The value of high-resolution HLA in the perioperative period of non-sensitized lung transplant recipients

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Background: The importance of HLA antigen matching is widely recognized and accepted worldwide. With the improvement of diagnostic methods, recent studies have shown that eplet mismatched for organ transplantation is essential. In the field of lung transplantation, eplet mismatch (MM) is closely related to chronic rejection after lung transplantation. To further investigate the relationship between early graft failure and acute rejection, we performed high-resolution HLA analysis on 59 patients in our center.

Methods: We conduct high-resolution HLA matching and Donor specific antibody (DSA) monitoring on 59 lung transplantation donors and recipients from April 1, 2018, to June 30, 2019. Baseline data were collected composed of both recipient characteristics and transplant-related features. Clinical outcomes were primary graft dysfunction (PGD) and acute rejection (AR).

Results: Overall, for these 59 patients, HLA antigen mismatch is 7.19±1.61, eplet mismatch is 8.31±1.75 (P=0.0005). As the number of mismatch sites increases, the severity of PGD increased significantly, especially when presented both eplet mismatch and HLA-DQ mismatch. In this group of patients, 2 cases of antibody-mediated rejection (AMR) occurred after transplantation, eplet MM 9 (HLA-DQ MM 2) and eplet MM 5 (HLA-DQ MM1). Both patients developed DSA after operation, and they are DQB1 06:01 and C07:02, respectively. There were 9 cases of death during the perioperative period. Five of them died of severe PGD, and 4 died of severe infection. All these 9 patients were with high-level eplet MM and HLA-DQ MM.

Conclusions: Perioperative PGD and AR closely related to HLA mismatches, especially eplet and HLA-DQ MM. It might be noteworthy to do complementary detection of eplet matching and DSA in lung transplant donors and recipients, to predict the risk of early PGD and acute rejection after lung transplantation.

Keywords: Lung transplantation; histocompatibility leukocyte antigen (HLA); antigen matching; eplet matching

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Introduction

Polymorphism analysis of histocompatibility leukocyte antigen (HLA) is essential for recipients in organ transplantation, which has been widely recognized to improve graft survival significantly and recipient prognosis (1,2). Especially for kidney transplantation, HLA-ABDR matching has been used as an important parameter for organ distribution in the worldwide. However, due to

scarcity of lung grafts and high requirement of maintenance, currently, it is impossible to distribute donor lung according to HLA worldwide (3).

At present, most organ transplant centers use two-digit low-resolution HLA (LR-HLA) typing, also known as "Serological equivalent HLA antigen". With the improvement of diagnostic methods, the number of alleles has increased rapidly. The practice has proved that the precise degree of HLA allele matching plays a key role and is a crucial factor affecting the long-term prognosis of transplanted organs (4). In recent years, immunologists and surgical experts have suggested that high-resolution HLA (HR-HLA) typing should be used at least in highly sensitized kidney transplant recipients (5). Recently studies (6) have shown that HLA class II eplet mismatch (MM) (DRB 1/3/4/5 + DQA/B) were poor prognosis indicators after lung transplantation, especially related to chronic lung allograft dysfunction (CLAD), contributing to the limited survival expectation of the lung transplant recipients.

In the acute phase or short-term after transplantation, eplet epitope mismatch might affect the occurrence of perioperative primary graft dysfunction (PGD) and acute rejection (AR). Thus, we conducted high-resolution HLA analysis for 59 lung transplant recipients and donors, to figure out the correspondence of HLA eplet MM and recipients' prognosis.

Methods

Study population

We routinely conducted LR-HLA matching on all lung transplant recipients and donors from April 1, 2018, to June 30, 2019, in the center. We further conducted HR-HLA matching and Donor specific antibodies (DSA) monitoring for some of the patients considering the economic burden issue. We collected perioperative clinical data from this subset of patients with HR-HLA matching information to compare the differences between the two types of matching and the correlation between clinical PGD and AR. Donor lung distribution was automatically assigned by the National Transplant allocation system.

