Editorial

Beating the odds: long-term survival after lung transplantation

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In a recent issue of *Journal of Thoracic Disease*, Miggins and colleagues report recipient and donor factors identified in the United Network for Organ Sharing (UNOS) database that are associated with long-term survival beyond 20 years of lung transplant conditional to one-year survival (1). Specifically, these authors analyzed data on over 6,000 patients and found younger recipient age, female-to-female gender matching, minimal human leukocyte antigen (HLA) mismatch, waitlist time >1 year, donor cause of death: head trauma, and bilateral lung transplant as independent predictors for 20-year survival. On the contrary, a pre-transplant diagnosis of chronic obstructive pulmonary disease/emphysema in the recipient, recipient blood groups O & AB, decreased glomerular filtration rate (GFR) in the recipient and donor, and donor smoking history were associated with a decreased likelihood of 20-year survival.

The identification and prevention of donor- and recipient-related predisposing factors to chronic lung allograft dysfunction (CLAD) are critical to the attainment of improved long-term survival outcomes in lung transplant recipients. Interestingly, there was no association between recipient body mass index (BMI), donor-recipient size matching and long-term survival which contradicts findings from recent International Society for Heart and Lung Transplantation (ISHLT) reports on recipient and donor characteristics (2,3). In these studies, increasing BMI and donor-recipient size mismatch were associated with decreased survival; undersized lungs were associated with a decreased survival for all end-stage lung disease diagnoses except interstitial lung disease. Since these reports examined 5-year survival outcomes, it is likely these variables have a transient impact on survival and fail to impact multi-decade survival outcomes.

Concurrent with prior reports, a long-term survival benefit was observed with bilateral (BLTs) over single lung transplants (SLTs) (2,4). Compared to SLT recipients, those who underwent BLTs were 30% less likely to suffer mortality within 20 years of their transplant. BLTs have been found to decrease the risk of acute cellular rejection, bronchiolitis obliterans (a predominant manifestation of CLAD), and improve long-term survival for lung transplant recipients (4). The relatively increased utilization of BLT over the last decade is likely reflective of this survival benefit.

Female patients undergoing lung transplantation demonstrate relatively improved survival outcomes (2). In the current analysis, female donor-recipient gender matching was notably associated with an increased likelihood of 20-year survival. The same trend was not observed with male donor-recipient gender matching. If gender matching alone was the driver of this survival benefit, the same trend would be expected with all allografts from gender-matched donors. It is unclear what biologic and immunologic characteristics in women confer this survival advantage. While it is plausible that the Y-chromosome derived antigens elicit an antibody response that compromises long-term allograft function with male-female donor-recipient gender mismatching, there are

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certainly more questions to be answered.

Although, not examined in the current analysis, outcomes of donor-recipient racial matching is an area of interest in thoracic organ transplantation. Using UNOS data, Allen *et al.* reported superior short-term survival outcomes among racially matched donor-recipient pairs undergoing lung and heart transplantation (5). These findings highlight the need for focused investigation into relevant gender- and racial-based hormonal, biologic and immunologic factors that may influence long-term survival outcomes of lung transplant recipients. Identifying these characteristics could create potential avenues for intervention that would help mitigate the existing challenge in the long-term survivorship of lung transplant patients.

Beyond gender matching, this paper highlights the potential benefits of more closely matching donors and recipients based on their HLA. Unfortunately, matching on several donor-recipient characteristics including HLA has not been feasible in the face of a limited donor pool. Potential solutions to the existing shortage in the donor pool are the increased utilization of extended criteria donors (ECD) and *ex-vivo* lung perfusion (EVLP) in carefully selected patients, while increasing public awareness surrounding organ donation (6). Recent studies have described comparable short- and medium-term survival with ECD and EVLP as compared to standard protocol lung transplantation (7,8). It is left to be seen how these grafts will compare to standard protocol grafts in terms of multi-decade survival outcomes. Notably, this study found no association between advanced donor age on 20-year survival after lung transplantation, which augurs well in view of the limited donor organ pool.

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Footnote

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