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Human Immunology 83 (2022) 749–754

Contents lists available at ScienceDirect

journal homepage: www.elsevier.com/locate/humimm

Short Communication

Association between SARS-CoV-2 infection and de novo HLA donor specific antibody production in lung transplant recipients: Single-center study

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ARTICLE INFO

Keywords:
HLA antibodies
Lung transplant
COVID-19

ABSTRACT

The COVID-19 pandemic has led to significant morbidity and mortality in lung transplant recipients. Respiratory viral infections may be associated with de-novo HLA donor-specific antibody production and impact lung transplant outcome. Since one of the immunomodulation strategies post-SARS-CoV-2 infection in lung transplant recipients include decreasing or holding anti-metabolites, concerns have been raised for higher incidence of de-novo HLA donor specific antibody production in lung transplant recipients. We performed a retrospective chart review of 24 consecutive lung transplant recipients diagnosed with COVID-19 to investigate this concern. We observed no significant differences in the CPRA or MFI levels of HLA class I and II antibodies pre- COVID-19 compared to 1 and 6 months post-COVID-19 diagnosis in 11/24 (45.8 %) LTR ($p = 0.98$ and $p = 0.63$ respectively). HLA class I and II DSA were detected in 5/24 LTR pre-COVID-19 diagnosis and persisted with no significant differences in the median MFI levels at 1 and 6 months post-COVID-19 diagnosis ($p = 0.89$). De-novo HLA class I and II DSA were detected in 1/24 (4.2 %) LTR at one month post-COVID-19 diagnosis and persisted with no significant differences in the median MFI levels at 1 and 6 months post-COVID-19 diagnosis ($p = 0.54$). Our results suggest that there was no significant association between SARS-CoV-2 infection and immunomodulation on pre-existing or de novo HLA donor specific antibodies.

1. Introduction

As of July 1st, 2022, the COVID-19 pandemic has led to 551 million confirmed SARS-CoV-2 infection cases and 6.3 million deaths globally as per report from World Health Organization [1]. Long term effects on morbidity and mortality in high-risk sub-group populations remains to be determined. One such high risk population is solid organ transplant recipients because of their immunocompromised status. Lung Transplant Recipients (LTR) within this cohort are most at-risk because lungs are the primary organs involved with SARS-CoV-2 infection. Respiratory viral infections (RVI) may be associated with de-novo HLA donor-specific antibodies (DSA) production and impact lung transplant outcome [2]. However, RVI did not influence pediatric lung transplantation outcomes raising the possibility that the immunologic impact of RVI in pediatric LTR is different than in adult LTR [3]. Isolation of *Pseudomonas Aeruginosa* in LTR was also associated with increased risk of HLA DSA development [4]. These studies raise concerns for impact of SARS-CoV-2 infection on de novo HLA DSA production in LTR.

Chronic Lung Allograft Dysfunction (CLAD) is the most important cause of long-term morbidity and mortality in LTR [5]. CLAD can present as an obstructive phenotype known as Bronchiolitis Obliterans Syndrome (BOS) or as restrictive phenotype with pulmonary fibrosis known as restrictive allograft syndrome (RAS) [6]. De-Novo HLA class I and II DSA can cause antibody mediated rejection (AMR), development of BOS resulting in increased graft loss and decreased patient survival [7–9]. It has been reported that HLA DSA formation precedes graft dysfunction and LTR with clearance of HLA DSA have a higher survival rate than those without DSA clearance [10]. The primary

Abbreviations: LTR, Lung Transplant Recipients; RVI, respiratory viral infections; AMR, antibody-mediated rejection; CLAD, Chronic Lung Allograft Dysfunction; BOS, Bronchiolitis Obliterans Syndrome; RAS, restrictive allograft syndrome; DSA, Donor-Specific Antibodies; ECMO, extra-corporeal membrane oxygenation; CAD, coronary artery disease; CKD, Chronic Kidney Disease, CLD, and Chronic Liver Disease; MFI, mean fluorescence intensity; CPRA, calculated panel reactive antibody.

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https://doi.org/10.1016/j.humimm.2022.07.007
Received 20 March 2022; Revised 8 July 2022; Accepted 18 July 2022
Available online 15 August 2022

purpose of our study was to assess the association between SARS-CoV-2 infection and pre-existing or de novo HLA DSA in LTR.

