Panel-Reactive and Donor-Specific Antibodies before Lung Transplantation can Affect Outcomes in Korean Patients Receiving Lung Transplantation

Sung Woo Moon1, Moo Suk Park1, Jin Gu Lee2, Hyo Chae Paik3, Young Tae Kim3, Hyun Joo Lee3, Samina Park3, Sun Mi Choi3, Do Hyung Kim3, Woo Hyun Cho6, Hye Ju Yeo6, Seung-il Park7, Se Hoon Choi7, Sang-Bum Hong8, Tae Sun Shim8, Kyung-Wook Jo8, Kyeongman Jeon8, Byeong-Ho Jeong8, Song Yee Kim1; and the Korean Organ Transplantation Registry Study Group

1Division of Pulmonology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul; 2Department of Thoracic and Cardiovascular Surgery, Severance Hospital, Yonsei University College of Medicine, Seoul; 3Department of Thoracic and Cardiovascular Surgery, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; 4Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; 5Department of Thoracic and Cardiovascular Surgery, Yangsan Hospital, Pusan National University School of Medicine, Yangsan; 6Department of Pulmonology and Critical Care Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul; 7Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul; 8Department of Pulmonology and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul; 9Division of Pulmonology and Critical Care Medicine, Department of Medicine, Samsung Medical Center, School of Medicine, Sungkyunkwan University, Seoul, Korea.

Purpose: Data on the distribution and impact of panel reactive antibodies (PRA) and donor specific antibodies (DSA) before lung transplantation in Asia, especially multi-center-based data, are limited. This study evaluated the prevalence of and effects of PRA and DSA levels before lung transplantations on outcomes in Korean patients using nationwide multicenter registry data.

Materials and Methods: This study included 103 patients who received a lung transplant at five tertiary hospitals in South Korea between March 2015 and December 2017. Mortality, primary graft dysfunction (PGD), and bronchiolitis obliterans syndrome (BOS) were evaluated.

Results: Sixteen patients had class I and/or class II PRAs exceeding 50%. Ten patients (9.7%) had DSAs with a mean fluorescence intensity (MFI) higher than 1000, six of whom had antibodies with a high MFI (≥2000). DSAs with high MFIs were more frequently observed in patients with high-grade PGD (≥2) than in those with no or low-grade (≤1) PGD. In the 47 patients who survived for longer than 9 months and were evaluated for BOS after the transplant, BOS was not related to DSA or PRA levels. One-year mortality was more strongly related to PRA class I exceeding 50% than that under 50% (0% vs. 16.7%, p=0.007).

Conclusion: Preoperative DSAs and PRAs are related to worse outcomes after lung transplantation. DSAs and PRAs should be considered when selecting lung transplant recipients, and recipients who have preoperative DSAs with high MFI values and high PRA levels should be monitored closely after lung transplantation.

Key Words: Transplantation immunology, lung transplantation, primary graft dysfunction, bronchiolitis obliterans, mortality

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Corresponding author: Song Yee Kim, MD, PhD, Division of Pulmonology, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea.
Tel: 82-2-2228-1940, Fax: 82-2-393-6884, E-mail: dobie@yuhs.ac

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INTRODUCTION

Lung transplantation is an established treatment for patients with end-stage lung disease. The graft of an organ from a living or deceased donor in a recipient causes many immunological reactions, which in many cases results in failure of the allograft within the recipient’s body. Whether grafts are destroyed by direct cytotoxicity mediated by cellular immune components, such as T cells and NK cells, delayed-type hypersensitivity reactions, or antibodies remains a critical question.1 Lung transplantation candidates may develop antibodies directed against human leukocyte antigens (HLA). Sensitization to polymorphic proteins, especially molecules of HLA classes I and II, can occur when a patient is exposed to cells from other individuals owing to pregnancy, transfusion, or transplantation. Immune sensitization before lung transplantation has been shown to be associated with increased alloreactivity and mortality following transplantation.2-4