The Institutional Ethics Committees of Wuxi People's Hospital afflicted to Nanjing Medical University, approved the study (No. 2018-323), including our retrospective review, verbal consent procedure, and analysis of data. All patient data were anonymous. Written informed consents were obtained from the patients or their next of kin. The research was conducted following the 2000 Declaration of Helsinki and the Declaration of Istanbul in 2008. None of the transplant donors were from a vulnerable population, and all donors or next of kin provided written informed consents that were freely given.

HLA antigen, high-resolution HLA typing, and eplet matching

In this case, HLA allelic genotyping (-A, -B, -C, -DRB1, and -DQB1/A1) was performed by sequence-based typing (SBT) based on the Luminex technology (One Lambda, Inc., Canoga Park, CA, USA). Where Luminex-based SSO results were issued, the common and well-documented (CWD) HLA alleles were listed, and in some cases, typing for HLA-DRB3/4/5 was distributed based on strong DRB1 associations. Eplet matching for all transplants was assessed by the HLA Matchmaker 500 pair (ABC and DRDQ eplet) program (http://www.hlamatchmaker. net/). All donors and recipients' HLA typing were entered, then the program assigned each paired eplet mismatch load.

Data collection

Baseline data were composed of both recipient characteristics and transplant-related features; the former consisted of age, sex, preoperative diagnosis, and blood type; the latter included single or bilateral lung transplantation, amount of bleeding, blood transfusion, percentage of peak panel-reactive antibody (PRA), total ischemic time, type of initial immunosuppressants (categorized as tacrolimus, cyclosporin A, mycophenolate mofetil, and prednisone), time of transplant, HLA antigen mismatch, and eplet mismatch between donors and recipients.

Clinical outcomes

The primary clinical outcomes of this study were PGD (defined as the syndrome of acute lung injury early after lung transplantation), acute cellular rejection (ACR) and antibody-mediated rejection (AMR, associated with measurable allograft dysfunction) within a perioperative period (1 month). These complications can significantly influence long-term complications and survival, having a significant impact on the recipient's quality of life and healthcare. The definition and severity grading of PGD were reported by the International Society for Heart and Lung Transplantation in 2016 (7). ACR is the consequence

of an immune response of the host against the lung graft, and graft biopsy is the gold standard technique to diagnose ACR (8). The diagnosis of AMR needs at least two of the following three standards: the presence of donor-specific anti–HLA antibody, positive C4d staining on immunofluorescence, and characteristic histologic changes of AMR (9).

Statistical analyses

Continuous data were expressed as mean ± standard deviations. Comparisons between the 2 groups were performed by chi-square or Fisher test, and Student's *t*-test, comparisons among three or more groups were made with one-way ANOVA analysis. Survival was estimated by Kaplan-Meier analysis. Statistical analyses were performed with the SPSS 22.0 software (SPSS Inc., USA), and P <0.05 was considered statistically significant.

Results

Study population

From April 1, 2018, to June 30, 2019, 150 cases of lung transplantation were performed in our hospital. At our center, LR-HLA matching was routinely applied to all recipients, and HR-HLA monitoring needed additional cost. Only 59 of these 150 patients received HR-HLA matching detection. There were 8 females (13.56%) and 51 males (86.44%). The average age at the time of operation was 55.73±10.78 years. The primary diseases included, 26 cases (44.07%) of interstitial lung disease (ILD) 14 cases of chronic obstructive pulmonary disease (COPD), 11 cases of pneumoconiosis, 2 cases of pulmonary hypertension (PH) , 1 case of bronchiectasis, 1 case of diffuse pantothenic bronchiolitis (DPB) and 1 case of pulmonary lymphangioleiomyomatosis (PLAM). There were 31 cases of single lung transplantation and 28 cases of double lung transplantation. The average operation time was 6.09±1.48 hours. The average bleeding volume of 1,032.71±749.16 mL with blood transfusion was 852.27±901.44 mL. The average cold ischemia time was 7.65±1.93 hours (*Table 1*).

Immune background and immunosuppressive therapy

The ABO blood types of the donors and recipients in this group of 59 patients were completely matched. LR-HLA mismatches were 7.19±1.61, HR-HLA mismatches were 8.31±1.75 (P=0.0005). There were no high sensitization recipients in this group before the operation, of which 56 patients were PRA <10% and 3 patients were PRA 11–30%. Considering the elevated risk of perioperative infection rate, no immune induction therapy was adopted. The postoperative routine used regimen was tacrolimus (FK) + mycophenolate mofetil (MMF) + prednisone (Pred) triple immunosuppressive therapy. Among those, 50 recipients received FK + Pred dual immunosuppression treatment due to perioperative pulmonary infection; 6 patients were treated with conventional FK+MMF+ Pred triple immunosuppressive therapy. The remaining three patients were unable to tolerate the side effects of tacrolimus, so they were treated with cyclosporine (CSA) +MMF + Pred (1 case) and CSA + Pred (2 cases).

PGD occurrence

Within one week after the operation, 8 cases presented PGD 1, 15 cases of PGD 2, 32 cases of PGD 3. The relationship between PGD and HLA mismatch is shown in *Table 2*. Regardless of LR-HLA or HR-HLA, or HLA-DQ locus, it showed that as the increase of mismatch sites number, the severity of PGD in the early postoperative period was significantly increased (*Table 2*). After dividing into two groups according to PGD0-2 and 3, mismatch of HLA antigen, eplet, and HLA-DQ were positively correlated with the severity of PGD, especially eplet MM and HLA-DQ mismatch (*Table 3*). Also, the severity of PGD was positively correlated with mechanical ventilation time. There was no statistically significant difference between PGD and cold ischemia time, ICU time, and ECMO assisting time.

ACR occurrence

In our cohort, one patient in this group developed ACR. The patient had to be re-intubated and mechanically ventilated due to severe ACR on post-operation day 7 (POD 7), and ECMO was used. After the treatment with large doses of glucocorticoids, ECMO and mechanical ventilation were successfully weaned. The patient's HLA antigen MM was 6, but eplet MM was as high as 9.

AMR occurrence

In this group of patients, 2 cases of AMR occurred after

Table 1 Clinical characteristics of lung transplant patients

Variable	Value
Female (n, %)	8 (13.56)
Age at transplantation (years, mean ± SD)	55.73±10.78
Diagnosis	
ILD (n, %)	27 (45.76)
COPD (n, %)	14 (23.74)
Pneumoconiosis (n, %)	11 (18.64)
PH (n, %)	2 (3.39)
Bronchiectasis (n, %)	3 (5.08)
Others (n, %)	2 (3.39)
PaO_2/FiO_2 ratio (mmHg, mean ± SD)	160.78±99.86
Operation ways (n, %)	
Right single lung transplantation	17 (28.81)
Left single lung transplantation	14 (23.73)
Bilateral lung transplantation	28 (47.46)
Blood loss (mL, mean ± SD)	1,032.71±749.16
Blood transfusion (mL, mean ± SD)	852.27±901.44
Operation time (h, mean ± SD)	6.09±1.48
Cold ischemic time (h, mean ± SD)	7.65±1.93
Peak PRA (n, %)	
≤10	56 (94.92)
11–30	3 (5.08)
≥30	0 (0)
HLA-DQ mismatch (n, %)	
0	2 (3.39)
1	15 (25.42)
2	42 (71.19)
HLA-A mismatch (n, %)	
0	0 (0)
1	24 (40.68)
2	35 (59.32)
HLA-B mismatch (n, %)	
0	1 (1.69)
1	13 (22.03)
2	45 (76.28)
HLA-C mismatch (n, %)	
0	2 (3.39)
1	18 (30.51)
2	39 (66.10)
HLA-DR mismatch (n, %)	
0	2 (3.39)
1	16 (27.12)
2	41 (69.49)
Immunosuppressive (n, %)	
FK+ Pred	50 (84.74)
FK+ MMF+ Pred	6 (10.18)
CSA+ MMF+ Pred	1 (1.69)
CSA + Pred	2 (3.39)