Methods.

1.1. Study subjects and source of samples

The study was approved by the Institutional Review Board at Mayo Clinic, Florida and all **study** participants provided informed written consent. All LTR, who were diagnosed with COVID-19 at our institution between February 2020 and August 2021, were tested for the presence of HLA class I and II DSA pre-COVID-19 and at 1, 3, 6 months post-COVID-19 diagnosis. Inclusion criteria included all primary and re-transplant LTR that were > 18 years old, irrespective of gender and race. Recipients undergoing multi-organ transplantation were excluded from the study. Demographic and clinical information of study subjects reviewed for this study included age, gender, race, ethnicity, comorbidities, date of transplant and type of lung transplant. Clinical parameters including lung function test, pathology post-transplant, immunosuppression therapy, HLA lab test results (HLA genotyping, HLA antibodies, and crossmatch results), and date of death whenever applicable was obtained from the medical records. In addition, the following variables were also reviewed: immunosuppression modulation at time of COVID-19 diagnosis, time (in years) from date of transplant to COVID-19 diagnosis, severity of COVID-19 disease; out-patient versus in-patient status, requirement for intensive care, mechanical ventilation, and extra-corporeal membrane oxygenation (ECMO).

1.2. HLA genotyping

DNA samples were extracted from peripheral blood mononuclear cell or lymph node cell samples by the salting method (Qiagen, Valencia, CA) according to the manufacturer's instructions [11]. HLA genotyping was performed as a clinical laboratory test by reverse polymerase chain reaction sequence specific oligonucleotide probe (One Lambda, Canoga Park, USA).

1.3. HLA antibody detection

Recipient serum samples were treated with EDTA to avoid the prozone effect and tested for IgG antibodies against HLA class I and II as a clinical laboratory test using the LABScreen single antigen beads (One Lambda-ThermoFisher, Inc.) per manufacturer protocol. Briefly, microbeads are coated with 100 purified HLA class I or II antigens and pre-optimized reagents to detect HLA antibodies in human sera. A negative control serum is used to establish the background value for each bead in a test batch. Test serum is incubated with LABScreen beads. Any HLA antibodies present in the test serum bind to the antigens on the beads and then are labeled with R-Phycoerythrin (PE)-conjugated goat anti-human IgG. The LABScan flow analyzer simultaneously detects the fluorescent emission of PE and a dye signature from each bead. The presence of DSA against HLA-A, -B, -C, -DRβ, -DQα/β, and -DPβ antigens is determined. DSA were defined as having a Mean Fluorescence Intensity of > 1000. A persistent HLA DSA were defined as having two or more positive antibody tests for the same HLA antigen at least 1 month apart.

1.4. COVID-19 diagnosis

Diagnosis of COVID-19 was defined by positive SARS-CoV-2 RNA by quantitative PCR assay from nasopharyngeal swab or bronchoalveolar lavage.

1.5. COVID-19 disease severity

COVID-19 disease severity was divided into 3 groups; mild, moderate, and severe. Mild disease was defined patients with diagnosis of COVID-19 who were stable enough to be treated as out-patient as listed below. Moderate disease was defined as patients who required admission to the hospital and were on < 10 L of oxygen at rest. Severe disease was identified as patients who required hospitalization and were on > 10 L of oxygen with or without ECMO.

1.6. COVID-19 treatment and immunosuppression immunomodulation protocol for lung transplant patients

The lung transplant recipients at our institution were asked to hold their cell cycle inhibitors for 20 days after diagnosis of COVID-19 as part of a standardized protocol. Patients who had mild disease were also treated with monoclonal antibodies and their prednisone was increased to 20 mg once a day as out-patient. The patients who had moderate disease were treated with dexamethasone 6 mg once a day for 10 days along with remdesivir for 5 days. Patients with higher inflammatory markers and had evidence of Adult Respiratory Distress Syndrome (ARDS) on their imaging were treated with dexamethasone 20 mg for 5 days followed by 10 mg for 5 days instead. Patients with severe disease and evidence of ARDS on their imaging were treated with dexamethasone 20 mg for 5 days followed by 10 mg for 5 days in addition to Remdesivir for 5 days and at times tocilizumab.