Allograft rejection is a serious complication following lung transplantation, leading to acute graft failure and, subsequently, chronic lung allograft dysfunction (CLAD).5 Bronchiolitis obliterans syndrome (BOS), the most common phenotype of CLAD, is the leading cause of late mortality and morbidity in lung recipients.5,6 Bronchiolitis obliterans is a small airway disease triggered by an insult to small airway epithelial and subepithelial cells, with the subsequent formation of excessive fibrosis and airway constriction.7 Furthermore, researchers have suggested that there is an immunologic link between CLAD and primary graft dysfunction (PGD) in the immediate post-lung transplant period.8 PGD of the lung is a syndrome of “acute lung injury” that occurs within 72 h of lung transplantation.9 PGD contributes to nearly half of the short-term mortality rate after lung transplantation.10

In our previous study, we reported the prevalence of pre-transplant anti-HLA antibodies and their impact on outcomes based on single center experience.11 However, data on the distribution and impact of panel reactive antibodies (PRA) and donor specific antibodies (DSA) before lung transplantation in Asia, especially multi-center based data, are limited, despite the increasing number of lung transplantsations in the region. The Korean Organ Transplant Registry (KOTRY) was established in 2014 as a service of the Korean Centers for Disease Control, and it began to register cases of lung transplantation.12 It is the first nationwide multi-center registry for cases of lung transplantation in Korea (Supplementary Table 1, only online).13 Patients received induction therapy with high-dose steroid or IL-2 receptor antagonist, followed by standard triple immunosuppressive therapy consisting of the triple combination of calcineurin inhibitors, antiproliferative agents, and low-dose steroid after lung transplantation whenever this therapy was not contraindicated. Pre-transplant immunological results did not affect the choice of immunosuppressant regimen.

MATERIALS AND METHODS

Study design and population

Lung transplantation data from the KOTRY were derived from patients who received lung transplantation at one of five tertiary teaching hospitals (Asan Medical Center, Pusan National University Hospital, Samsung Medical Center, Seoul National University Hospital, and Severance Hospital) in South Korea starting from March 2015. Between March 2015 and December 2017, 112 patients received lung transplantation. Among these patients, one patient who received heart-lung transplantation and eight patients who did not undergo evaluation of their PRA and/or DSA levels were not checked before transplantation were excluded, and finally, 103 patients were included in the study. The follow-up was completed in June 2018.

Clinical settings

Transplantation was performed regardless of the status of DSA because of donor shortage as per a medical urgency-based allocation system in Korea (Supplementary Table 1, only online).13 Patients received induction therapy with high-dose steroid or IL-2 receptor antagonist, followed by standard triple immunosuppressive therapy consisting of the triple combination of calcineurin inhibitors, antiproliferative agents, and low-dose steroid after lung transplantation whenever this therapy was not contraindicated. Pre-transplant immunological results did not affect the choice of immunosuppressant regimen.

Collected data and clinical outcomes

Information about the transplant recipients, donors, transplant operations, and postoperative follow-up results were prospectively collected. Data on recipients, including general demographic information, primary diagnosis, and pre-transplantation status, performance of desensitization protocol, and data on donors, including general demographic information, cause of brain death, and smoking status, were collected. KOTRY also includes data on post-transplantation results, including immediate complications, need for organ support, prevalence of PGD, serial pulmonary function (3, 6, 9, 12, and 24 months after lung transplantation), and outcomes, such as the length of hospital stay, in-hospital and 6-month mortality, function status at discharge, and co-morbidities. The most recent information for each patient was collected at 3, 6, 9, and 12 months after discharge, and then annually thereafter. The follow-up data were collected by the attending physician and stored using a web-based case report form.

Furthermore, all patients included in the study underwent PRA class I and II identification or single antigen assays (One lambda, Inc., West Hills, CA, USA or Gen-Probe Inc., San Diego, CA, USA) before lung transplantation. Anti-HLA antibodies against donor HLA were defined as DSAs. DSAs were quantified based on mean fluorescence intensity (MFI), and the highest MFI value was recorded. The DSAs were classified

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based on MFI as follows: MFI<1000, 1000≤MFI<2000, and >2000.

