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Effect of Calculated Panel Reactive Antibody Value on Waitlist Outcomes for Lung Transplant Candidates

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Background: We conducted a retrospective cohort study using United Network of Organ Sharing (UNOS) data to determine the effect of the calculated panel reactive antibody (cPRA) value on waitlist outcomes for lung transplant candidates.

Material/Methods: We divided lung transplant candidates into groups based on their cPRA value at the time of waitlist activation (0–25%, 25.1–50%, 50.1–75%, and 75.1–100%) and compared each group's waitlist outcomes to the lowest quartile ("minimally sensitized") group. The primary outcome was lung transplantation and the secondary outcome was waitlist mortality (a composite of death on the waitlist/delisting for clinical deterioration).

Results: Compared to the minimally sensitized group, candidates with a cPRA value of 25.1–50% did not have a significantly different likelihood of undergoing lung transplant or waitlist mortality, candidates with a cPRA value of 50.1–75% were 25% less likely to undergo lung transplant and 44% more likely to die on the waitlist, and candidates with a cPRA value of 75.1–100% were 52% less likely to undergo lung transplant and 92% more likely to die on the waitlist.

Conclusions: CPRA values of greater than 50% are associated with significantly lower rates of transplantation and higher waitlist mortality.

MeSH Keywords: Antibodies • Lung Transplantation • Waiting Lists

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Background

Lung transplantation in the setting of pre-formed donor-specific antibodies (DSA) is ideally avoided given the associated risk of hyperacute rejection and early antibody-mediated rejection [1]. Although the exact mechanisms of these complications are not fully elucidated, the binding of the antibody to allo-major histocompatibility complex (MHC) at least in part results in the activation of the complement cascade and other inflammatory cells that cause injury to the graft [2]. Identifying candidates' HLA antibodies prior to transplant allows transplant programs the opportunity to avoid donors to which there is a positive "virtual" cross-match (VCM) in an effort to reduce the risk of antibody-mediated complications [3]. However, not all HLA antibodies pose the same risk to the graft, and the characteristics that would differentiate high risk from low risk DSA are far from fully understood [4]. Currently, most transplant programs use solid-phase assays (SPA) to detect pre-transplant HLA antibodies, and rely on a combination of mean fluorescent intensities (MFI), complement-fixing abilities, and serial dilution studies to quantify their strength and stratify their risk, although each of these laboratory tests have limitations and debatable significance [3,5,6]. If an HLA antibody is determined to be high risk based on these results, the transplant program may deem its corresponding antigen to be "unacceptable." Donors with these unacceptable antigens are then avoided for the candidate during the United Network of Organ Sharing (UNOS) matching process. The percentage of donors that would be avoided on the basis of the unacceptable antigens that are recorded for a candidate can be estimated by the calculated panel reactive antibody (cPRA) value, based on HLA and ethnic frequencies in the donor population [7].

The obvious disadvantage of unacceptable antigens is that they effectively limit candidates' access to donor lungs and therefore their likelihood of receiving an offer. In 2017, Kransdorf et al. utilized UNOS data to quantify the extent to which a candidate's cPRA value negatively impacts the likelihood of receiving a heart transplant [8]. However, to date, only 1 single-center study has examined the negative effect of the cPRA value on lung transplant rates [9]. To this end, we conducted a retrospective cohort study using UNOS data to determine the impact of cPRA values on waitlist outcomes for lung transplant candidates across the United States.

Material and Methods

Subjects

A dataset of all candidates listed for lung transplant between May 4, 2005 (the advent of the lung allocation score (LAS)) and June 30, 2017 was obtained from UNOS. Candidates were included in the study if at the time of waitlist activation they were at least 18 years old. Candidates were excluded if they ultimately received a living donor transplant, were listed at more than 1 center, or did not have all pertinent data recorded. Candidates were censored on the date they were delisted if the reason for waitlist removal was recorded as: refused transplant, condition improved, unable to contact candidate, delisted in error, or "other."

Study design

In this retrospective cohort study, we first compared the waitlist outcomes for candidates who had unacceptable antigens recorded while on the waitlist to candidates who did not. The unacceptable antigens entered in the UNOS database reflect what was recorded at the candidate's listing center according to the center's definition of unacceptable antigen. How each center defined unacceptable antigen, including the HLA antibody detection techniques and MFI cut-offs that were used to inform which antigens were unacceptable, was not known. The primary outcome was lung transplantation. The secondary outcome was a composite of death on the waitlist or delisting for clinical deterioration.

We then compared the waitlist outcomes for candidates based on their cPRA value at the time of waitlist activation. Unacceptable antigens were considered to be entered at the time of waitlist activation if they were recorded at any time prior to or up to 1 week after the date of waitlist activation to allow for laboratory and administrative delays. For candidates with unacceptable antigens entered at the time of waitlist activation, the cPRA value of the unacceptable antigens was calculated using the online UNOS cPRA calculator. For subjects with unacceptable antigens entered more than once in the period prior to 1 week after waitlist activation, the cPRA value of the last recorded unacceptable antigens was recorded as the cPRA value at the time of waitlist activation. For candidates who did not have unacceptable antigens entered at the time of waitlist activation, the cPRA value at the time of waitlist activation was recorded as 0%. Candidates were divided into 4 groups based on their cPRA value at the time of waitlist activation (0–25%, 25.1–50%, 50.1–75%, and 75.1–100%). Candidates with a cPRA value of 0–25% were considered "minimally sensitized" based on prior evidence that a PRA value of 0–25% is considered low risk for rejection and mortality in transplant recipients [10]. The minimally sensitized candidates were used as the reference group to which candidates in each of the other groups were compared, with the primary outcome being lung transplantation and the secondary outcome being death on the waitlist/delisting for clinical deterioration.

This study was approved by the Columbia University Institutional Review Board.

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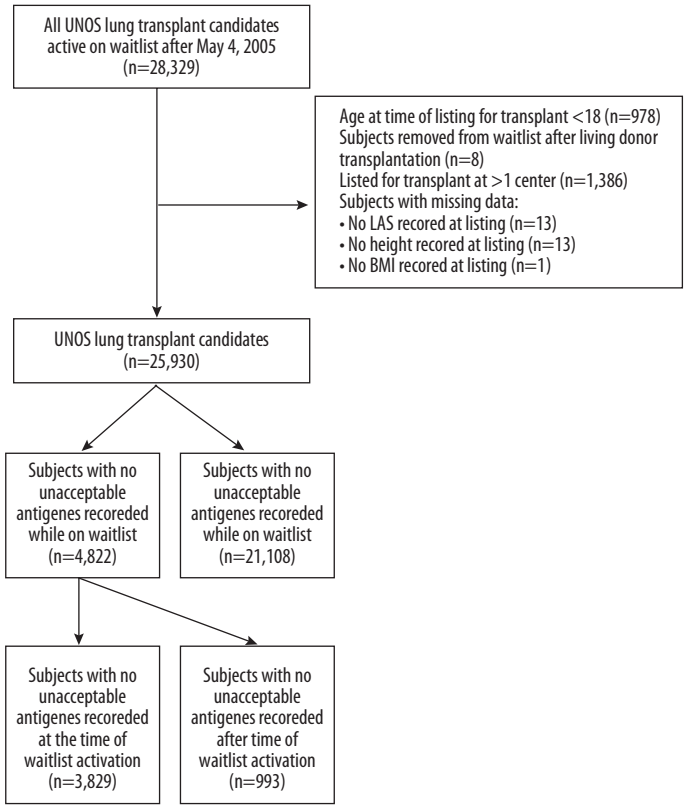

Figure 1. Candidate selection. A dataset of all lung transplant candidates listed between 2005 and 2017 was obtained from UNOS. Candidates were included in the study if at the time of waitlist activation they were at least 18 years old. Candidates were excluded if they ultimately received a living donor transplant, were listed at more than 1 center, or did not have all pertinent data recorded. UNOS – United Network of Organ Sharing; LAS – lung allocation score; BMI – body mass index.

Statistical analysis

Statistical analysis was performed using Stata/SE version 15.1. Continuous variables were compared with the *t* test and categorical variables were compared using the chi-square test. A competing risk regression model was used to examine associations between having unacceptable antigens on the waitlist and waitlist outcomes and the cPRA value at the time of waitlist activation and waitlist outcomes. Variables otherwise known to be associated with waitlist outcomes were included in the model: age, sex, ethnicity, height, weight, blood type, lung disease, LAS at the time of listing, and double lung transplant requirement. Given the extremely low number of candidates excluded for missing data (0.1%), a complete case analysis was performed.

Results

A total of 28 329 lung transplant candidates were active on the waitlist between May 4, 2005 and June 30, 2017. Of these, 25 957 candidates who were age 18 and older, did not undergo living donor transplant, and were listed at only 1 transplant center were included in our study. A small number of additional candidates were excluded for missing pertinent data (13 candidates did not have LAS recorded at time of listing, 13 candidates did not have height recorded at time of listing, and 1 candidate did not have BMI recorded at time of listing). Of the 25 930 included candidates, 4822 (18.6%) had unacceptable antigens recorded while on the waitlist. Of the 4822 candidates with unacceptable antigens recorded while on the waitlist, 3829 candidates had them recorded at the time of waitlist activation, while 993 candidates had them recorded more than 7 days after waitlist activation (Figure 1).

The characteristics of candidates who had unacceptable antigens recorded while on the waitlist were compared to candidates who never had unacceptable antigens recorded while on the waitlist (Table 1). Candidates with unacceptable antigens were more frequently female and African-American, and were more likely to have undergone prior lung transplant and to have required a cross-match at the time of transplant. Compared to candidates without unacceptable antigens, candidates with unacceptable antigens were transplanted less frequently (69.5% *vs.* 77.9%, p<0.001) and died on the waitlist/were delisted for clinical deterioration more frequently (17.5% *vs.* 13.7%, p<0.001). By study end, a higher proportion of candidates with unacceptable antigens were still waiting for transplant compared to candidates without unacceptable antigens (13.1% *vs.* 8.3%, p<0.001).

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Table 1. Characteristics and waitlist outcomes of subjects with no unacceptable antigens (UA) recorded while on waitlist and subjects with unacceptable antigens recorded while on waitlist.

	Subjects with no UA while on waitlist (n=21,108)	Subjects with UA while on waitlist (n=4,822)	p-Value
Median age	59 (49–64)	58 (48–64)	<0.001
Female gender (%)	39.9	58.8	<0.001
Ethnicity (%)			<0.001
Caucasian	81.9	78.4	
African-American	8.8	12.6	
Hispanic	6.8	6.2	
Other	2.6	2.8	
Blood group (%)			0.42
A	39.2	39.2	
B	11.2	11.3	
AB	3.8	3.3	
O	45.7	46.1	
Median BMI	25.6	25.4	0.034
Lung disease (%)			<0.001
Obstructive lung disease	29.6	28.9	
Pulmonary vascular disease	4.0	5.5	
CF	10.8	9.4	
ILD	51.3	50.1	
CLAD	4.2	6.0	
Prior transfusion (%)	3.8	4.4	0.062
LAS (%)			<0.001
<40	60.8	62.2	
40–49	20.6	21.0	
50–79	11.6	11.3	
80–100	7.1	5.5	
Cross-match required	2.9	11.2	<0.001
Waitlist outcome (%)			<0.001
Still waiting	8.3	13.1	
Transplanted	77.9	69.5	
Died/too sick for transplant	13.7	17.5	

UA – unacceptable antigens; BMI – body mass index; CF – cystic fibrosis; ILD – interstitial lung disease; CLAD – chronic lung allograft dysfunction; LAS – lung allocation score

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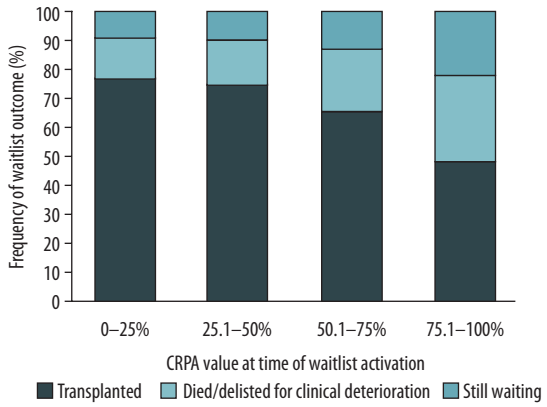

Figure 2. Frequency of waitlist outcomes by cPRA value at time of waitlist activation. cPRA – calculated panel-reactive antibodies.

The number of candidates with unacceptable antigens recorded while on the waitlist rose from 132 (8% of listed candidates) in 2006 to 571 (22% of listed candidates) in 2016. Of the 4822 candidates with unacceptable antigens recorded while on the waitlist, 4762 candidates (99%) had unacceptable antigens recorded at multiple points while on the waitlist, but 60 candidates (1%) had unacceptable antigens recorded only once while on the waitlist. Of the subjects with multiple unacceptable antigen recordings, the cPRA value (percentage) remained the same for 3335 candidates (70%), increased for 859 candidates (18%), and decreased for 568 candidates (12%) between the first and last unacceptable antigens recorded.

The frequency of waitlist outcomes by cPRA value at the time of waitlist activation are presented in Figure 2. Of the candidates with a cPRA value 0–25% at the time of waitlist activation, 77% were transplanted, 14% died on the waitlist/were delisted for clinical deterioration, and 9% were still waiting by study end. Of the candidates with a cPRA value of 25.1–50% at the time of waitlist activation, 75% were transplanted, 15% died on the waitlist/were delisted for clinical deterioration, and 10% were still waiting by study end. Of the candidates with a cPRA value of 50.1–75% at the time of waitlist activation, 65% were transplanted, 22% died on the waitlist/were delisted for clinical deterioration, and 13% were still waiting by study end. Of the candidates with a cPRA value of 75.1–100% at the time of waitlist activation, 48% were transplanted, 30% died on the waitlist/were delisted for clinical deterioration, and 22% were still waiting by study end.

Competing risk analysis with adjustment for covariates was used to evaluate the relationship between cPRA value and waitlist outcomes. The subhazard ratios (sHR) for lung transplantation and for the combined endpoint of death on the waitlist/delisting for clinical deterioration are presented in Tables 2 and 3, respectively. The reference group is candidates who had a cPRA value of 0–25% at the time of waitlist activation (considered "minimally sensitized"). Candidates with a cPRA value of 25.1–50% at the time of waitlist activation did not have a significantly different likelihood of undergoing transplant compared to the minimally sensitized group (sHR 0.99, 95% CI 0.91–1.06, p=0.707), nor did they have a significantly different likelihood of death on the waitlist/delisting for clinical deterioration compared to the minimally sensitized group (sHR 0.92, 95% CI 0.77–1.10, p=0.363).

Candidates with a cPRA value of greater than 50% at the time of activation had a significantly reduced likelihood of undergoing transplant and a significantly higher likelihood of death on the waitlist/delisting for clinical deterioration compared to minimally sensitized candidates. Candidates with a cPRA value of 50.1–75% were 25% less likely to undergo transplant and were 44% more likely to die on the waitlist/be delisted for clinical deterioration than the minimally sensitized group (sHR for lung transplant: 0.75, 95% CI 0.68-0.82, p<0.001; sHR for death on waitlist/delisting for clinical deterioration: 1.44, 95% CI 1.22–1.71, p<0.001). Candidates with a cPRA value of 75.1–100% were 52% less likely to undergo transplant and were 92% more likely to die on the waitlist/be delisted for clinical deterioration than the minimally sensitized group (sHR for lung transplant: 0.48, 95% CI 0.43-0.53, p<0.001; sHR for death on waitlist/delisting for clinical deterioration: 1.92, 95% CI 1.64–2.24, p<0.001). The cumulative incidences of lung transplant (A) and death on the waitlist/delisting for clinical deterioration (B) are presented in Figure 3.

Discussion

The goal of this study was to determine the effect that unacceptable antigens have on waitlist outcomes for lung transplant candidates across the United States. Using a large UNOS database, we demonstrated that candidates who have unacceptable antigens recorded while on the waitlist have a significantly lower rate of lung transplantation and a significantly higher rate of death on the waitlist/delisting for clinical deterioration than candidates who do not have unacceptable antigens. However, unacceptable antigens negatively affect the likelihood of lung transplantation only when the associated cPRA value is greater than 50%. The likelihood of transplantation for candidates with a cPRA value of greater than 50% at the time of waitlist activation is 75% that of minimally sensitized candidates (with a cPRA value of 0–25%), and the likelihood of transplantation for candidates with a cPRA value of greater than 75% at waitlist activation is less than one-half that of minimally sensitized candidates.

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Table 2. Competing hazard models for lung transplantation by cPRA score at the time of waitlist activation.

Variable at time of waitlist activation	sHR	95% CI	p-Value
cPRA score			
0-25%	Reference	Reference	Reference
25.1–50%	0.99	0.91–1.06	0.707
50.1–75%	0.75	0.68–0.82	<0.001
75.1–100%	0.48	0.43–0.53	<0.001
Male gender	1.14	1.09–1.19	<0.001
Age (years)			
<45	Reference	Reference	Reference
45–54	1.00	0.94–1.06	0.991
55–64	1.10	1.04–1.16	<0.001
≥65	1.26	1.19–1.34	<0.001
Ethnicity			
Caucasian	Reference	Reference	Reference
African-American	0.91	0.86–0.96	<0.001
Hispanic	0.91	0.85–0.97	0.005
Other	0.78	0.71–0.86	<0.001
Blood group			
O	Reference	Reference	Reference
A	1.10	1.06–1.13	<0.001
B	1.07	1.02–1.12	0.011
AB	1.24	1.14–1.34	<0.001
Height (per cm)	1.02	1.01–1.02	<0.001
BMI (per kg/m^2)	0.99	0.99–0.99	<0.001
Lung disease			
Obstructive lung disease	Reference	Reference	Reference
Pulmonary vascular disease	0.75	0.75	<0.001
CF	1.14	1.14	<0.001
ILD	1.14	1.14	<0.001
CLAD	0.86	0.86	0.001
Listed for double lung transplant only	0.96	0.93–0.99	0.006
LAS			
<40	Reference	Reference	Reference
40–49	1.38	1.32–1.43	<0.001
50–79	1.41	1.33–1.50	<0.001
80–100	0.98	0.90–1.08	0.727

cPRA – calculated panel reactive antibodies; BMI – body mass index; CF – cystic fibrosis; ILD – interstitial lung disease; CLAD – chronic lung allograft dysfunction; LAS – lung allocation score.

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Table 3. Competing hazard models for death on the waitlist/delisting for clinical deterioration by cPRA score at the time of waitlist activation.

Variable at time of waitlist activation	sHR	95% CI	p-Value
cPRA score			
0-25%	Reference	Reference	Reference
25.1–50%	0.92	0.77–1.10	0.363
50.1–75%	1.44	1.22–1.71	<0.001
75.1–100%	1.92	1.64–2.24	<0.001
Male gender	1.01	0.92–1.11	0.87
Age (years)			
<45	Reference	Reference	Reference
45–54	1.11	0.98–1.24	0.09
55–64	1.06	0.95–1.18	0.31
≥65	1.04	0.91–1.18	0.59
Ethnicity			
Caucasian	Reference	Reference	Reference
African-American	1.14	1.02–1.27	0.02
Hispanic	1.07	0.95–1.21	0.27
Other	1.10	0.91–1.32	0.32
Blood group			
O	Reference	Reference	Reference
A	0.92	0.86–0.99	0.025
B	1.01	0.91–1.13	0.812
AB	0.92	0.77–1.11	0.388
Height (per cm)	0.97	0.97–0.98	<0.001
BMI (per kg/m^2)	1.00	0.99–1.00	0.315
Lung disease			
Obstructive lung disease	Reference	Reference	Reference
Pulmonary vascular disease	2.07	1.79–2.41	<0.001
CF	1.16	0.99–1.35	0.065
ILD	1.23	1.12–1.36	<0.001
CLAD	1.84	1.58–2.15	<0.001
Listed for double lung transplant only	1.12	1.04–1.21	0.002
LAS			
<40	Reference	Reference	Reference
40–49	1.26	1.15–1.38	<0.001
50–79	2.04	1.84–2.26	<0.001
80–100	4.35	3.90–4.85	<0.001

cPRA – calculated panel reactive antibodies; BMI – body mass index; CF – cystic fibrosis; ILD – interstitial lung disease; CLAD – chronic lung allograft dysfunction; LAS – lung allocation score.

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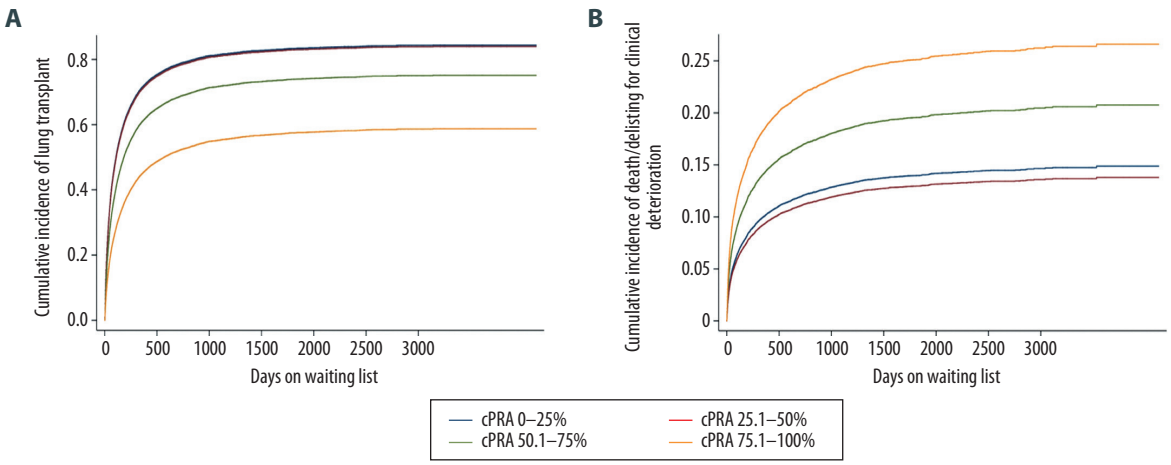

Figure 3. Competing risk analysis of waitlist outcome by cPRA value. (**A**) Cumulative incidence of lung transplant for candidates grouped by cPRA value. (**B**) Cumulative incidence of death/delisting for clinical deterioration for candidates grouped by cPRA value. cPRA – calculated panel-reactive antibodies.

Our results are similar to those reported in a similar study by Kransdorf et al. in heart transplant candidates. They divided 3855 heart transplant candidates into 5 groups by their initial cPRA value entered while on the waitlist, and demonstrated that the percentage of candidates who were transplanted declined and the percentage who died on the waitlist increased as cPRA value rose [8]. Several renal transplant studies have shown significantly prolonged waiting times for candidates with unacceptable antigens, although the cPRA threshold at which the effect is seen has been reported as anywhere from greater than 10% to greater than 50% [11–14]. A recently published single-center study examining the impact of sensitization in lung transplant candidates also showed that an increasing cPRA value was associated with a decreased likelihood of transplantation and an increased risk of death [9].

Several possible methods of improving access to transplant for candidates with high cPRA values have been investigated. Studies evaluating the use of pre-operative desensitization protocols for heart, lung, and renal transplant candidates with high cPRA values have reported mixed results. Although some programs have successfully used regimens of intravenous immunoglobulin (IVIG)/rituximab and IVIG/bortezomib for highly sensitized heart and renal transplant candidates [15–17], others have found that similar protocols resulted in no significant reduction in cPRA values [18,19]. The largest study of pre-operative desensitization for broadly sensitized lung transplant candidates also did not demonstrate a significant reduction in cPRA values, despite using plasmapheresis, solumedrol, IVIG, bortezomib, and rituximab [20].

Another strategy to mitigate the impact of unacceptable antigens on transplant rates involves increasing the priority of highly sensitized candidates on the waitlist. Through altering the allocation scoring or utilizing a sharing algorithm at the national level, or a combination of the 2 strategies, several countries have increased transplant rates for highly sensitized heart and renal transplant candidates [21–23]. However, at present, these waitlist modifications are not made for highly sensitized lung transplant candidates in the United States.

Lastly, a small number of transplant centers use a peri-operative regimen of plasmapheresis, IVIG, and thymoglobulin for sensitized candidates who have a positive virtual cross-match and/or positive actual cross-match at the time of transplant. This type of strategy, as described by The Toronto Lung Transplant Program as safe in both the short-term and long-term post-transplant periods [24], effectively equalizes access to transplant across all levels of sensitization since no donor lungs are rejected on the basis of having unacceptable antigens. Similar protocols are being adopted by other organ transplant programs [25].

We propose that lung transplant centers in the United States that do not use such peri-operative strategies for highly sensitized candidates start to adopt strategies to otherwise improve access to transplant for these patients, considering their disadvantage. When a center records unacceptable antigens for a candidate in the UNOS system, the allocation score should be increased proportionally to offset the expected reduction in donor offers, with the intention to allow more highly sensitized candidates a more equitable opportunity for lung transplant.

This study has several limitations. Firstly, our analysis did not account for the variation in candidates' cPRA values during their time on the waitlist. We analyzed the effect of the cPRA

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value at the time of waitlist activation on candidates' likelihood of lung transplantation and death on the waitlist/delisting for clinical deterioration, but 99% of the candidates who had unacceptable antigens recorded while on the waitlist had multiple cPRA values recorded. Although 70% of these candidates had stable cPRA values over time, 18% had cPRA values that increased and 12% had cPRA values that decreased, and our analysis did not include the cPRA values at other time points on the waitlist that may have affected outcomes. To achieve this, an analysis of the cPRA value as a time-dependent covariate would be needed. Secondly, a cPRA value may not be an accurate reflection of the percentage of the donor population that is unacceptable to a candidate in certain areas of the country. In more ethnically homogeneous areas, the frequency each HLA antigen may differ from what is used in the cPRA calculation, which is based on national ethnic and HLA frequencies. It is possible that the cPRA value of candidates in these areas significantly differs from what their cPRA value would be if it were calculated based on their local donor pool only. In our study population, it is possible that the cPRA values of candidates in some areas are poorly correlated with their wait time for a transplant in their geographical area. This unavoidable issue with cPRA accuracy may have affected the relationship between cPRA value and waitlist outcomes for some candidates. Thirdly, each center's definition of unacceptable antigen is not currently recorded in the UNOS database. While some centers may use an MFI cut-off, others may use newer techniques such as C1q-binding and serial dilution to assess which antigens are unacceptable. It would be of interest to know to what extent the definition varies between programs across the country and how this could impact waitlist outcomes. It is also possible that some centers included in the database did not consider any antigen unacceptable prior to transplant, but instead made the decision to accept or refuse the offer based on consultation with their HLA lab or a prospective cross-match. This could have resulted in lower rates of transplantation than expected among some candidates who had cPRA values of 0% recorded because offers were declined after HLA lab review or a positive prospective cross-match. Indeed, when candidates were instead divided into 5 groups based on their cPRA value at the time of waitlist activation (0%, 0.1–25%, 25.1–50%, 50.1–75%, and 75.1–100%), candidates with a cPRA value of 0.1–25% at the time of waitlist activation had a significantly higher likelihood of undergoing transplant compared to candidates with a cPRA value of 0% (sHR 1.18, 95% CI 1.11–1.25, p<0.001). They also had a significantly lower likelihood of death on the waitlist/delisting for clinical deterioration than candidates with a cPRA value of 0% (sHR 0.79, 95% CI 0.68–0.92, p=0.002). The remainder of the results were unchanged (data not shown). This suggests that some sensitized candidates had no unacceptable antigens recorded in UNOS and therefore a cPRA value of 0%, but their likelihood of transplant still reflected what their cPRA value would have been if their unacceptable antigens were recorded. Finally, the method of HLA antibody detection that was used to quantify and qualify candidates' unacceptable antigens at each center was not known. Over the past 20 years, HLA antibody screening has evolved from the use of cytotoxic (cell based) assays to the significantly more sensitive solid-phase assays (enzyme-linked immunosorbent assays (ELISA) and fluorescently labelled microbeads). Microbead assays are up to 10% more sensitive than ELISA, which is up to 10% more sensitive than cytotoxic-based assays [26,27]. Given this, it is very likely that the shift in methodology over the years at least in part contributed to our finding that the number of candidates with unacceptable antigens recorded while on the waitlist rose from 2006 to 2016. It is also probably safe to assume that the use of more sensitive detection techniques increases candidates' cPRA values and reduces their likelihood of transplant. However, this could not be demonstrated with certainty in the absence of the recording of the detection methods used in the UNOS database.

Conclusions

Our study provides a comprehensive evaluation of the impact of unacceptable antigens and cPRA values on lung transplantation rates and waitlist mortality in the United States. Considering the significantly lower rate of transplantation and higher waitlist mortality associated with cPRA values of greater than 50%, further development and implementation of strategies to mitigate this disadvantage while still avoiding post-operative antibody-mediated complications is critical for highly sensitized candidates.

Conflicts of interest

None.

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