3204	4738	*	*
A36	18,102	17,881	8398	6371	**B62**	17,659	16,253	6056	2091	**B18**	20,167	19,306	3107	3306	**B77**	3130	4242	*	*
Cw5	17,944	14,683	3019	2696	**B49**	16,902	16,091	6993	2679	**B72**	20,153	19,140	3205	3363	**B52**	3070	3789	*	*
A1	17,870	17,574	8643	6428	**B45**	13,931	13,829	2175	*	**B48**	20,146	18,589	3470	3620	**B57**	3018	5112	*	*
A32	17,782	17,310	4733	4104	**A34**	11,769	11,562	1058	*	**B42**	20,014	19,258	3266	3329	**B58**	2886	4322	*	*
A3	17,633	16,939	13,014	11,234	**B38**	11,073	10,902	1821	*	**B76**	19,939	18,528	3137	3270	**B63**	2736	4863	*	*
A74	17,432	17,640	12,154	9281	**B57**	10,995	9283	1946	*	**B81**	19,918	18,592	3530	3770	**A23**	2608	4015	*	*
Cw2	17,035	14,063	4379	4086	**B63**	10,967	9874	2468	*	**B45**	19,901	18,800	2925	3185	**B53**	2601	3898	*	*
B62	16,767	13,962	1911	1714	**A32**	10,769	9060	1958	*	**B62**	19,873	19,212	2984	3137	**B13**	1869	1622	*	*
B50	15,885	12,845	1667	1408	**B41**	10,672	9094	*	*	**B41**	19,611	18,611	3021	3258	**B27**	1848	2856	*	*
B49	15,694	13,364	1801	1526	**A25**	10,573	9495	1445	*	**B50**	19,481	18,707	3088	3351	**A24**	1600	2424	*	*
A30	14,947	14,617	4771	3566	**B51**	10,324	9911	1764	*	**B54**	19,257	17,661	2774	2968					
B63	14,456	12,696	1776	1728	**B52**	10,057	9165	1295	*	**B64**	18,736	18,499	2933	3184	**DQ6**	1250	1245	*	*
B57	13,854	11,939	1835	1674	**B58**	10,053	9335	1617	*	**B56**	18,582	18,730	2776	2858					
Cw18	13,731	10,858	1664	1319	**B77**	9823	8699	1322	*	**B55**	18,115	18,460	2652	2865					
B56	12,892	10,658	1021	1065	**B59**	9605	8903	1495	*	**B35**	17,573	17,866	2570	2569					
B76	12,651	11,897	*	1103	**B44**	9327	8305	1600	*	**B78**	17,468	17,317	2360	2579					
B13	12,622	9148	1136	*	**B53**	9279	8985	1400	*	**B71**	17,375	17,506	2521	2652					
B77	12,345	10,003	1055	*	**B60**	9088	8979	*	*	**B75**	17,127	17,139	2454	2550					
B75	11,531	9007	1254	1145	**A23**	8688	7364	1036	*	**B65**	15,352	15,214	1967	1997					
Cw6	11,525	9237	*	*	**A24**	8260	7659	*	*	**B82**	14,949	15,621	1857	2029					
B72	11,497	9506	*	*	**B27**	7579	6596	*	*	**B27**	13,966	12,557	3605	3849					
A34	11,434	11,550	3523	2684	**B47**	7564	6859	*	*	**B73**	12,004	11,548	1331	1431					
B71	10,570	8263	*	*	**B13**	6979	5500	1172	*	**Cw8**	11,946	11,054	1199	1383					
B45	8789	8262	*	1488	**A33**	6886	5099	*	*	**B46**	10,821	10,388	1159	1209					
B46	8441	6162	*	*	**B56**	6683	5274	*	*	**Cw14**	10,159	10,500	1014	1085					
Cw17	7603	5065	*	*	**B71**	6563	5137	*	*	**Cw1**	9504	9677	*	1058					
B44	7086	8036	*	1195	**B37**	6486	5137	*	*	**Cw10**	9115	8313	1035	1141					
B41	6086	4199	*	*	**B55**	4606	3606	*	*	**Cw9**	7976	7471	*	*					
B58	5658	4668	*	*	**A26**	4092	3092	*	*	**B13**	6271	6346	*	*					
B60	5619	3538	*	*	**B64**	3855	2855	*	*	**Cw7**	5839	6066	*	*					
A43	5560	5085	*	*	**B54**	3795	2795	*	*	**Cw16**	5227	5060	*	*					
B61	5464	3664	*	*	**B8**	3240	2240	*	*	**B47**	4825	5062	*	*					
A66	5324	5204	*	*	**B18**	3147	2147	*	*	**Cw12**	4143	4422	*	*					
A26	5249	4883	1211	*	**Cw6**	2935	1935	*	*	**A66**	2610	2797	*	*					
Cw4	4650	3153	*	*	**A66**	2831	1831	*	*	**Cw2**	1151	1063	*	*					
B47	4387	3034	*	*	**B65**	2776	1776	*	*										