Table 1
Demographics and clinical characteristics of study participants.

	Total (N = 24)
Age at transplant (years) [a]	55.5 (22 – 70)
Gender (M/F ratio)	1.66: 1
Ethnicity	
(A) Caucasian	19
(B) African-American	5
Laterality [b]	
Single	4 (16.7 %)
Bilateral	20 (83.3 %)
Co-morbidities [c]	
(A) CAD	23 (95.8 %)
(B) CKD	18 (75 %)
(C) CLD	2 (8.3 %)
BMI [d]	24 (18 – 41)
Months post transplant till COVID-19 diagnosis [e]	56 (< 1–204)
Severity of COVID-19 infection [f]	
(1) Out-patient	17 (70.8 %)
(2) Hospitalized	6 (25 %)
(3) ECMO	1 (4.1 %)
HLA matches [g]	3 (1.76)
CPRA [h]	9.9 (25.1)

[a] Age. Median values and range in between **parenthesis**.

[b] Number of recipients received single or double lung transplant and percent in between **parenthesis**.

[c] Co-morbidities. Number and percent of lung transplant recipients with (A) coronary artery disease (CAD) (B) Chronic Kidney Disease (CKD) (C) Chronic Liver Disease (CLD).

[d] Body Mass Index. Median values and range in between **parenthesis** at the time of transplant.

[e] Median values and range in between **parenthesis**.

[f] Severity of COVID-19 infection. Number and percent of lung transplant recipients that where (1) treated as out-patients (2) Hospitalized (3) Hospitalized and on ECMO.

[g] Mean values and standard deviation of the number of HLA-A, B, C, DRβ1, DQβ1, and DPβ matches between lung transplant recipients and donors.

[h] Mean values and standard deviation in between **parenthesis** at the time of transplant.

Table 2
Association Between SARS-CoV-2 Infection and HLA class I and II antibodies.

Patient ID	CPRA [a]			HLA antibodies [b]		
	Pre-Covid	1 month post	6 months post	Pre-Covid	1 month post	6 months post
1	0	0	0	DP5 (1239)DP1 (2737)	DP1 (1353)	DP1 (1835)
2	53	53	53	B44 (1126)B45 (1365)B76 (1291)DQ2 (1349)	B44 (1522)B45 (2108)B76 (1262)DQ2 (1014)	B44 (1793)B45 (1683)B76 (1232)DQ2 (1014)
3	62	62	62	DR52 (2769)	DR52 (3403)	DR52 (3213)
4	93	81	86	A2 (13101)A68 (12183) A69 (11815)DR14 (1138)DR52 (1338)DQ7 (2571)DQ8 (2787)DQ9 (1745)DP13 (1361)DP10 (1039)	A2 (3464)A68 (2679)A69 (2693) DQ7 (1494)DQ8 (2080)DQ9 (1160)DP13 (1025)DP10 (1808)	B77 (7664)B51 (6276)B49 (4054)B63 (2116)B38 (1689) DR14 (1581)DR52 (1712)DQ7 (2761)DQ8 (3224)DQ9 (2039)DP13 (1588)DP10 (1318)
6	76	76	76	A66 (2324)A68 (1150)A69 (1634)A34 (1908)A80 (1862)DR51 (1593) DP9 (1475)DP17 (1163)DP19 (1102)	A66 (2358)A68 (1045)A69 (1846)A80 (1775)DR51 (1442)DP9 (1105) DP17 (1003)	A66 (1061)A68 (1001)A80 (1750)DR51 (1225)DP9 (1117)DP17 (1314)DP20 (1400)
7	84	84	84	DQ2 (4579)DQ4 (1518)DQ7 (3780)DQ8 (7475)DQ9 (5735)	DQ2 (6110)DQ4 (4804)DQ7 (3826)DQ8 (6836)DQ9 (8811)	DQ2 (6989)DQ4 (8028)DQ7 (3802)DQ8 (9076)DQ9 (12410)
13	17	17	0	B75 (2379)B8 (1102)DQ2 (2245)DQ7 (1108)DP5 (1305)DP1 (2059)	B75 (2271)B8 (1069)DP5 (1878)DP1 (2696)	B75 (3589)DP5 (1462)DP1 (1637)
15	48	53	53	B37 (3510)DR7 (1355)DR51 (1419)	B37 (1682)DR7 (3425)DR14 (1326)DR51 (1288)DP5 (2247)	B37 (1615)DR7 (3200)DR14 (1343)DR51 (1018)DP5 (2236)
17	37	37	37	DQ6 (2965)	DQ6 (1511)	DQ6 (1095)
22	26	26	26	DR15 (1068)	DR15 (1534)	B78 (1867)DR15 (1436)
23	81	74	81	A80 (6477)A26 (6014)A43 (5965)A29 (2946)A1 (2818)A33 (2226)A25 (1788)A30 (1563)A66 (1388)A36 (1271)B67 (8414)B39 (2174)B61 (1267)B42 (1163) *C*2 (2458)DR9 (1011)DQ7 (1524) DQ2 (1515)DP11 (1118)	A33 (7275)A26 (2083)A43 (2068)A80 (1705)A68 (1167)B67 (5812)DQ2 (3632)DQ7 (3268)	A33 (11027)A26 (3674)A43 (3954)A80 (3435)A68 (2614)A34 (2394)A29 (2307)A1 (1614)A66 (1270)A30 (1235)A31 (1226)B67 (5812)B39 (1164)DQ2 (5774)DQ7 (5813)
Median	53	53	53	1689.5	1878	1835
p value		0.98			0.63	

