# High-resolution human leukocyte antigen typing and early post-transplant outcomes: more than meets the eye

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Human leukocyte antigen (HLA) compatibility guides organ distribution across different solid organ transplants. However, for lung transplantation (LTx), this proves unmanageable due to the scarcity of available lung allografts and the limited graft ischemic time. This shortcoming has several consequences; studies have shown that HLA antigen mismatches increase the risk of *de novo* donor-specific antibody (DSA) development which leads to an increased risk of chronic lung allograft dysfunction (CLAD) and subsequent mortality after LTx (1-4). Even though complete HLA compatibility for lung transplant recipients is unattainable, avoidance of certain HLA is necessary in specific patient populations (i.e., patients on the lung transplant waiting list who already show pre-transplant anti-HLA antibodies).

In this issue of the *Annals of Translational Medicine*, Zhang *et al.* present data on the value of high-resolution HLA in the perioperative period of lung transplant recipients. The authors conducted high-resolution HLA analysis, along with the routinely conducted low-resolution HLA typing, for 59 lung transplant recipients and their donors, and assessed the association between eplet mismatches and primary graft dysfunction (PGD), acute cellular rejection (ACR) and antibody mediated rejection (AMR) within a perioperative period of 1 month. From their data, the authors conclude (I) that perioperative PGD and ACR are closely related to HLA mismatches, especially eplet and HLA-DQ mismatches, and (II) that complementary detection of eplet mismatches and DSA in lung transplant recipients could be useful to predict the risk of early PGD and acute rejection after LTx.

The data presented by Zhang *et al.* is interesting as most studies on HLA mismatches have focused on long-term outcomes after LTx and the authors are among the first to investigate effects in the perioperative period. Additionally, HLA compatibility is commonly determined via low-resolution typing at the antigen level, while high-resolution typing at the epitope level is now increasingly being used since it has been recognized that antibodies are not formed to entire antigens but to eplets within an epitope (5,6). These eplets are polymorphic 3Å regions on the surface of an HLA antigen that bind to the specificity-determining area of an antibody, with each HLA antigen having a large number of eplets (6). Recognition of foreign/donor HLA eplets as nonself is a predominant driver of alloimmune response after transplantation, via increased immunogenicity and antibody production, resulting in graft injury (7,8).

It is noteworthy that there is a high number of PGD cases in this cohort, given that literature supports PGD incidences of ca. 30% early after transplantation (9), and of the 59 lung transplant recipients included in this study, 55 cases presented PGD; 8 with PGD 1, 15 with PGD 2, and 32 with PGD 3. Cold ischemic time of the graft was

similar, while ICU stay and intubation time was significantly higher in the group with PGD 3 compared to PGD 0–2. Interestingly, time on ECMO was not different between these groups. In contrast, only 1 patient in the cohort developed ACR and only 2 patients were diagnosed with AMR, all these patients showed a high eplet mismatch load.

When looking at the relationship between PGD and HLA mismatches, the severity of PGD increases as the number of mismatches increases. Moreover, when the cohort was divided into two groups according to PGD 0–2 and PGD 3, the number of mismatches was significantly higher in the PGD 3 group. This is indeed interesting and novel, as no other groups have looked into the relation between HLA mismatches and PGD after LTx. However, as the authors address, this relation can be seen—and the difference in number of mismatches is significant—at both the low-resolution (HLA antigen) as the high-resolution (eplet) level. Therefore, the question remains whether high-resolution typing brings added value in this setting and is necessary to predict the risk of early PGD.

Although the results reported by Zhang *et al.* are intriguing, one should recognize the following constraints. First of all, there are several risk factors for PGD that were not considered in their analyses. For example, the primary diagnosis underlying LTx is an important modifier of the risk of developing PGD (9), with sarcoidosis, idiopathic pulmonary arterial hypertension (IPAH) and idiopathic pulmonary fibrosis (IPF) shown to be independent predictors of increased PGD (10,11). As almost 46% of patients in this cohort were diagnosed with some form of interstitial lung disease leading to their LTx, it would be of interest to distinguish how many of these patients had sarcoidosis, IPAH or IPF. Secondly, the authors did not consider that, while the number of eplet mismatches is clearly increased in patients with PGD grade 3, not all mismatches are similarly immunogenic, i.e., have the same ability to elicit an immune response, which is determined by factors such as anti-body accessibility, hydrophobicity, and electrostatic potential (12-14). Thirdly, drawing firm conclusions from individual patient data is difficult, especially with small numbers such as only one occurrence of ACR. The authors do emphasize that the results are preliminary and indeed, further investigation is warranted with confirmation in large cohorts. Lastly, considering the increased costs and perhaps time associated with prospective—not only high-resolution, but also regular low-resolution—HLA matching, implementing this into routine clinical practice will be difficult.