Table 2 (*continued*)

Pt-1: CPRA 100%					**Pt-2:** CPRA 100%					**Pt-3:** CPRA 98%					**Pt-4:** CPRA 89%				
	Neat Serum		1:16 dilution			Neat Serum		1:16 dilution			Neat Serum		1:16 dilution			Neat Serum		1:16 dilution	
Specificity	Pre-COVID (11/2020)	Post-COVID (02/2021)	Pre-COVID (11/2020)	Post-COVID (02/2021)	**Specificity**	Pre-COVID (05/2019)	Post-COVID (06/2020)	Pre-COVID (05/2019)	Post-COVID (06/2020)	**Specificity**	Pre-COVID (06/2020)	Post-COVID (09/2020)	Pre-COVID (06/2020)	Post-COVID (09/2020)	**Specificity**	Pre-COVID (07/2019)	Post-COVID (12/2020)	Pre-COVID (07/2019)	Post-COVID (12/2020)
A2	4038	3924	*	*															
B51	2940	1951	*	*	**DR103**	18,912	16,021	2647	*										
B35	2217	1321	*	*	**DR13**	17,077	15,581	2280	1178										
					DR16	12,657	11,038	1612	*										
DQ5	21,490	21,079	10,649	10,550	**DR12**	10,545	9452	1130	*										
DQ6	20,189	21,090	11,767	11,604	**DR11**	9841	8881	1099	*										
DR52	18,731	17,740	9929	10,244	**DR51**	8926	7890	1913	*										
DR18	15,979	12,031	1311	1032	**DR8**	8650	7807	*	*										
DR17	15,639	12,122	1198	*	**DR4**	8150	7405	2183	*										
DQ4	14,801	12,724	1597	1509	**DQ6**	7049	6216	*	*										
DR13	13,826	10,789	1304	1153	**DR1**	6010	5778	*	*										
DQ8	12,802	10,877	1896	1765	**DQ5**	5806	4570	*	*										
DR11	12,530	9320	1067	*	**DP19**	5541	4563	*	*										
DR14	12,496	9305	1096	*	**DP20**	5300	4953	*	*										
DQ9	12,183	9986	1619	1528	**DR10**	4257	3044	*	*										
DR12	8084	5501	*	*	**DP3**	3594	3276	*	*										
DR8	7147	5216	*	*	**DQ2**	3390	2600	*	*										
DR7	2116	1104	*	*	**DP10**	3288	2988	*	*										
DR9	1890	1167	*	*	**DP6**	3186	2206	*	*										
					DP14	2909	2140	*	*										
					DP9	2868	2417	*	*										
					DP17	2770	1506	*	*										
					DR9	2734	1326	*	*										
					DQ8	2699	2015	*	*										
					DP15	2375	1843	*	*										
					DR7	2228	1066	*	*										
					DQ4	2216	1870	*	*										
					DP11	2207	1502	*	*										
					DP1	2063	1844	*	*										
					DP5	2060	1418	*	*										

* <1000 MFI (negative).

unchanged in all patients, and there was no perceptible increase in the risk of rejection based on the HLA antibody profiles of the patients before and after COVID-19 infection. Moreover, retesting of pre- and post-COVID sera obtained from four highly sensitized patients with a CPRA value of over 80% with 1:16 dilutions confirmed that no HLA antibody specificity was missed due to inhibitory effects commonly observed in sera of high cPRA patients (Table 2).