HLA, histocompatibility leukocyte antigen; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease; PH, pulmonary hypertension; FK, tacrolimus; MMF, mycophenolate mofetil; Pred, prednisone; CSA, cyclosporin A.

the operation, eplet MM 9 (HLA-DQ MM 2) and eplet MM 5 (HLA-DQ MM 1). Both patients developed DSA after operation, and they were DQB1 06:01 and C07:02, respectively.

Death

There were 9 cases of death during the perioperative period. Five of them died of severe PGD and 4 died of severe infection. The 9 patients' eplet MMs were at average of 9.4, HLA-DQ MMs were at an average of 1.9.

Discussion

The status of HLA in organ transplantation has been widely recognized. HLA matching improved organ transplantation results and benefited recipients (10,11). HLA matching supplied benefits in improving outcomes in kidney transplantation and remained part of the kidney allocation. HLA-ABDR was included in the allocation, but HLA-DQ was not considered (12-14). However, due to the short cold ischemia time requirement of donated lungs, it has not been

Table 2 PGD and HLA mismatch

Variable	PGD			
	0	1	2	3
HLA antigen mismatch (n)				
0–2	0	0	0	0
3–4	2	0	2	0
5–6	2	1	5	6
7–8	0	6	6	17
9–10	0	1	2	9
Eplet mismatch (n)				
0–1				
3–4	1	0	2	0
5–6	3	0	2	0
7–8	0	3	7	6
9–10	0	5	4	26
HLA-DQ mismatch (n)				
0	1	1	1	0
1	2	4	8	8
2	1	3	6	24
Cold ischemic time (h, mean ± SD)	8.52±1.52	7.31±1.68	7.37±2.29	7.76±2.84
Tracheal intubation (day, mean ± SD)	2.50±1.12	2.13±0.78	3.13±1.86	4.42±2.77
ICU (day, mean ± SD)	3.75±1.48	4.88±3.41	4.73±2.72	8.41±9.92

PGD, primary graft dysfunction; HLA, histocompatibility leukocyte antigen.

Table 3 PGD and HLA mismatch

Characteristic	PGD		P
	0,1,2	3	
HLA antigen mismatch (n, mean ± SD)	6.48±1.73	7.87±1.13	0.016
Eplet mismatch (n, mean ± SD)	7.33±1.94	9.13±0.99	<0.0001
HLA-DQ mismatch (n, mean ± SD)	1.26±0.64	1.75±0.43	0.0012
Cold ischemic time (h, mean ± SD)	7.52±2.03	7.76±1.84	0.6407
Tracheal intubation (day, mean ± SD)	2.74±1.58	4.42±2.77	0.0084
ICU (day, mean ± SD)	4.63±2.83	8.41±6.92	0.0116
ECMO (day, mean ± SD)	2.57±1.45	3.59±3.23	0.2873

PGD, primary graft dysfunction; HLA, histocompatibility leukocyte antigen.

possible to allocate donors according to the degree of HLA matching in lung transplantation in the past. HLA typing has been more used in retrospective analysis at the lung transplant center to guide later immunosuppressive therapy.