Despite these imperfections, this study further underlines the important role for eplet mismatches within the post-LTx setting given that PGD significantly decreases overall graft survival and is associated with the development of CLAD (15-18). Recent studies by Walton *et al.* also demonstrated that HLA class II eplet mismatches could predict the formation of *de novo* DSA after LTx and that eplet HLA matching could protect against CLAD development (2,19). Therefore, it would be interesting to follow this specific cohort and analyze the long-term results, specifically looking at the development of DSA, (chronic) AMR and CLAD.

In summary, Zhang *et al.* report that PGD is closely related to HLA mismatches, especially eplet and HLA-DQ mismatches, and applied high-resolution HLA typing to an interesting new setting by investigating its value in the perioperative period after LTx. Although implementing prospective (high-resolution) HLA matching into routine clinical practice remains problematic given the likely logistic constraints, high-resolution HLA typing could help identify patients who may benefit from tailored immunosuppression regimens and increased post-transplant monitoring.

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## 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.

## References


1. Yamada Y, Langner T, Inci I, et al. Impact of human leukocyte antigen mismatch on lung transplant outcome. Interact Cardiovasc Thorac Surg 2018;26:859-64.
2. Walton DC, Cantwell L, Hiho S, et al. HLA class II eplet mismatch predicts de novo DSA formation post lung transplant. Transpl Immunol 2018;51:73-5.
3. Hayes D Jr, Black SM, Tobias JD, et al. Influence of human leukocyte antigen mismatching on bronchiolitis obliterans syndrome in lung transplantation. J Heart Lung Transplant 2016;35:186-94.
4. Verleden SE, Vanaudenaerde BM, Emonds MP, et al. Donor-specific and -nonspecific HLA antibodies and outcome post lung transplantation. Eur Respir J 2017. doi: 10.1183/13993003.01248-2017.
5. Duquesnoy RJ. A structurally based approach to determine HLA compatibility at the humoral immune level. Hum Immunol 2006;67:847-62.
6. Duquesnoy RJ. HLA epitope based matching for transplantation. Transpl Immunol 2014;31:1-6.
7. Loupy A, Lefaucheur C. Antibody-mediated rejection of solid-organ allografts. N Engl J Med 2018;379:1150-60.
8. McCaughan JA, Tinckam KJ. Donor specific HLA antibodies & allograft injury: mechanisms, methods of detection, manifestations and management. Transpl Int 2018;31:1059-70.
9. Diamond JM, Arcasoy S, Kennedy CC, et al. Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: epidemiology, risk factors, and outcomes-a 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2017;36:1104-13.
10. Diamond JM, Lee JC, Kawut SM, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. Am J Respir Crit Care Med 2013;187:527-34.
11. Liu Y, Liu Y, Su L, et al. Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. PLoS One 2014;9:e92773.
12. Lucas DP, Leffell MS, Zachary AA. Differences in immunogenicity of HLA antigens and the impact of cross-reactivity on the humoral response. Transplantation 2015;99:77-85.
13. Kosmoliaptsis V, Bradley JA, Sharples LD, et al. Predicting the immunogenicity of human leukocyte antigen class I alloantigens using structural epitope analysis determined by HLAMatchmaker. Transplantation 2008;85:1817-25.
14. Kosmoliaptsis V, Chaudhry AN, Sharples LD, et al. Predicting HLA class I alloantigen immunogenicity from the number and physiochemical properties of amino acid polymorphisms. Transplantation 2009;88:791-8.
15. Christie JD, Kotloff RM, Ahya VN, et al. The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med 2005;171:1312-6.
16. Burton CM, Iversen M, Milman N, et al. Outcome of lung transplanted patients with primary graft dysfunction. Eur J Cardiothorac Surg 2007;31:75-82.
17. Whitson BA, Prekker ME, Herrington CS, et al. Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant 2007;26:1004-11.
18. Huang HJ, Yusen RD, Meyers BF, et al. Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant 2008;8:2454-62.
19. Walton DC, Hiho SJ, Cantwell LS, et al. HLA matching at the eplet level protects against chronic lung allograft dysfunction. Am J Transplant 2016;16:2695-703.


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