4. Discussion

Knowledge about the immune response in patients that recover from COVID-19 is evolving, but it is clear the virus can induce a relatively unique immune dysregulation [11]. Cytomegalovirus, influenza virus, herpes virus, and varicella virus infection have been shown to result in HLA antibody development through T-cell cross-reactivivity [12–14], termed heterologous immunity. Notably, male patients without any known sensitizing events donating convalescent serum after COVID-19 infection were found to have HLA antibodies [7]. Therefore, it is essential for transplant providers to consider the possibility of the existence of either de novo HLA antibodies or increased MFI of existing antibodies after recovery from infection with COVID-19 in patients awaiting kidney transplantation.

Patients nearing the top of the waiting list undergo expensive quarterly monitoring for HLA antibodies to permit moving forward with transplant using a virtual crossmatch as the final pretransplant crossmatch. HLA antibody testing is time-consuming and therefore is usually not possible after an organ offer is received, and many centers are moving away from physical crossmatching for a majority of patients. There is no consensus to date about whether or not patients who have recovered from COVID-19 infection need repeat HLA antibody testing prior to moving forward with kidney transplantation if they receive an organ offer prior to the next quarterly single antigen testing. A larger body of published literature suggests that viral infection does not cause HLA antibody development [15–18] compared to the evidence viral infection can cause HLA antibodies [7,12–14]. Understandably, many transplant centers elect to perform a physical crossmatch at the time of transplant in a waitlisted patient who has recovered from COVID, increasing cost and potentially decreasing access to transplant.

Based on this series of patients with end-stage renal failure awaiting a kidney transplant, we found no evidence of HLA antibody development resulting from COVID-19 infection. It is interesting to note that patients with COVID-19 display a complex immune dysregulation characterized by lymphopenia and down-regulation of HLA class II molecules, which could form defective antigen-presentation and thus impaired alloantibody response [11,19]. Additionally, the above-mentioned report by Juskewitch et al. [7] certainly deserves further investigation. One additional patient not described in Table 1 received both doses of the COVID-19 vaccine and then underwent deceased donor kidney transplantation. Similar to the patients described in Table 1, this additional patient who received both doses of vaccine did not have any HLA antibodies. The impact of mRNA vaccinations on sensitization will need to be determined, but our one patient that was vaccinated remains unsensitized.

The weakness of this study is the size of the series of patients. Despite the size of this study, we feel it is important to share these results because a final conclusion about this issue will not be possible until an extensive series of patients is available. This will likely take a multi-institutional effort. Therefore, in the intervening months to years, transplant providers will continue to be pressured to make real-time risk-benefit decisions about patients at the time of organ offer. This series is the first step in assisting providers who are currently considering organ offers for patients that have recovered from COVID-19 without time for a physical crossmatch.

In summary, transplant providers need to continue to be vigilant about the possibility of HLA antibody development in patients infected with COVID-19. This series of patients has not identified de novo HLA antibodies or the presence of a memory response in highly sensitized patients awaiting kidney transplant undergoing serial single antigen testing after infection. Our institutional plan is to continue to treat COVID-19 infection as we do other infections in this population. Therefore, we do not delay transplant to perform a physical crossmatch or repeat single antigen testing after COVID-19 infection or vaccination with the goal of reducing barriers to transplantation, but other opinions are valid. We will continue to monitor the development of HLA antibodies following vaccination and COVID-19 infection to validate our current strategy. We look forward to a more comprehensive understanding of the immune response to COVID-19 infection and vaccination in patients awaiting transplant.

5. Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by Human Immunology.

6. Financial disclosure

The authors declare that no financial support was received to perform this study.

Author contributions

Garrett R. Roll: Participated in research design, performance of the research, writing of the paper.
Tyler Lunow-Luke: Participated in performance of the research.
Hillary J. Braun: Participated in performance of the research.
Owen Buenaventura: Performed HLA antibody testing.
Mirelle Mallari: Collected and managed the data.
Peter G. Stock: Participated in performance of the research, editing of the paper.
Raja Rajalingam: Participated in research design, performance of the research, writing of the paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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