Although HLA-DQ and -DR may be closely related at an antigen level, it has been shown that small differences in one or more epitopes between donors and recipients at either locus were sufficient to generate a humoral and/or T cell-mediated immune response (15,16). In 2015, Hahn reported that a 41-year-old female patient received a 0 MM kidney and pancreas in 1998 and 2000, respectively. However, when she planned to undergo a second kidney transplant in 2014, PRA level was as high as 84%, while an antibody that conflicted with its HLA-A2 site existed. This case report illustrated the importance of high-resolution HLA typing, suggesting that low-resolution HLA typing was problematic and unreliable (17). Huang *et al.* retrospectively analyzed the data of HR-2F HLA in solid organ transplantation applications at Children's Hospital of Philadelphia and Temple Hospital, a better result could be seen when HLA typing was performed at the HR-2F level (18). Our data showed that this group of patients had LR-HLA mismatch 7.19±1.61, eplet mismatch 8.31±1.75, showing that there was a significant difference between the two methods' presentation. When analyzing the relationship between the two matching methods and clinical PGD manifestation, there was still statistically discrepancy. We further need to evaluate the joint results of organ acquisition, transit time, pulmonary artery pressure, blood loss and other factors related to surgical operations and treatments.

A recent "Personal Viewpoint" paper addressed the concept that HLA typing at the four-digit or allele level offered a more exact approach to find suitable donors for sensitized patients (5). Our recipients were non-sensitized, and the results showed that eplet matching was closely related to perioperative PGD. This suggested the importance of precise matching in lung transplantation. Huang *et al.* conducted HR-2F HLA typing results showed that the most frequent use of HR-2F HLA typing was for postoperative monitoring of DSA. As in our study, 2 patients had AMR with DSA. Without HR-HLA data of donor and recipient, it would be hard for determination and prediction. However, our results were quite preliminary, and further work should be done to investigate the relationship of the HLA MM and clinical prognosis.

In 2016, Lim *et al.* published a median follow-up of 2.8 years for 788 recipients of kidney transplantation in Australia. Among these patients, 321 (40.7%) patients were with HLA-DQ 0 MM, 467 (59.4%) with 1–2 MM (19). The research showed an independent association between HLA-DQ mismatches and acute rejection, including AMR. It is important to point out that most of the acute rejection (80%) occurred within the first 6 months after transplantation, suggesting the potential contribution of pre-transplant donor-specific anti-HLA-DQ antibody to the risk of early rejection. Therefore, the authors suggested that the degree of HLA-DQ site matching should be added to the current deceased donor kidney distribution system (20,21). HLA-DQ mismatching was associated with lower graft survival independent of HLA-ABDR in living donor kidney transplants and deceased donor kidney transplants, with a higher 1-year risk of acute rejection (22). In acute graft versus host disease after hematopoietic stem cell transplantation, donor-recipient incompatibility at the HLA-DQ locus was associated with a two-fold greater risk of acute graft-versus-host disease, independent of compatibility at the HLA-DR locus (23,24). Accordingly, once the recipient had a *de novo* DSA to HLA-DQ, the risk of AMR increased as to 10-fold, which was often associated with early graft loss (25-27). This study found that HLA-DQ MM was strongly associated with severe PGD after lung transplantation. At the same time, we also observed a total of 9 patients died in this group, 5 died of severe PGD, 4 died of severe infection, especially that they all had elevated levels of eplet MMs and HLA-DQ MMs.

In conclusion, perioperative PGD and long-term CLAD were the most detrimental results with managing difficulties in lung transplantation. Pre-detection of eplet matching and DSA could accurately reflect the genetic background of donors and recipients; thus predicting the risk of early PGD and acute rejection after lung transplantation. Donations can be made more effective if the organ distribution can be further guided by HLA eplet matching in lung transplantation. Thus, the allografts can survive even longer with postoperative complications and immunosuppressive strength to be reduced.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest

to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Institutional Ethics Committees of Wuxi People's Hospital afflicted to Nanjing Medical University, approved the study (No. 2018-323), including our retrospective review, verbal consent procedure, and analysis of data. All patient data were anonymous. Written informed consents were obtained from the patients or their next of kin.

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