[a] CPRA for HLA class I and II with MFI > 1000 in LTR pre-covid, 1 month, and 6 months post-covid diagnosis.
[b] Specificity and mean fluorescence intensity (MFI) in between parenthesis of HLA class I and II antibodies with MFI > 1000 in LTR pre-covid, 1 month, and 6 months post-covid diagnosis.

1.7. Statistical analysis

Continuous variables were summarized as mean (SD) and median (range), while categorical variables were reported as frequency (percentage). Groups were compared in LTR pre- and post-COVID-19 diagnosis using the Kruskal-Wallis or Mann-Whitney U tests. Analysis was performed with PRISM software version 9.4.0 (Graph-Pad). Statistical significance was defined as $p < 0.05$.

2. Results

2.1. Patient demographics and clinical characteristics

Twenty-four consecutive LTR who were diagnosed with SARS-CoV-2 infection at Mayo Clinic in Florida between February 2020 and August 2021 were included in the study. None of the study participants had received a SARS-CoV-2 vaccine prior to infection. Baseline demographic and clinical characteristics of the study participants are summarized in Table 1. All LTR had a negative cytotoxicity, and flow cytometry crossmatches on the day of transplant. All patients in the study were treated post-transplant with a standard immunosuppressive regimen incorporating systemic corticosteroids, calcineurin inhibitor, and an antimetabolite. The median age (in years) at transplant and number of months post-transplant till COVID-19 diagnosis was 55.5 and 56 respectively. The majority of LTR received bilateral lung transplants (83.3 %). All study participants were diagnosed with various co-morbidities including coronary artery disease (CAD), Chronic Kidney Disease (CKD), and Chronic Liver Disease (CLD) prior to COVID-19 diagnosis. The majority of LTR 17/24 (70.8 %) demonstrated mild symptoms of SARS-CoV-2 infection and received outpatient treatment. Only 6/24 (25 %) of LTR in our cohort had moderate disease requiring hospitalization and 1/24 (4.2 %) with severe disease requiring ECMO.

2.2. Association between SARS-CoV-2 infection and HLA DSA

No significant differences were observed in the CPRA or MFI levels of HLA class I and II antibodies pre- COVID-19 compared to 1 and 6 months post-COVID-19 diagnosis in 11/24 (45.8 %) LTR ($p = 0–98$ and $p = 0.63$ respectively) (Table 2). HLA class I and II DSA were detected in 5/24 LTR pre-COVID-19 diagnosis and persisted with no significant differences in the median MFI levels at 1 and 6 months post-COVID-19 diagnosis ($p = 0.89$) (Table 3). De-novo HLA class I and II DSA were detected in 1/24 (4.2 %) LTR at one month post-COVID-19 diagnosis and persisted with no significant differences in the median MFI levels at 6 months post-COVID-19 diagnosis ($p = 0.54$) (Table 4). Differences in the CPRA, MFI levels of HLA class I and II antibodies, and DSA pre- COVID-19 compared to 3 months post-COVID-19 diagnosis were not statistically significant (data not shown).