Clinical outcomes included PGD, BOS, and death within 1 year after transplantation. PGD after lung transplantation represents an injury to the transplanted lung that develops in the first 72 h after the transplantation. The diagnosis and grading of PGD were based on the ratio of arterial oxygen pressure to the inspired oxygen concentration, as well as the presence of infiltration on chest radiographs, according to the International Society for Heart and Lung Transplantation (ISHLT) criteria.14 BOS was identified as a progressive decline in forced expiratory volume in 1 s (FEV₁) after excluding other etiologies. BOS was diagnosed according to the ISHLT criteria. BOS was defined as a >20% decrease in FEV₁ from baseline. A potential BOS stage was defined as a 10–19% decrease in FEV₁ and/or a ≥25% decrease in FEF₂⁵–₇⁵ from baseline.15,16 The development of BOS was evaluated in patients who survived for longer than 9 months.

Statistical analysis
Descriptive statistics are reported as a number with proportions or medians with min-max values. Fisher’s exact test was used to compare categorical variables between two groups. The Mann-Whitney U test was used to compare continuous variables between the two groups. Multivariate logistic regression models with backward variable selection were used to estimate the odds ratios for death within 1 year after transplantation while controlling for age and sex. The Kaplan-Meier method was used to compare survival based on pre-transplant calculated panel-reactive antibody (cPRAs) and DSAs. All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A p value of <0.05 was considered statistically significant.

Ethics statement
Written informed consent is obtained from each patient prior to transplantation. If patients are unable to provide consent due to disease severity, informed consent is obtained from a relative or legal representative. This KOTRY study was reviewed and approved by the Institutional Ethics Committees of each participating organization including the Institutional Review Board of Severance Hospital (IRB no. 4-2018-1187).

RESULTS

Baseline characteristics
The baseline characteristics of the recipients according to the

| Table 1. Characteristics of Recipients With or Without Donor-Specific Antibodies |
|-------------------------------------------------|
| All | Donor-specific antibody | p value |
|----------------------------------|----------------|--------|
| Age (yr) | 58 (25–73) | 58 (25–73) | 55 (44–62) | 0.262 |
| Male | 65 (63.1) | 63 (67.7) | 2 (20) | 0.005 |
| BMI (kg/m²) | 21.2 (12.3–29.0) | 21.3 (12.3–29.0) | 19.8 (14.4–24.8) | 0.612 |
| ABO blood type | A | 41 (39.8) | 38 (40.9) | 3 (30) | 0.017 |
| | B | 25 (24.3) | 25 (26.9) | 0 (0) |
| | AB | 12 (11.7) | 8 (8.6) | 4 (40) |
| | O | 25 (24.3) | 22 (23.7) | 3 (30) |
| Primary diagnosis | COPD | 4 (3.9) | 4 (4.3) | 0 (0) |
| | Idiopathic pulmonary fibrosis | 56 (54.4) | 53 (57.0) | 3 (30) |
| | Idiopathic pulmonary artery hypertension | 1 (1.0) | 1 (1.1) | 0 (0) |
| | Bronchiectasis | 3 (2.9) | 2 (2.2) | 1 (10) |
| | Bronchiolitis obliterans syndrome after HSCT | 10 (9.7) | 10 (10.8) | 0 (0) |
| | Connective tissue disease related ILD | 17 (16.5) | 14 (15.1) | 3 (30) |
| | Lymphangioleiomyomatosis | 2 (1.9) | 2 (2.2) | 0 (0) |
| | Others* | 10 (9.7) | 7 (7.5) | 3 (30) | 0.220 |
| Smoking | Ever smoker | 50 (48.5) | 47 (50.5) | 3 (30) |
| | <20 pack-years | 15 (14.6) | 13 (14.0) | 2 (20) |
| | ≥20 pack-years | 35 (34.9) | 34 (36.5) | 1 (10) |
| | Never smoker | 53 (51.5) | 46 (49.5) | 7 (70) | 0.317 |
| | Bilateral lung transplantation | 99 (95.1) | 90 (95.8) | 9 (90) | 0.340 |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; HSCT, hematopoietic stem cell transplantation; ILD, interstitial lung disease.
Values are presented as the median (min-max) or number of patients (%).
*Acute respiratory distress syndrome, eisemnenger syndrome.
presence of DSAs are shown in Table 1. Ten patients (9.7%) had DSAs before lung transplantation. The median patient age was 58 years (min 25, max 78 years), and 65 recipients (63.1%) were male. The primary diagnosis was idiopathic pulmonary fibrosis in 56 cases (54.4%), chronic obstructive pulmonary disease in four cases (3.9%), idiopathic pulmonary artery hypertension in one case (1.0%), bronchiectasis in three cases (2.9%), BOS after stem cell transplantation in 10 cases (9.7%), interstitial lung disease with connective tissue disease in 17 cases (16.5%), lymphangioleiomyomatosis in two cases (1.9%), and other diseases in 10 cases (9.7%). The proportion of patients who were male or had ABO blood type B was higher in the group of patients who did not have DSAs than in the group of patients with DSAs.

The prevalence of cPRAs and DSAs are shown in Table 2. Among the patients, high levels of class I or II cPRAs (≥50%) were detected in 16 patients (15.5%), low levels of class I and/or II cPRAs (<50%) were detected in 40 patients (38.9%), and cPRAs were not detected in 47 patients (45.6%). In terms of the distribution of MFIs of DSAs, four patients (3.9%) had anti-HLA antibodies with MFI of 1000–2000, and six (5.8%) had an MFI higher than 2000.

The characteristics of 10 patients who had DSAs are shown in Table 3. Among the 10 patients, four patients underwent a desensitization process before lung transplantation. Of these four patients, three died within 1 year after the lung transplantation, and the remaining one patient had grade 3 BOS (patient number 1). Among the six patients who did not undergo desensitization, three patients (patient number 5, 8, and 9) had MFIs higher than 2000, of whom two patients (patient number 5 and 9) survived for over 1 year and did not develop high-grade BOS. Among the four patients (patient number 3, 6, 8, and 10) who died within 1 year, two patients (patient number 3 and 8) died of respiratory failure.

Outcomes
As shown in Table 4, patients were divided into two groups based on PGD grade: grade 0–1, non-high-grade PGD group, and grade ≥2, high-grade PGD. Twenty-two patients (21.4%) developed high-grade PGD. Furthermore, high-grade PGD developed more frequently in patients with DSAs that had MFI values higher than 2000 than in patients with DSAs that had MFI values lower than 2000 (p=0.029). A high cPRAs (≥50%)

### Table 2. Prevalence of Pre-Transplant Panel-Reactive and Donor-Specific Antibodies

| Variable                              | Total | Class I* | Class II† |
|---------------------------------------|-------|----------|-----------|
| Calculated panel-reactive antibody    |       |          |           |
| Not detected                          | 47 (45.6) | 62 (60.2) | 70 (68.0) |
| PRA <50%                              | 40 (38.9) | 34 (33.0) | 24 (23.3) |
| PRA ≥50%                              | 16 (15.5) | 7 (6.8)   | 9 (8.7)   |
| Donor-specific antibody MFI           |       |          |           |
| <1000                                 | 93 (90.3) | 98 (95.1) | 97 (94.2) |
| 1000–2000                             | 4 (3.9)   | 2 (1.9)   | 2 (1.9)   |
| ≥2000                                 | 6 (5.8)   | 3 (2.9)   | 4 (3.9)   |

PRA, panel reactive antibodies; MFI, mean fluorescence intensity. Values are presented as the number of patients (%).
*HLA-A, HLA-B, and HLA-C; †HLA-DQ and HLA-DR.

### Table 3. Characteristics of Patients with Donor-Specific Antibodies with MFI ≥1000

| Pt   | Sex/age (yr) | DSA (MFI) | cPRA (%) | Desensitization | PGD grade | BOS | Death within 1 year after lung transplantation | Cause of death |
|------|--------------|-----------|----------|-----------------|-----------|-----|-----------------------------------------------|----------------|
| 1    | Female/47    | DR12 (2920) | 100      | Yes             | 1         | BOS grade 3 | No                           | -              |
| 2    | Male/52      | A11 (1246) | 0        | No              | 0         | BOS grade 1 | No                           | -              |
| 3    | Female/59    | A2 (3046)  | 6        | Yes             | 2         | N/A*        | Yes                          | Asphyxia       |
| 4    | Female/62    | D07 (1300) | 28       | No              | 0         | N/A*        | N/A†                          | -              |
| 5    | Female/59    | DR14 (3150) | 98       | No              | 3         | No          | No                           | -              |
| 6    | Female/44    | B39 (11037) | 75       | Yes             | 0         | N/A*        | Yes                          | Unknown        |
| 7    | Female/56    | DR52 (1160) | 0        | No              | 0         | No          | No                           | -              |
| 8    | Male/61      | B44 (5026) | 61       | No              | 2         | N/A*        | Yes                          | Respiratory failure |
| 9    | Female/53    | DR4 (7180) | 44       | No              | 3         | BOS grade 0p | No                           | -              |
| 10   | Female/54    | B13 (379)  | 56       | Yes             | 0         | N/A*        | Yes                          | Unknown        |

MFI, mean fluorescence intensity; cPRA, calculated panel-reactive antibody; PGD, primary graft dysfunction; BOS, bronchiolitis obliterans syndrome; N/A, not applicable.
*Could not perform pulmonary function test sufficiently to evaluate BOS; †Was not followed-up up to 1 year.
was not associated with the development of high-grade PGD for both class I and II antibodies.

As shown in Table 5, patients were divided into two groups based on BOS grade: grade 0–0p, non-BOS; and grade ≥1, BOS. Forty-seven patients who survived longer than 9 months after lung transplantation and underwent regular pulmonary function tests were evaluated. Among the 47 patients, the median follow-up time was 27.5 months (min 5.6 months and max 38.6 months), and BOS developed in 10 patients (21.3%). BOS development was not related to cPRA or the MFI of DSAs for both class I and II antibodies.

Forty-seven patients survived for longer than 9 months after lung transplantation and underwent pulmonary function test for chronic lung allograft dysfunction.

DISCUSSION

The major strength of this study was that it was a nationwide study using thoroughly collected data, enhancing our ability to generalize the study results. The KOTRY allowed investigation of the prevalence of PRA and DSA levels in Korean lung transplantation patients prior to lung transplant and how PRA was associated with the development of high-grade PGD for both class I and II antibodies.

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and DSA levels before lung transplantation are related to patient outcomes. A high level of DSAs was related to high-grade PGD, and class I cPRA levels exceeding 50% were related to a higher number of deaths within 1 year after transplantation.

In this nationwide registry, the prevalences of high cPRA (≥50%) (class I, 6.8%; class II, 8.7%; total, 15.5%) and DSA (MFI ≥1000) (class I, 4.8%; class II 5.8%; total 9.7%) levels were comparable to data for Western countries. In a study performed in Belgium, 17% of the patients had MFI for DSAs higher than 500, as detected by the Luminex assay.17 In a study performed in France, 89% of the patients had either anti-HLA class I or II antibodies, and 32% had DSA (MFIs higher than 300), as detected by the Luminex assay.18 Additionally, in a single center study performed in the United States, 8.9% of the patients had DSA with MFIs greater than 1000, as detected by the Luminex assay. There were inconsistencies between the data from Belgium and France and data from the United States and this study; however, these inconsistencies may be attributable to differences in MFI cutoffs. The proportion of patients with a high cPRA (>50%) (class I, 7.9%; class II, 5.3%; total, 11.8%) in our previous single-center study was similar to that in a multi-center study.11

