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DQA1 Eplet Mismatch Load As an Independent Risk Factor of CLAD After Lung Transplantation

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Background. Lung transplantation remains the treatment of choice for end-stage lung diseases, and recipient selection is currently based on clinical urgency, ABO compatibility, and donor size. The risk of allosensitization is classically based on HLA mismatch, but eplet mismatch load is increasingly seen to be important in long-term outcomes in solid organ transplantation. Chronic lung allograft dysfunction (CLAD) is relatively common and relevant, affecting almost 50% of patients 5 y after transplantation and being the first cause of death from the first year after transplantation. The overall class-II eplet mismatch load has been associated with CLAD development. **Methods.** Based on clinical data, 240 lung transplant recipients were eligible for CLAD, and HLA and eplet mismatch was analyzed using the HLAMatchmaker 3.1 software. **Results.** A total of 92 (38.3%) lung transplant recipients developed CLAD. The time free-of-CLAD was significantly decreased in patients with presence of DQA1 eplet mismatches (P = 0.015). Furthermore, when other previously described CLAD risk factors were studied in a multivariate analysis, the presence of DQA1 eplet mismatches was found to be independently associated with the early onset of CLAD. **Conclusions.** The concept of epitope load has arisen as a new tool to better define donor–recipient immunologic compatibility. The presence of DQA1 eplet mismatches potentially would increase the likelihood of developing CLAD.

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Lung transplantation is the best choice for end-stage lung disease, and recipient selection is currently based on clinical urgency, ABO compatibility, and donor size.[1] However, HLA matching has a significant impact on long-term graft survival.[2] In lung transplantation, HLA mismatch (MM) between donor and recipient was associated with early acute rejection[3] and poor graft outcome.[4,5]

In the last few years, the concept of eplets has arisen as a new way to assess compatibility.[6,7] This approach fine-tunes the antigen (Ag) HLA risk and better defines the immunologic disparities between donor and recipients.[8] Eplets are defined as short polymorphic amino acid residues that are spatially close to, and compatible in size with, the complementarity determining region of the immunoglobulin's hypervariable region.[6,9]

Several studies have demonstrated a relationship between donor–recipient eplet disparity and better long-term graft outcome in renal transplantation.[10-12]

The main long-term clinical problem in lung transplantation is the chronic lung allograft dysfunction (CLAD). There are several well-identified parameters involved in CLAD development such as recipient age, cytomegalovirus infection, primary graft dysfunction (PGD), acute cellular rejection, antibody-mediated rejection (AMR), gastroesophageal reflux disease, and autoimmunity[13]; however, the role of HLA MM is not clearly identified. Eplet MM (Ep MM) better characterizes the immunology risk between donor and recipient than HLA MM, and Ep MM load has been proposed as a better parameter to define immunologic risk before solid organ transplantation.[14] Potentially, Ep MM load could be considered as a selection criterion before lung transplantation and for risk stratification posttransplantation, the same way it is already used in the case of kidney transplants.[15] The first evidence for

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the independent impact of HLA-DRB1/3/4/5+DQA/B Ep MM in CLAD was observed several years ago.[16] Subsequent studies demonstrated that HLA class-II Ep MM were able to predict de novo HLA class-II donor specific antibodies (DSAs).[17] Moreover, specific Ep MMs associated with DSA development in cardiothoracic transplantation were identified.[18]

Several studies have demonstrated an association between de novo DSA (dnDSA) formation with CLAD development in lung transplantation. Nevertheless, there are no clear data on the prevalence of dnDSAs in lung transplantation between the different studies, ranging from 12% to 47%.[19-22] Regarding HLA class-II dnDSAs, Tikkanen et al[20] demonstrated an increased risk of CLAD when HLA-DQ dnDSAs were present.

In order to increase the evidence of the impact of Ep MM on CLAD and the usefulness of eplet class-II load in lung recipient selection, we assessed the independent potential role of Ep MM load in the development of CLAD in a larger lung transplant recipient (LTR) cohort.

