Editorial

# Time is ticking: the role of time after primary transplant and functional impairment on survival after redo lung transplant

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Lung transplantation (LTx) is a life-prolonging therapy for select patients with end-stage lung disease. Nonetheless, posttransplant outcomes are marred by unacceptably high rates of allograft failure, particularly compared to transplantation of other solid organs. In some candidates, lung re-transplantation is an option for definitive treatment of allograft failure, albeit with worse morbidity and mortality relative to the primary operation. Extensive efforts have been invested toward defining the factors associated with poorer outcomes after redo LTx. The importance of patients' preoperative functional status on posttransplant outcomes has attracted generous attention in recent solid organ transplant literature. Specifically, the Karnofsky Performance Status (KPS) scale, designed to determine cancer patients' ability to tolerate chemotherapy, has been repurposed to define the functional impairment (status) of transplant recipients. Multiple studies have shown its predictive value for outcomes after both primary and redo LTx (1,2). Aggarwal and colleagues (3) addressed a potential utility for preoperative functional status when analyzed against patients' time between primary and redo LTx. Namely, when redo LTx recipients are categorized by both variables, it reveals two distinct "phenotypes" of patients with dichotomous clinical and prognostic outcomes.

These authors present a retrospective review of the Scientific Registry of Transplant Recipients, including 739 patients with a recorded functional status who underwent redo LTx from 2005 to 2019. Patients were organized into 3 groups according to preoperative KPS scale: those requiring no assistance (80–100%), some assistance (50–70%), or total assistance (10–40%). Most patients (64%) required total assistance before redo LTx, which was associated with the highest mean lung allocation score (LAS) (66.6) and highest need for pre-redo LTx mechanical ventilation (40.6%), extracorporeal membrane oxygenation (17.3%) as a bridge to redo LTx, and pre-redo LTx intensive care management (53.2%). Of the redo LTx procedures completed within the first year after the primary transplant, 81.3% were performed on patients requiring total assistance. Survival of patients transplanted within one year of their primary transplant was significantly worse compared to that of patients who underwent redo LTx beyond the first year.

The authors subsequently contrasted the cause of primary allograft failure necessitating redo LTx between these patient subsets (i.e., redo LTx at 0–1 *vs.* >1 posttransplant years). Primary non-function and acute rejection were leading causes of primary allograft failure in patients re-transplanted within one year, while chronic rejection was the leading cause in the latter group. Altogether, the results

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from this study define a clear relationship: lower pre-redo LTx functional status and earlier interval between primary and redo LTx correlate with worse post-redo LTx survival; additionally, such patients were more likely to be sicker (higher LAS) and require redo LTx as a consequence of primary graft dysfunction or acute rejection. Taken together, the findings beg the question, is redo LTx less appropriate for patients with early allograft failure and poor functional status when there is a marked difference in prognosis compared to patients re-transplanted for chronic rejection who trended toward less functional impairment and a longer interval between primary and redo LTx? The answer, certainly nuanced, carries a heavy weight, especially from an ethical perspective.

Centers performing redo LTx typically have their own criteria for listing patients for re-transplant. The decision remains multifactorial and ultimately considers details such as the cause for allograft failure, comorbid disease, psychosocial factors, and two variables of dynamic relevance—patient age and functional status. In the modern era, many LTx candidates are transplanted at increasingly older ages with greater frailty, comparatively. Although traditionally, numerical age thresholds have served as relative and absolute contraindications to primary LTx based on consensus statements from the International Society for Heart and Lung Transplantation (4), these recommendations are actively being reconsidered (5) in lieu of an aging transplant waiting list as well as practice changes observed in a majority of larger centers, particularly over the last decade. We recently reported our experience in transplanting patients over 70 years of age, finding comparable long-term survival with patients older than 65 years (6). Studies reporting the safety and feasibility of LTx in the elderly seem to warrant a more "holistic" evaluation of patients' "biological" age, emphasizing overall physical and cognitive fitness. Frailty, often manifested by weakness, lower physical capabilities, and greater functional need, is now a well-recognized and meaningful way to qualify the cumulative sum of age-associated dysfunction and its influence on outcomes after transplant (7). