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HLA Sensitization in Patients Bridged to Lung Transplantation With Extracorporeal Membrane Oxygenation

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Background. Lung transplantation is a definitive therapy for many end-stage lung pathologies. Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a bridge to lung transplantation (BTT). HLA sensitization is a major barrier to lung transplantation. The development of HLA sensitization while undergoing ECMO support as a BTT has recently been reported in a 2-patient series. **Methods.** We performed a retrospective analysis of patients undergoing ECMO as a BTT at a single large academic medical center from January 2016 to April 2022. The study was approved by the institutional review board. We selected patients who had undergone ECMO support for at least 7 d with either negative HLA before cannulation or initial negative HLA on ECMO (3 patients). **Results.** We identified 27 patients bridged to lung transplantation with available HLA data. Of this group, 8 patients (29.6%) developed significant HLA sensitization (>10%). We did not identify any factors predisposing to sensitization, including infection episodes or blood product transfusion. Sensitized patients demonstrated a trend toward an increased primary graft dysfunction rate, a need for posttransplant ECMO support, and a decreased 1-y survival; however, these did not meet statistical significance. **Conclusions.** Our study is the largest series today describing the association between HLA sensitization and ECMO therapy. We suggest that interaction between the immune system and ECMO circuit contributes to allosensitization pretransplant, similar to that occurring with ventricular assist device. Further work is needed to better characterize the incidence of HLA sensitization in a multicenter cohort and to identify potentially modifiable factors associated with HLA sensitization.

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Since the first successful operation in 1983 (Cooper, Toronto), lung transplantation has become the standard of care for selected patients with end-stage lung diseases of various casues. About 2000 lung transplants are performed annually in the United States, with an increasing number of patients bridging with extracorporeal membrane oxygenation (ECMO) support. Initial experience with ECMO was discouraging because of high mortality and complications; however, more recent improvements in technology, especially the development of polymethylpentene oxygenators, and use of portable and durable circuits allowed for results that were comparable with that of patients transplanted without ECMO support.[1]

One of the main barriers to finding a suitable donor is HLA sensitization. Sensitized patients have a longer waiting time, increased risk of dying on the waitlist, or developing antibody-mediated rejection (AMR) after transplant. Prior exposure to non–self-antigens during pregnancies, blood transfusions, and organ transplantation are well-known sensitizing factors. The effect of ventricular assist device (VAD)–associated sensitization has been recently described.[2-4] Our center's experience suggests that ECMO therapy may have a similar allosensitizing effect as VAD. To date, there have been only 2 cases of HLA sensitization in lung transplant candidates supported by ECMO in the literature. This study aimed to assess new HLA antibody development in patients bridged to lung transplantation with ECMO and determine whether ECMO-associated sensitization affects posttransplant outcomes.

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MATERIALS AND METHODS

We conducted a single-center retrospective analysis of all patients undergoing ECMO support (including venovenous [VV] and venoarterial [VA]) as a bridge to lung transplantation from January 2016 to April 2022. The study was approved by the institutional review board (approval # 300009022) and complied with guidelines established by the Health Insurance Portability and Accountability Act. We selected patients who had undergone ECMO support for at least 7 d and had an anti-HLA antibody test performed before ECMO cannulation and at least 1 subsequent test after cannulation. We included 3 patients who had their first anti-HLA test after ECMO cannulation because both class I and II antibodies were negative, and we presumed that these patients had not been sensitized before cannulation. Multiorgan transplant recipients (7 heart-lung and 1 lung-kidney) were also included in the study. The final cohort consisted of 27 patients. None of the patients underwent desensitization therapy.

The following patient demographics and medical data were collected: pulmonary diagnosis, cytomegalovirus (CMV) status, panel reactive antibody (PRA) (%) before and following ECMO cannulation, number of blood products received (including packed red blood cells [PRBCs], fresh frozen plasma, pooled platelets, and cryoprecipitate), infection events (suspected and confirmed infections), and outcome data (hospital/intensive care unit length of stay, mortality before transplant, mortality within 1 y of transplant, CMV viremia posttransplant, and need for mechanical ventilation or ECMO support >24 h posttransplant).

Our center has been using a universal leukoreduction protocol for all blood product transfusions. Infection events were defined as confirmed in the presence of positive blood cultures or tissue culture with a systemic inflammatory response or suspected if culture results were negative. Acute cellular rejection (ACR) was diagnosed by biopsy if lymphocyte-predominant inflammatory response was detected around blood vessels and/or airways and graded per International Society for Heart and Lung Transplantation recommendations.[2] AMR was diagnosed according to the International Society for Heart and Lung Transplantation consensus recommendations.[3]

HLA Antibody Testing and Analysis

HLA antibody testing for class I and class II anti-HLA antibodies was measured by Luminex single-antigen bead assay and reported in mean fluorescent intensity (MFI). An MFI threshold <1500 was considered negative. The United Network of Organ Sharing calculator was used to measure PRA values from the Luminex single-antigen bead results (http://optn.transplant.hrsa.gov). HLA sensitization was defined as either class I PRA or class II PRA >10%. Following ECMO cannulation, PRA was considered increased if it was elevated by ≥10% or if a new antibody was identified. Timing of PRA measurement after ECMO cannulation was at the discretion of the treating physicians.

Statistical Analysis

Categorical variables are expressed as the corresponding number (n) and percentage. Continuous variables are expressed as median with interquartile range. The Fisher exact test was used to compare categorical variables between sensitized and nonsensitized patients. The Mann-Whitney *U* test was used to compare continuous variables. A *P* value of <0.05 was considered statistically significant.

RESULTS

Between January 1, 2016, and April 30, 2022, 27 patients (15 men and 12 women) supported by ECMO as a bridge to lung transplantation for at least 7 d and with HLA tests available were analyzed. Twenty-four patients were evaluated or listed for transplant before ECMO cannulation, and 3 patients had expedited lung transplant evaluation after ECMO cannulation. Indications for VV ECMO therapy were refractory hypercapnic or hypoxemic respiratory failure despite noninvasive ventilation or high-flow oxygenation affecting patients' ability to participate in physical therapy and maintain adequate nutrition. Eleven patients were bridged with VA ECMO, the majority (7/11) awaiting heart-lung transplantation. Indications for VA ECMO support were hemodynamic instability secondary to severe right ventricular (8 patients) or left ventricular failure (3 patients). All patients were awake and ambulating. All patients underwent tracheostomy and required mechanical ventilation at least during night time. Patients remained on ECMO support as long as they were eligible for transplant. If a patient developed severe ECMO-related complications or other end-organ failures, did not meet nutritional requirements, and became incapable of participating in daily physical therapy, then their transplant eligibility was reevaluated. In our study group, 1 patient died before transplant from ECMO-related complications, 1 died following stroke, and 7 patients became noneligible for transplant and had care withdrawn. Demographic data are presented in **Table 1**.

Table 2 demonstrates relevant clinical variables during the use of ECMO as a bridge to lung transplantation, including PRA values, blood products transfused, infection episodes, and survival. In this cohort, 59.3% were supported with VV

TABLE 1.

Patient demographics (N = 27)

Variable	Median (IQR, 25%–75%)
Age, y	44 (29.5–57.5)
Female	12 (44.4%)
Diagnosis: IPF	5 (18.5%)
COPD	1 (3.7%)
Cystic fibrosis	5 (18.5%)
Pulmonary hypertension	3 (11.1%)
CTD-ILD	8 (29.6%)
Other diagnosis	5 (18.5%)
BMI	23.0 (21.6–28.9)
CMV IgG positive	16 (59.3%)
DM	6 (22.2%)
GERD	10 (37.0%)
Blood group O	11 (40.7%)
Blood group A	9 (33.3%)
Blood group B	4 (14.8%)
Blood group AB	2 (7.4%)

Other diagnosis: ARDS/DAD, non-CF bronchiectasis, NSIP, inhalational injury.
ARDS, acute respiratory distress syndrome; CF, cystic fibrosis; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; DAD, diffuse alveolar damage; DM, diabetes; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; IgG, immunoglobulin G; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; NSIP, non-specific interstitial pneumonitis.

TABLE 2.

Clinical variables during ECMO as bridge to lung transplantation (N = 27)

Variables	Median (IQR, 25%–75%)
ECMO strategy VV/VA	16/11 (59.3%/40.7%)
ECMO duration, d	50 (26.5–81.5)
PRA class I pre ECMO, n (%)	0 (0%)
PRA class II pre ECMO, n (%); mean PRA	3 (11.1%); 33.3
PRA class I during ECMO, n (%); mean PRA	7 (25.9%); 65.6
PRA class II during ECMO, n (%); mean PRA	4 (14.8%); 59.8
Time to increased PRA, d	25 (20.5–39.3)
PRBC transfusion	7 (4–23.5)
PLT transfusion	0 (0–3)
Plasma transfusion	0 (0–2.5)
Cryoprecipitate transfusion	1 (0–3)
Suspicion for infection	24 (88.9%)
Confirmed infection	14 (51.9%)
Survival to transplant	18 (66.7%)

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; PLT, platelet; PRA, panel-reactive antibody; PRBC, packed red blood cell; VV/VA, venovenous/venoarterial.

ECMO, and the median ECMO treatment duration was 50 d (range, 26.5–81.5 d). Before ECMO cannulation, none of the patients were sensitized to class I HLA. Three patients (11.1%) were sensitized to class II HLA, with a median PRA of 33.3%.

Following ECMO cannulation, 8 patients (29.6%) developed new HLA sensitization. New class I PRA was detected in 7 of 8 patients (87.5%), with a median PRA of 65.6%. New sensitization to class II PRA was detected in 4 of 8 patients (50%), with a median PRA of 59.8%. The median time to HLA sensitization was 25 d (range, 20.5–39.25 d). **Figure 1** demonstrates freedom from sensitization after ECMO cannulation. It is unclear whether the appearance of new PRA reflects new sensitization against foreign antigens originating from blood products or general enhancement of antibody production caused by systemic inflammation. Total immunoglobulin G (IgG) and IgG subclasses levels were measured for all patients and were within normal range, not significantly different between sensitized and nonsensitized patients. We did not assess the presence of non-HLA antibodies. The most frequently transfused blood product was PRBCs (median 7 units PRBC per patient). Other blood products such as platelets and cryoprecipitate were rarely transfused. During ECMO therapy, 14 patients (51.9%) had episodes of confirmed infection, whereas 88.9%of patients received antibiotics for suspected infection. Of 27 patients, 18 (66.7%) survived to transplant

To assess potential risk factors for the development of sensitization during ECMO therapy, we compared 8 sensitized patients with 19 patients who did not develop sensitization during ECMO therapy with respect to diagnosis, ECMO strategy, age, gender, duration of ECMO support, number of blood products transfused, and episodes of infection (**Table 3**). We did not identify any statistically significant risk factors predicting HLA sensitization while on ECMO therapy. Patients with underlying connective tissue disease and pulmonary hypertension tended to develop HLA sensitization more frequently. We noted a higher percentage of preformed HLA

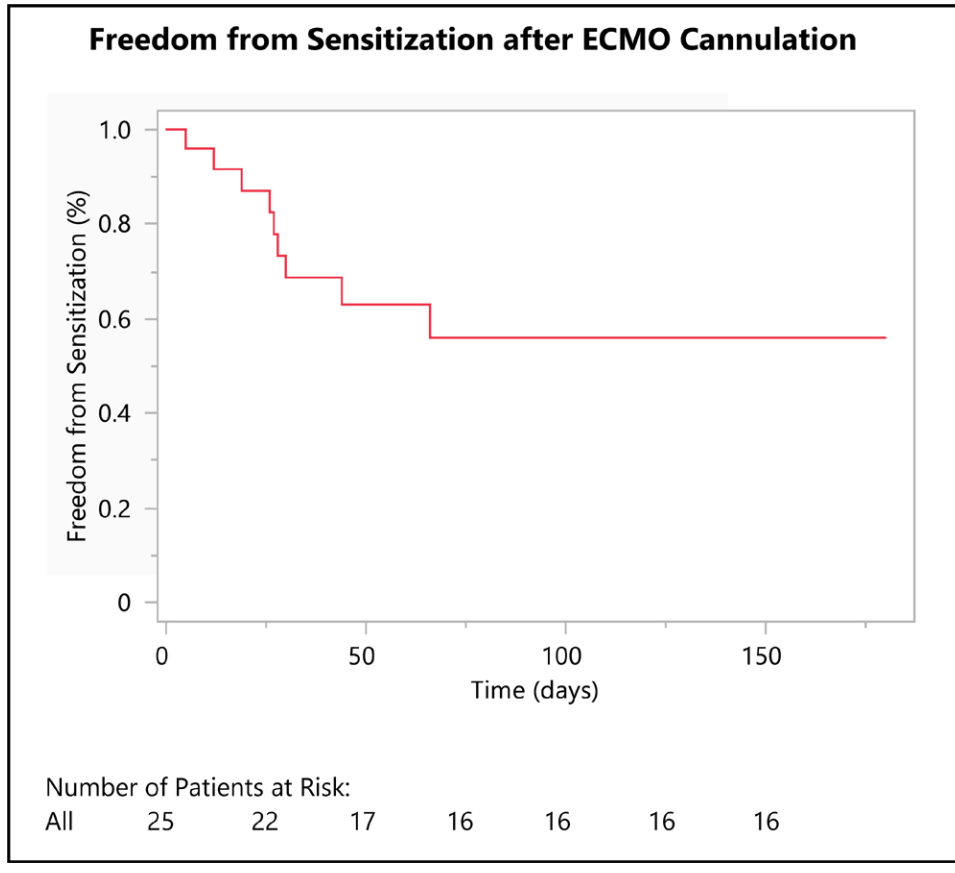

FIGURE 1. Freedom from sensitization after ECMO cannulation. ECMO, extracorporeal membrane oxygenation.

TABLE 3.

Factors associated with development of HLA sensitization during ECMO

Variable	HLA sensitized (N = 8)	Non-HLA sensitized (N = 19)	*P*
Age, y, median (IQR)	42.5 (32.8–54.5)	44 (26.5–59)	0.90
Female	4 (50%)	8 (42.1%)	1
Diagnosis IPF	1 (12.5%)	4 (21.1%)	1
COPD	0 (0%)	1 (5.3%)	1
Cystic fibrosis	1 (12.5%)	4 (21.1%)	1
Pulmonary hypertension	2 (25%)	1 (5.3%)	0.20
CTD-ILD	3 (37.5%)	4 (21.1%)	0.63
Other diagnosis	1 (12.5%)	4 (21.1%)	1
BMI	26 (22.4–29.5)	22.9 (21.3–27.6)	0.41
CMV IgG positive	6 (75%)	10 (52.6%)	0.40
DM	1 (12.5%)	5 (26.3%)	0.63
GERD	4 (50%)	8 (42.1%)	1.0
ECMO strategy VV/VA	50%/50%	63.2%/36.8%	0.68
ECMO duration, d	81.5 (33–99.3)	41 (25.5–65.5)	0.19
PRA class I pre ECMO (%)	0 (0%)	0 (0%)	1.0
PRA class II pre ECMO, n (%); mean PRA	2 (25%); 29.5	1 (5.3%); 41	0.20
PRBC transfusion	16.5 (5–29.5)	9 (3–19)	0.79
PLT transfusion	0 (0–2.5)	1 (0–2.5)	0.69
Plasma transfusion	1.5 (0–3)	0 (0–2)	0.28
Cryoprecipitate transfusion	0 (0–4.25)	1 (0–2.5)	0.79
Infection confirmed	4 (50%)	10 (52.6%)	1.0
Infection suspicious	4 (50%)	16 (84.2%)	0.53
Survival to transplant	6 (75%)	12 (63.2%)	0.68

BMI, body mass index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CTD-ILD, connective tissue disease-associated interstitial lung disease; DM, diabetes; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; IgG, immunoglobulin G; IPF, idiopathic pulmonary fibrosis; IQR, interquartile range; PLT, platelet; PRA, panel-reactive antibody; PRBC, packed red blood cell; VV/VA, venovenous/venoarterial.

class II antibodies in the sensitized group. However, none of these comparisons met statistical significance.

Survival to transplant was similar for both groups (75% in the sensitized and 63.2% in the nonsensitized group). Of 9 patients who did not reach transplantation, 1 died following a stroke, and 1 died from ECMO-related complications (bleeding). The other 7 patients not transplanted became poor candidates while on ECMO, and care was eventually withdrawn.

None of the sensitized patients underwent desensitization therapy before transplant. Our practice is to perform a virtual crossmatch using recipient's several serum samples tested for anti-HLA antibodies, followed by the prospective Luminex flow cytometry crossmatch during the transplant. We found suitable HLA donors without crossing donor-specific antibodies (DSAs) in 7 sensitized patients. One patient was transplanted with positive flow cytometry crossmatch (T and B cells). She had preformed low level of DSAs to Bw4 and DR 12 and subsequently developed early AMR that was successfully treated with thymoglobulin, eculizumab, and IVIG. During the following 6 mo, she slowly cleared DSA to the undetectable level. Notably, none of the other sensitized patients who underwent transplantation developed DSA during the first-y follow-up posttransplant. Our center routinely uses induction protocol, including intravenous solumedrol 500 mg and basiliximab (d 0 and d 4), followed by triple immunosuppression (tacrolimus, mycophenolate mofetil, and prednisone). We monitor DSA level biweekly for the first 3 mo followed by monthly until the end of the y, then once per y or as needed.

TABLE 4.

Outcomes in patients surviving to transplant

Variable	HLA sensitized (N = 6)	Non-HLA sensitized (N = 12)	*P*
PGD grade 3	3 (50%)	3 (25%)	0.34
Need for ECMO posttransplant	2 (33.3%)	1 (8.3%)	0.25
Mechanical ventilation >24 h posttransplant	6 (100%)	11 (91.7%)	1
ACR grade A1	1 (16.7%)	6 (50%)	0.32
AMR	1 (16.7%)	0 (0%)	0.33
CMV viremia	3 (50%)	6 (50%)	1
Survival 1 y posttransplant[a]	2 (40%)	9 (90%)	0.08

[a]Not excluded 1 patient HLA sensitized and 2 patients not sensitized not currently 1 y posttransplant.

ACR, acute cellular rejection; AMR, antibody-mediated rejection; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; PGD, primary graft dysfunction.

Overall, 18 patients (6 in the sensitized group and 12 in the nonsensitized group) underwent lung transplantation. We compared sensitized and nonsensitized posttransplant patient outcomes with regard to primary graft dysfunction (PGD) grade 3 at 72 h, need for ECMO, CMV viremia, and 1-y survival (**Table 4**). Sensitized patients more often had a higher degree of PGD and required ECMO support posttransplant; however, these differences did not reach statistical significance. No patient had an A2 or higher degree of ACR. One patient in the sensitized group and 6 patients in nonsensitized group had A1 ACR. One patient in the sensitized group had AMR and was treated with thymoglobulin and eculizumab. Two of 5 sensitized patients survived to 1 y posttransplant (40%), compared with 9 of 12 patients in the nonsensitized group (75%). One recipient in the sensitized group and 2 in the nonsensitized group are alive but have not yet achieved 1-y survival.

DISCUSSION

Sensitization to HLAs is a widely recognized barrier to lung transplantation. Highly sensitized patients have a prolonged waiting time, decreased access to the donor pool, and increased waitlist mortality. Development of sensitization through alloimmunity has been identified in patients undergoing pregnancy, blood transfusions, and organ transplantation and, more recently, in patients undergoing extracorporeal support as a bridge to (namely heart) transplantation.

VAD has recently emerged as an important causal agent for the development of HLA antibodies. Several studies reported that 17% to 66% of patients undergoing VAD therapy developed anti-HLA antibodies, with variable effects on transplant outcomes, including rejection and graft loss.[4-6] Different methods of PRA assessment, definitions of sensitization, patient population, and use of immunomodulating therapies likely contribute to inconsistent conclusions in the literature. In the setting of VAD-associated sensitization, blood transfusion, especially platelets, and homograft exposure in prior surgery have been suggested as contributing factors.[7] However, several studies have not identified an association between blood product transfusion and allosensitization.[6-8]

The mechanism of VAD-induced sensitization has not been fully elucidated. VAD-induced alteration of immune function,

with aberrant activation of antigen-presenting cells and selective activation-induced T-cell death with resultant B-cell hyperreactivity, is proposed as possible mechanisms. These mechanisms are elicited by blood exposure to the textured VAD chamber surface, polyurethane diaphragm, and polytetrafluoroethylene components.[9-12] This possibility is consistent with data showing that the latest generation of axial flow pumps led to lower rates of sensitization than their older versions.[13] The neointima (area of tissue abutting VAD) contains abundant T cells, macrophages, and monocytes and reflects the constant interaction of blood with the device. Studies have shown that after VAD implantation, circulating CD4 and CD8 cells had elevated levels of CD95, a T-cell activation marker associated with apoptosis that reflects systemic activation.[14-16] Finally, patients with VAD support have been demonstrated to possess higher levels of circulating anti-HLA antibodies and antiphospholipid antibodies, consistent with systemic polyclonal B-cell activation.[17]

Whether VAD truly has immunologic properties that lead to the formation of de novo antibodies or is merely an instigator of inflammation that stimulates existing memory B cells, thereby creating reexpression of antibodies formed at a previous antigenic exposure, is unknown. A majority of the antibodies detected in the first 30 d persisted over time. Recent data suggest that HLA antibody production can also be associated with infections and vaccination. Infectious pathogens might induce alloreactivity directly via molecular mimicry (heterologous immunity) or alternatively by providing costimulatory factors for bystander activation of alloreactive leukocytes.[18] Despite widespread use and similarities between ECMO and VAD, there is no substantive data regarding the effect of ECMO on HLA sensitization.

Although our findings suggest an association between sensitization and ECMO exposure, we acknowledge that other events associated with sensitization, namely blood transfusion and infection, may have also contributed.[18] Infections have been associated with sensitization in candidates awaiting solid organ transplantation, presumably because of their proinflammatory effects on immunity; however, as demonstrated recently with coronavirus disease 2019, infections may generate a transient antibody response that does not necessarily result in a positive crossmatch with the corresponding antigens at the proper MFI.[19] Use of leuko-reduced blood for transfusion reduces but does not entirely eliminate the risk of HLA sensitization. Interestingly, avoidance of blood product transfusion may not prevent allosensitization in VAD recipients and, therefore, potentially ECMO patients.[20] Also, it is possible that the ECMO cannula alone, with biofilm deposits or bacteria trapped in the circuit or oxygenator, may contribute to HLA sensitization.[21-23]

We found only 1 published case report on ECMO-related HLA sensitization. Hayes et al[24] described 2 patients, aged 13 and 55 y, supported by VV ECMO while awaiting lung transplantation. Before ECMO cannulation, the 13-y-old patient was not sensitized, but the 55-y-old had preformed antibodies to HLA class I (54%). Both patients developed new sensitization to class II HLA within 2 to 3 wk of ECMO treatment. The authors suggested a possible relationship between antibody production and blood transfusions the patients received. As an explanation, the authors hypothesized that some leukocytes could escape the filtering process. Alternatively, the entrapment of antigen-presenting cells or lymphocytes in the fibrin sheath within the ECMO circuit could contribute to the allosensitization process.

Our study has several limitations. Unfortunately, with the small sample size, we were unable to distinguish potential predisposing factors to sensitization, such as the number of blood products transfused, time undergoing ECMO support, and number of infectious episodes, all of which have been postulated or identified as potential contributors to the development of sensitization. Despite these significant limitations, we believe that our work is of interest in that we present the largest to date cohort of patients developing sensitization while on ECMO and identifying this as a potential area for further research both to better characterize the true incidence of sensitization while on ECMO and to identify the importance of risk factors for sensitization such as those mentioned above. Future studies and possibly aggregated data from multiple centers will help to better elucidate risk factors for developing sensitization and its implications on transplant outcomes. Additionally, because of the retrospective nature of the study, serial PRA sampling was not available to assess the sustainability of antibodies and the duration of sensitization.

In conclusion, our study is the largest series to date describing the association between HLA sensitization and ECMO therapy. We observed that 29.6% of patients develop new or increased HLA antibodies within the first 30 d of ECMO support. We did not identify any factors predisposing to sensitization, including infection or blood product transfusion. Sensitized patients demonstrated a trend toward an increased PGD rate, a need for posttransplant ECMO support, and a decreased 1-y survival; however, these did not meet statistical significance. We suggest that interaction between the immune system and ECMO circuit contributes to allosensitization pretransplant, similar to that occurring with VAD.

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