MATERIALS AND METHODS

Patients

A total of 272 LTR were recruited from October 2008 to December 2017 at the Marques de Valdecilla University Hospital (Santander, Spain). Based on the clinical records, a total of 240 patients were eligible for the assessment of CLAD. CLAD, PGD,[23] and acute cellular rejections[24] were established according to the International Society of Heart and Lung Transplantation recommendations.[25,26] These patients were treated with an immunosuppression protocol based on the combination of an anticalcineurin inhibitor (tacrolimus), an antimetabolite (mycophenolate mofetil), and corticosteroids after transplantation. Regarding induction treatment, since January 2016, all the patients received Basiliximab. Before this date, it was exclusively administered in high-risk patients: those over the age of 65, with chronic renal failure and/or a high risk of postoperative hemodynamic instability, such as those with severe pulmonary hypertension. Since January 2017, azithromycin has also been used as an immunomodulator at a dosage of 250 mg 3 times per week.[27] The presence or absence of anti-HLA antibodies was determined before lung transplantation, 3- and 6-wk posttransplantation, and then during the 3rd, 6th, 9th, 12th, 18th, and 24th mo by Luminex (LABScreen Mix, One Lambda, CA). For those patients with a negative result for anti-HLA antibodies, the follow-up was annual. The identification of anti-HLA antibody reaction after a positive result was performed by Luminex (LABScreen Single Antigen, One Lambda, CA). When dnDSAs were found without evidence of rejection, patients were given a higher dose of immunosuppression (tacrolimus and mycophenolate mofetil) as well as immunoglobulins.[28] In recipients with confirmed AMR, the immunosuppression treatment was also increased, including plasmapheresis and rituximab. The demographic, clinical, and immunologic parameters of LTR are summarized in Table 1.

HLA Typing

Recipients' and donors' HLA class I (A, B, C) and class II (DR, DQ) typing was performed by a high-resolution sequence-specific primer (Life Technologies, Brown Deer, WI).

Eplet Mismatch Analysis

To assess eplet matching, the HLAMatchmaker 3.1 software[6,7] was used (from HTTP:// www.epitopes.net/downloads.html). To proceed with the HLA MM algorithm, a 4-digit for HLA typing is mandatory. When high-definition typing of donor and recipient was unresolved due to ambiguities (65.97%), the most frequent haplotypes were assigned based on the HaploStats website (https://www.haplostats.org).

Statistical Analysis

All data were expressed as mean and SD, or median and interquartile range for quantitative variables when they did not follow a normal distribution. In case of categorical variables, frequencies and percentages were used. To know if continuous quantitative variables were normally distributed, the Kolmogorov–Smirnov test was applied. One-way ANOVA and *t* tests were used for normally distributed data, and the nonparametric Mann–Whitney *U* test was used for non-normally distributed data. The chi-square test was used to study the association between 2 qualitative variables, and for CLAD-free survival analysis, the Kaplan–Meier test with the log-rank was used. In the survival analysis, the HLA and Eplet MM cutoff value to indicate the minimal risk of CLAD development was determined using the first tercile (the cutoff values, area under the curve, sensitivity, and specificity) are summarized in Table 2. For the assessment of the independent variables involved on the risk of early CLAD development, a multivariate Cox regression analysis was conducted with those parameters involved in CLAD development. All *P* values were 2-tailed, and a *P*-value of <0.05 was considered statistically significant. Statistical analysis of the data was performed with IBM SPSS 24 (SPSS Inc, Chicago, IL).

RESULTS

Antigen HLA Mismatch and CLAD

A total of 92 (38.33%) LTR developed CLAD. To look for immunologic risk factors of CLAD, we evaluated the Ag HLA MM between donor recipient and LTR, but no association with CLAD was found (Table 1). As expected, a positive correlation between Ag HLA-ABCDRDQ MM with total (class-I and class-II) Ep MM (Spearman test $P = 0.001$) was confirmed (Figure 1A). However, less time, free of CLAD, was not observed for increased HLA MM and Ep MM load (log-rank test $P = 0.809$ and $P = 0.251$, respectively; Table 2).