Although a relationship between PGD and DSAs has been previously shown and studies have investigated the association between BOS and anti-HLA antibodies, the relationship between BOS and anti-HLA antibodies is unclear.18-21 BOS and anti-HLA antibodies were not found to be related in this study probably because we were only able to analyze the presence of BOS in only 47 patients, and among them, only 10 had BOS. Further, the follow-up duration was relatively short. A more accurate assessment would be possible if further data of transplant patients are accumulated. Furthermore, PGD has multifactorial causes, and based on previous studies, as well as the results of this study, an immunological response may be one of the mechanisms of PGD.22 Furthermore, PGD is considered a risk factor for CLAD23; therefore, PGD being related to anti-HLA antibodies could imply an immunological link between CLAD and PGD in the immediate post-lung transplantation period.8

The cut-off values for cPRA and DSA MFI in lung transplantation patients differ among studies.18-22 This study used cut-off values of 50% for cPRAs and 1000 and 2000 for DSA MFI. The Stanford pre-lung transplant HLA antibody management protocol recommends intervention if cPRA values are higher than 50%.24 Some labs define DSA MFI >1000 as DSA-positive, while some consider DSA MFI >2000 to be clinically significant DSA-positive.25 Further studies including prospective studies are needed to clarify the cut-off point for lung trans-

| Table 6. Associations for Pre-Transplant Panel-Reactive and Donor-Specific Antibodies with Death Within 1 Year |
|----------------|----------------|
|                    | Survival for more than 1 year (n=48) | Death within 1 year (n=30) | p value |
| Total             |                              |                           |         |
| cPRA              |                              |                           |         |
| Not detected or cPRA <50% | 44 (91.7)            | 22 (73.3)                 | 0.050   |
| cPRA ≥50%         | 4 (8.3)                     | 8 (26.7)                  |         |
| Donor-specific antibody MFI | 0.719                       |                           |         |
| <1000             | 44 (91.7)                   | 26 (86.7)                 |         |
| 1000–2000         | 2 (4.2)                     | 1 (3.3)                   |         |
| ≥2000             | 2 (4.2)                     | 3 (10)                    |         |
| Class I           |                              |                           |         |
| cPRA              |                              |                           |         |
| Not detected or cPRA <50% | 48 (100)                | 25 (83.3)                 | 0.007   |
| cPRA ≥50%         | 0 (0)                       | 5 (16.7)                  |         |
| Donor-specific antibody MFI | 0.053                        |                           |         |
| <1000             | 47 (97.9)                   | 26 (86.7)                 |         |
| 1000–2000         | 1 (2.1)                     | 1 (3.3)                   |         |
| ≥2000             | 0 (0)                       | 3 (10)                    |         |
| Class II          |                              |                           |         |
| cPRA              |                              |                           | >0.999  |
| Not detected or cPRA <50% | 44 (91.7)                | 27 (90)                   |         |
| cPRA ≥50%         | 4 (8.3)                     | 3 (10)                    |         |
| Donor-specific antibody MFI | >0.999                         |                           |         |
| <1000             | 45 (93.8)                   | 29 (96.7)                 |         |
| 1000–2000         | 1 (2.1)                     | 0 (0)                     |         |
| ≥2000             | 2 (4.2)                     | 1 (3.3)                   |         |

cPRA, calculated panel-reactive antibody; MFI, mean fluorescence intensity. Values are presented as the number of patients (%).
plantation patients.

This study showed differences in 1-year mortality between patients with HLA class I and II antibodies. There is growing evidence that class I and II antibodies are associated with clinically different outcomes. In patients undergoing renal transplantation, the presence and level of class II DSAs and its level at the time of transplantation are associated with worse outcomes, while that of class I DSA is not. However, we cannot confirm if our results were different because a different organ was studied or because of other reasons; therefore, further studies in this regard are needed.

In this study, desensitization was performed in only four out of 10 patients with DSA of moderate to high MFIs; however, the prognosis of patients who underwent desensitization was poor. Desensitization for each patient was based on the clinical practice of the individual center rather than the trial protocol. The Toronto Lung Transplant Program developed a protocol for the management of sensitized transplant candidates guiding organ allocation, perioperative desensitization, and maintenance immunotherapy. However, evidence on the efficacy of desensitization in patients undergoing lung transplantation is insufficient. In the study by Snyder, et al., an aggressive multi-modal desensitization protocol that included plasmapheresis, steroids, bortezomib, and rituximab did not significantly reduce the levels of pre-transplant HLA antibodies. Further studies are required to examine the efficacy and indication of desensitization in patients with high levels of cPRAs or DSAs before lung transplantation.