Table 3
Association between SARS-CoV-2 infection and persistent HLA DSA.

Patient ID	Persistent HLA DSA [a]		
	Pre-Covid	1 month post	6 months post
1	DP1 (2737)	DP1 (1353)	DP1(1835)
2	DQ2 (1349)	DQ2 (1014)	DQ2 (1010)
4	DP10 (1039)	DP10 (1808)	DP10 (1318)
6	DR51 (1593)	DR51 (1442)	DR51 (1225)
7	DQ7 (1962)	DQ7 (2992)	DQ7 (4197)
Median	1593	1442	1318
p value	0.89		

[a] Specificity and mean fluorescence intensity (MFI) in between parenthesis of HLA DSA with MFI > 1000 in LTR pre-covid, 1 month, and 6 months post-covid diagnosis.

3. Discussion

SARS-CoV-2 infection has led to a high mortality in LTR. A multicenter study showed that 39 % of LTR admitted for COVID-19 pneumonia died from the infection with higher severity of the disease at presentation being a predictor of subsequent mortality [12]. Similar mortality rates of 39 % were seen in another study of 1046 LTR in Germany [13]. Kamp et al. also found a significant decline in exercise capacity and decline in total lung capacity and diffusion capacity in the survivors after 3 months [13]. Transplant community has been concerned that SARS-CoV-2 infection itself and immunosuppression strategies used to mitigate disease severity in these LTR may lead to AMR. These concerns arise from the association between RVI and allograft rejection in LTR [14–19]. A recent case control study demonstrated that LTR with COVID-19 were at risk to develop secondary infections but did not observe post COVID-19 cellular rejection or AMR [20].

The majority of LTR in our study had mild COVID-19 disease that may have contributed to the lack of significant increase in de-novo HLA DSA production and MFI levels of pre-existing HLA DSA in LTR within 6 months post-COVID-19 diagnosis. In addition, all LTR in our study that were admitted to the hospital with SARS-CoV-2 infection received an individualized treatment plan resulting in improved outcomes. Gandolfini et al. investigated the production of HLA DSA post-SARS-CoV-2 infection in a kidney transplant recipient cohort and found similar results [21]. None of the kidney transplant recipients developed de novo HLA antibodies, but all of them had detectable anti-SARS-CoV-2 IgM and IgG. One patient had HLA DSA before COVID-19 diagnosis but neither the MFI nor their HLA specificities increased after COVID-19 diagnosis. Similarly, Masset et al recently reported the incidence of HLA DSA post-SARS-CoV-2 infection was low despite a significant decrease in immunosuppression [22]. No de novo HLA antibodies or an increase in preexisting HLA antibodies was observed post-SARS-CoV-2 infection in a cohort of patients on the kidney transplant waiting list [23]. The long-term effect of COVID-19 pandemic on allograft function and AMR in LTR remain yet to be determined in large prospective studies.

Only one out of twenty-four LTR in our study developed de novo HLA DSA within the first 6 months post-COVID diagnosis. She is an African American female who received a bilateral lung transplant. The patient was diagnosed with interstitial lung disease and had a high CPRA but no HLA DSA at the time of transplant. Her case was unique as COVID-19 diagnosis was made on a routine first bronchoscopy post-transplant and developed severe COVID-19 disease requiring ECMO. She was successfully extubated but developed worsening hypoxic respiratory failure lasting 10 days post-transplant. She was treated with remdesivir for 10 days and convalescent plasma with improvement of symptoms. During her course she also developed right hemothorax requiring video assisted thoracoscopy and evacuation of hematoma. Her post-operative course was complicated by acute hypoxic respiratory failure a week after transplant requiring high flow nasal cannula. The patient developed de novo HLA class I and II DSA within one-month post-transplant with high MFI that persisted in subsequent testing within the first 6 months post-COVID-19 diagnosis. The patient was treated for AMR and developed BOS 6 months after transplantation and COVID-19 diagnosis. The patient demonstrated severe SARS-CoV-2 infection that may have contributed to HLA antibody production and chronic allograft dysfunction.