Total Class-II Eplet Mismatch Analysis and CLAD After Lung Transplantation

To further characterize the potential role of Ep MM load in CLAD development, we focused on class-II Ep MM in LTR. A correlation between Ag HLA class-II and class-II Ep MM was observed (Figure 1B). The number of total class-II Ep MM was measured based on the HLA-Matchmaker algorithm, and the presence of Ep MM between donor and recipient was used to assess CLAD risk. The time free of CLAD was not increased in those patients with <15 class-II Ep MM (log-rank test $P = 0.379$; Table 2). Moreover, when HLA-DQA/B and HLA-DRB1 Ep MM was independently assessed, but the time free of CLAD did not reach statistical significance ($P = 0.718$ and $P = 0.611$, respectively; Table 2).

TABLE 1.

Demographic, clinical, and immunologic characteristics of the cohort of lung transplant recipients

	All patients (n = 240)	CLAD (n = 92)	Non-CLAD (n = 148)	*P*
Recipient gender, male/female	153/87	56/36	97/51	0.464
Recipient age at transplant, y, mean ± SD	55.13 ± 10.62	56.00 ± 10.07	54.58 ± 10.95	0.487
Type of lung transplant, n (%)				
Single lung	86 (35.8)	34 (37.0)	52 (35.1)	0.775
Double lung				
CLAD type, n (%)			–	–
BOS	68 (28.3)	68 (73.9)		
RAS	24 (10.0)	24 (26.1)		
Disease, n (%)				0.963
COPD	79 (32.9)	32 (34.8)	47 (31.8)	
ILD	116 (48.3)	44 (47.8)	72 (48.6)	
Bronchiectasis-CF	22 (9.2)	8 (8.7)	14 (9.5)	
PAH	7 (2.9)	3 (3.3)	4 (2.7)	
Others	16 (6.7)	5 (5.4)	11 (7.4)	
CMV infection, n (%)	87 (36.3)	30 (32.6)	57 (38.5)	0.421
Acute cellular rejection, n (%)	105 (43.8)	44 (47.8)	61 (41.2)	0.174
Pretransplant HLA-I, n (%)	13 (5.4)	3 (3.3)	10 (6.8)	0.284
Pretransplant anti-HLA-II, n (%)	12 (5.0)	6 (6.5)	6 (4.1)	0.338
Posttransplant anti-HLA-I, n (%)	24 (10.0)	12 (13.0)	12 (8.1)	0.178
Posttransplant anti-HLA-II, n (%)	21 (8.8)	10 (10.9)	11 (7.4)	0.311
De novo anti-HLA-I, n (%)	14 (5.8)	9 (9.8)	5 (3.4)	**0.032**
De novo anti-HLA-II, n (%)	16 (6.7)	8 (8.7)	8 (5.4)	0.282
Anti-HLA-I DSAs, n (%)	2 (0.8)	1 (1.1)	1 (0.7)	0.673
Anti-HLA-II DSAs, n (%)	8 (3.3)	5 (5.4)	3 (2.0)	0.108
Antigen HLA class-I MM, mean ± SD	4.23 ± 1.59	4.28 ± 1.51	4.20 ± 1.64	0.707
Antigen HLA class-II MM, mean ± SD	2.50 ± 1.19	2.57 ± 1.18	2.47 ± 1.20	0.534
All class-I and -II Ep MM, mean ± SD	36.76 ± 15.16	37.50 ± 15.54	36.30 ± 14.95	0.553
All class-I Ep MM, mean ± SD	16.82 ± 7.53	17.09 ± 8.06	16.66 ± 7.21	0.667
All class-II Ep MM, mean ± SD	19.94 ± 11.19	20.41 ± 11.02	19.65 ± 11.32	0.608
All DRB1 Ep MM, mean ± SD	9.65 ± 5.69	9.73 ± 5.81	9.60 ± 5.64	0.867
All DQB1 Ep MM, mean ± SD	7.95 ± 5.72	8.00 ± 5.57	7.92 ± 5.83	0.915
All DQA1 Ep MM, mean ± SD	2.34 ± 2.24	2.68 ± 2.22	2.13 ± 2.23	0.062
All DQ Ep MM, mean ± SD	10.29 ± 7.07	10.68 ± 6.95	10.05 ± 7.16	0.498

The significant *P* value is in bold.
BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; DSAs, donor-specific antibodies; Ep, eplet; ILD, diffuse interstitial lung disease; MM, mismatch; PAH, pulmonary arterial hypertension; RAS, restrictive allograft syndrome; y, years.

TABLE 2.

Assessment of chronic lung allograft disease based in pretransplant immunologic risk parameters

Immunologic risk parameter	AUC	95% CI	Cutoff	Sensitivity	Specificity	*P*
Total Ag HLA class-I and -II MM	0.524	0.448-0.600	6	35.14	65.22	0.809
Total class-I and -II Ep MM	0.514	0.439-0.589	32	33.78	69.57	0.251
Total class-II Ep	0.527	0.452-0.602	15	40.54	68.48	0.379
Total DRB1 Ep	0.504	0.429-0.580	6	29.73	70.65	0.611
Total DQ Ep	0.534	0.459-0.609	7	34.46	68.48	0.718
Total DQB1 Ep	0.510	0.435-0.585	5	32.43	66.30	0.918
Total DQA1 Ep	0.582	0.508-0.655	1	35.81	78.26	**0.015**

The significant *P* value is in bold.
Ag, antigen; AUC, area under the curve; CI, confidence interval; Ep, eplet; MM, mismatch.

Total DQA1 and DQB1 Eplet Mismatches and CLAD Development

Subsequently, independent DQA1 and DQB1 Ep MMs were analyzed. A correlation between total class-II Ep MM and both DQA1 and DQB1 Ep MM was found (Spearman $P = 0.001$; Figure 1C). The time free of CLAD was significantly decreased in those patients with presence of DQA1 Ep MM (log-rank test $P = 0.015$) Table 2; Figure 2). However, the presence of >5 DQB1 Ep MM did not show statistical significance (log-rank test $P = 0.918$).

DQA1 Ep MM as Independent Factor of Early CLAD Development

To assess the role of DQA1 Ep MM on early onset of CLAD, a univariate analysis was addressed together with

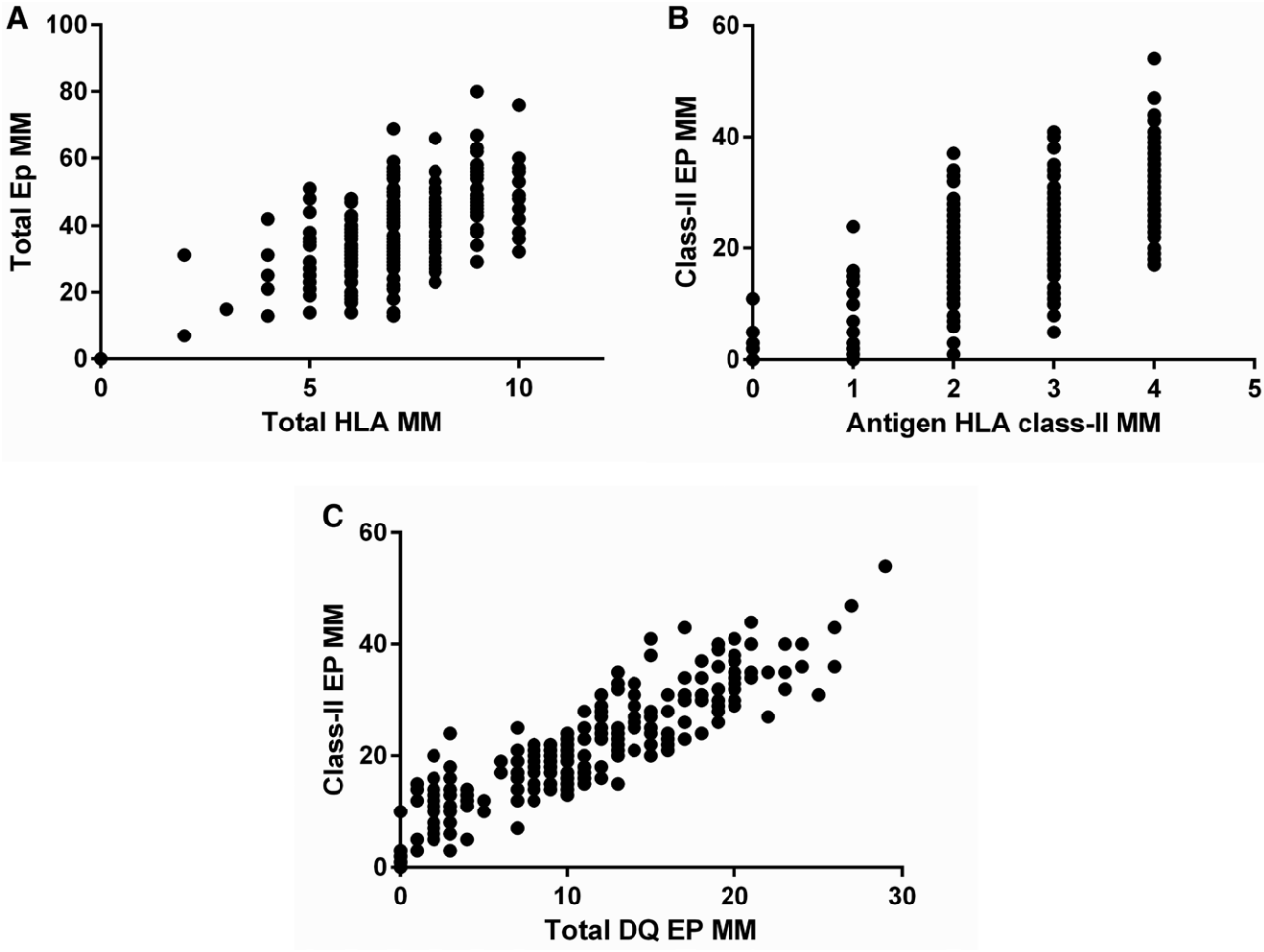

FIGURE 1. Comparison of total HLA (class-I and class-II), total Ep, class-II Ep, total DQ Ep, and DQA1 Ep MMs. The correlation between total (class-I and class-II) HLA (total HLA MM) and total Ep MMs (total Ep MM) are depicted in (A). The comparison of HLA class-II and class-II Ep MMs (class-II Ep MM) are shown in (B), whereas the comparison of total DQ Ep MM and total class-II Ep MM are depicted in (C). Ep, eplet; MM, mismatch.

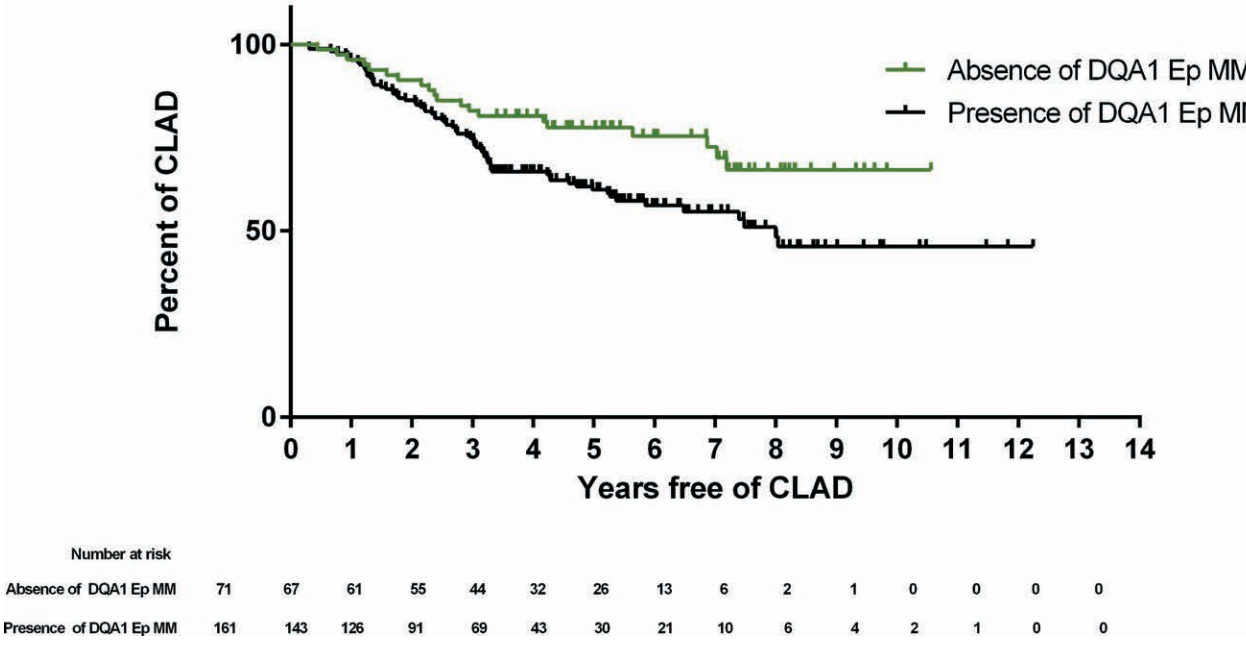

FIGURE 2. Time free of CLAD and DQA1 Ep MM load. The time free of CLAD was evaluated regarding the total load of DQA1 Ep MM, the lung transplant recipients with presence of Ep MMs in DQA1 locus (DQA1 Ep MM) (black line) had lower time free of CLAD than those without DQA1 Ep MM (green line). The time free of CLAD was assessed by Kaplan–Meier. CLAD, chronic lung allograft dysfunction; Ep, eplet; MM, mismatch.

other previously described parameters with involvement in CLAD: type of transplant (unilateral or bilateral), underlying disease, number of acute rejections, age at transplant, induction therapy, cytomegalovirus infection, Ag HLA class-II MM, PGD, donor-specific anti-HLA (DSA) class-I and/or class-II antibodies posttransplant, and the presence of DQA1 Ep MM.

All parameters were included in a multivariate backward conditional Cox logistic regression model and only the number of acute rejections, induction treatment, the development of DSA class-I and/or class-II antibodies posttransplant, and the presence of DQA1 Ep MM were independently associated with the early onset of CLAD (Table 3).

DISCUSSION

The Ag HLA MM is widely used as a selection criterion for kidney transplant candidates in histocompatibility laboratories. However, recently the concept of epitope "load" in solid organ transplantation has arisen as a new tool to better define donor–recipient immunologic compatibility. However, in lung transplant, other parameters are more critical in recipient selection, such as allograft size.[1]

Although there is a clear correlation between Ag HLA MM and Ep MM (Figure 1A), the Ep MM load may differ with the same Ag HLA MM. The same correlation between Ag HLA class-II MM and class-II Ep MM was observed (Figure 1B). Although there are evidences about eplet immunogenicity based on different characteristics such as electrostatic charge or polar amino acid mutations,[29] the present work was focused in all Ep MM loads (including antibody verified and others) following the strategy in most of the reports where an association with chronic rejection was found.[12] In the present work, low class-II Ep MM load was not associated with more time free of CLAD. These results are discordant with previous studies where DRB1/3/4/5+DQA/B Ep MM predicts CLAD.[16] This could be because in our study, the class-II Ep MM only include DRB1+DQA/B. Although several groups have demonstrated the independent role of Ep MM load in chronic rejection after solid organ transplantation,[30-34] there is no consensus about the amount of Ep MM to establish the risk of CLAD development.

To our knowledge, this work is the first to show an association between the presence of DQA1 Ep MM with reduced time free of chronic rejection of lung allograft in the CLAD form.

Recently, McCaughan et al[18] described the association of the persistence of dnDSA formation with the presence of DQA1*05/DQB1*02 and/or DQA1*05/DQB1*03 (combining the analysis of the alpha and beta chain) in the donor (risk Ep MM), the eplets involved are 45GE3 (DQB1*02), 74A (DQA1*05) and 45EV (DQB1*03:01) all of them are within the most immunogenic DQB1 eplets described by Schawalder et al.[35] In the present study, we could not establish a link between Ep MM load and dnDSA development in our cohort because only 10 patients had class-I or class-II dnDSAs. The low incidence of dnDSA development in long-term monitoring studies for anti-HLA antibodies in lung transplantation could be due to different assays to perform anti-HLA screening in the last decades. In our institution, the anti-HLA screening is performed by Luminex platform from 2011. In the present study, the old samples were retrospectively studied to avoid bias. Although the dnDSA development rate is far from previously published data, clinical AMR have been reported without evidence of DSA in LTRs.[36] In our cohort we identified 26 LTR with clinical AMR without DSA, but there the role of non-HLA antibodies in CLAD remain to be demonstrated.

One of the limitations of this study was the DQ high-resolution typing of the 65.97% of the patients because the donors HLA typing before 2016 was performed only low resolution for HLA A, B, and DR Ags, with a potential bias in Ep MM calculation.[37] Moreover, no DP Ep MM load was assessed due to the lack of DP typing in both donor and lung recipients. Recently DPB Ep MM was associated with graft loss in pediatric heart transplantation.[38]

Another limitation is the lack of data about gastroesophageal reflux disease in the prediction model for CLAD development and the potential role of other parameters such as non-HLA antibodies.[39] However, most of the parameters involved in CLAD has been included in the time free of CLAD prediction model where the presence of DQA1 Ep MM was identified as an independent factor from earlier development of CLAD. Independent lung transplant cohorts should be

TABLE 3.

Univariate and multivariate analysis of potential variables associated with early chronic lung allograft dysfunction development

	Univariate analysis		Multivariate analysis[a] (backward conditional model)		Multivariate analysis[b] (enter model)	
Variable	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
All DQA1 Ep	0.549 (0.334-0.901)	**0.018**	0.455 (0.226-0.915)	**0.027**	0.513 (0.291-0.903)	**0.021**
Induction treatment	1.858 (1.099-3.141)	**0.021**	1.794 (0.972-3.310)	0.062	1.981 (1.100-3.567)	**0.023**
Anti-HLA class-I and/or class-II DSAs	0.404 (0.174-0.935)	**0.034**	0.333 (0.135-0.825)	**0.018**	0.393 (0.166-0.927)	**0.033**
Number of acute rejection	1.188 (1.015-1.390)	**0.032**	1.206 (1.011-1.439)	**0.038**	1.183 (1.000-1.399)	**0.050**
Primary graft dysfunction	1.274 (0.743-2.184)	0.379	1.389 (0.693-2.784)	0.355		
Antigen HLA class-II MM	1.080 (0.907-1.285)	0.388	0.901 (0.709-1.146)	0.397		
Transplant type	0.908 (0.594-1.388)	0.655	0.916 (0.504-1.665)	0.774		
Disease	0.931 (0.617-1.405)	0.734	1.073 (0.650-1.733)	0.782		
CMV infection	1.192 (0.768-1.848)	0.434	1.064 (0.627-1.805)	0.818		
Age	1.007 (0.986-1.028)	0.523	0.999 (0.972-1.439)	0.943		

[a]Backward conditional model.
[b]Enter model.
The significant *P* values are in bold.
CI, confidence interval; CMV, cytomegalovirus; DSAs, donor specific antibodies; Ep, eplet; MM, mismatch; OR, odds ratio.

assessed to confirm the involvement of DQA1 Ep MM load in CLAD.

Although Ag HLA match is not considered in the selection of lung transplant candidates, recent evidence points to a delay in CLAD development with better Ag HLA class-II, DQB1, and DQA1 matches.[16] Moreover, in the context of precision medicine, the utility of class-II Ep MM has been suggested as a tool to identify transplant recipient candidates to reduce immunosuppression load. More studies should be conducted to assess the potential value of Ep MM measurement to select transplant recipients to reduce immunosuppressive loads.

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