As mentioned earlier, sensitization to HLA class I and II molecules can occur when a patient is exposed to cells from other individuals due to pregnancy, transfusion, or transplantation. This may explain why the prevalence of DSAs was higher in female patients. Furthermore, sensitizing events, such as blood transfusions, which result in the accumulation of pre-transplant antibodies, should be avoided as much as clinically feasible. The majority of patients receive at least three units of red blood cells in the perioperative period. Blood transfusion before lung transplantation is known to be a negative predictive factor and is associated with transfusion-related acute lung injury and transfusion-associated circulatory overload, pneumonia, and Epstein-Barr virus infection.

Our study had some limitations. First, this was a relatively small retrospective study with a short follow-up period. Thus, adjustment for many prognostic factors that could affect survival among lung transplantation patients could not be performed in this study. However, this was the first multi-institutional attempt to evaluate the impact of anti-HLA antibodies in Korean patients using nationwide lung transplantation cohort data. Second, post-transplant DSAs were not routinely checked or included in the analysis. Moreover, restrictive allograft syndrome, a form of CLAD other than BOS, was surveyed but could not be included in this study because only two patients showed a restrictive allograft syndrome phenotype.

Third, donor lungs are allocated to the most urgent cases based on the Korean Network for Organ Sharing urgency status instead of the lung allocation score system, which is the most widely used allocation system in the world.

In conclusion, KOTRY data were used to demonstrate how PRA and DSA levels before lung transplantation are related to outcomes in the Korean population. High levels of DSAs were related to high-grade PGD, and a PRA class I level exceeding 50% was related to 1-year mortality. DSA and PRA levels should be considered in selecting lung transplantation recipients, and recipients who have high preoperative DSA MFIs and PRA should be monitored closely after lung transplantation.

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AUTHOR CONTRIBUTIONS

Conceptualization: Sung Woo Moon and Song Yee Kim. Data curation: all authors. Formal analysis: Sung Woo Moon. Funding acquisition: Song Yee Kim. Investigation: all authors. Methodology: Sung Woo Moon and Song Yee Kim. Project administration: Song Yee Kim. Resources: all authors. Software: all authors. Supervision: Song Yee Kim. Validation: all authors. Visualization: Sung Woo Moon and Song Yee Kim. Writing—original draft: Sung Woo Moon and Song Yee Kim. Writing—review & editing: all authors. Approval of final manuscript: all authors.

ORCID iDs

Sung Woo Moon https://orcid.org/0000-0001-9917-9802
Moo Suk Park https://orcid.org/0000-0003-0829-7015
Jin Gu Lee https://orcid.org/0000-0003-2767-6505
Hyo Chae Paik https://orcid.org/0000-0001-9309-8235
Young Tae Kim https://orcid.org/0000-0001-9066-4881
Hyun Joo Lee https://orcid.org/0000-0002-3092-2167
Samina Park https://orcid.org/0000-0001-9625-2672
Sun Mi Choi https://orcid.org/0000-0002-0742-6065
Do Hyung Kim https://orcid.org/0000-0002-8774-3397
Woo Hyun Cho https://orcid.org/0000-0002-8299-8006
Hye Ju Yeo https://orcid.org/0000-0002-8483-5730
Seung-il Park https://orcid.org/0000-0002-8729-0498
Se Hoon Choi https://orcid.org/0000-0002-9961-9289
Song-Bum Hong https://orcid.org/0000-0003-7273-7695
Tae Sun Shim https://orcid.org/0000-0001-6653-816X
Kyung-Wook Jo https://orcid.org/0000-0002-5949-248X
Kyeongman Jeon https://orcid.org/0000-0002-4822-1772
Byeong-Ho Jeong https://orcid.org/0000-0002-3124-1718
Song Yee Kim https://orcid.org/0000-0001-8627-486X

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