4. Limitations

The single-center nature of this study poses obvious limitations. We also recognize that any observed associations are not definitive and do not establish cause and effect. In-vitro immunologic data often do not adequately address and mirror the complexity of in-vivo immune pro-

Table 4
Association between SARS-CoV-2 infection and de novo HLA DSA.

Patient ID	HLA antibodies [a]			*p* value
	Pre-Covid	1 month post	6 months post	
24	A2 (1408)A32 (1381)B57 (5395)B58 (3332)DR4 (1322)	A2 (1256) **A3 (3189)** [b]A23 (15265)A24 (13248)A25 (14685)A32 (14400)B58 (14437)B63 (15358)B77 (14785)B44 (14540)B37 (14385)B53 (14339) B59 (14203)B38 (13871)B27 (13052)B13 (12891)B52 (12806)B45 (12761)B49 (12757)B47 (12479)B57 (12366)B76 (10687)B82 (6246)DR4 (19145) **DR15 (13776)**DR16 (10968)DR14 (2723) **DR51 (5678)** **DQ4 (1520)** **DQ6 (7431)**DQ7 (8601)DQ8 (13570)DQ9 (11686)	**A3 (1247)** [b]A32 (11103)A23 (8805)A24 (6596)A25 (8810)B57 (11027)B58 (9543)B49 (10594)B51 (9657)B63 (8929)B38 (8432)B59 (7712) B77 (7635)B53 (7333)B27 (6835)B52 (5787)B44 (5640)B37 (5203)B13 (4893)B47 (4479)B45 (1576)DR4 (8888)DR14 (3921) **DR15 (9365)**DR16 (3044) **DR51 (2397)** **DQ4 (1799)** **DQ6 (5724)**DQ7 (2359)DQ8 (4126)DQ9 (3381)	
Median	1408	12,981	6595	< 0.0001
Median of de novo DSA		5678	2397	0.54
CPRA	69 %	99 %	99 %	

[a] Specificity and mean fluorescence intensity (MFI) in between parenthesis of HLA class I and II antibodies with MFI > 1000 in LTR pre-covid, 1 month, and 6 months post-covid diagnosis.
[b] Underlined and in bold is the specificity and mean fluorescence intensity (MFI) in between parenthesis of de novo HLA DSA.

cesses. However, this study provides novel insights on the impact of SARS-CoV-2 infection on de-novo DSA production in LTR. Kinetic analysis of HLA DSA to determine the peak production post-SARS-CoV-2 infection is unclear. Persistent DSA were defined as having a MFI > 1000 on two or more antibody tests for the same HLA antigen at least 1 month apart. The presence of DSA at very low levels below the lower limit of detection of the HLA antibody test is a limitation of the study. However, Persistent DSA were not detected at higher MFI levels post-transplant. We assessed HLA class I and II DSA at various times post- SARS-CoV-2 infection. The lack of kinetic analysis to determine the peak of HLA DSA production in this study may not have allowed for optimum HLA DSA detection affecting our results. Furthermore, the lack of sample size power calculation may not have permitted a significant correlation between SARS-CoV-2 infection and de novo HLA DSA production. The cross-sectional design does not permit definitive analysis of the predictive value of SARS-CoV-2 infection on de novo DSA production. Nevertheless, our results support the design of subsequent longitudinal studies to directly examine the association between SARS-CoV-2 infection and de-novo DSA production in LTR.

5. Conclusion

In conclusion, our study examines the association between SARS-CoV-2 infection and pre-existing or de novo HLA in LTR. SARS-CoV-2 infection was not associated with a significant increase in de novo HLA DSA production or MFI levels of pre-existing HLA DSA compared to pre-COVID-19 diagnosis in LTR. These results provide a valuable insight on the effects of SARS-CoV-2 infection on immunogenicity in LTR. Our results create the foundation for future prospective studies to confirm our findings and explore the long-term effect of SARS-CoV-2 infection on allograft function in LTR.

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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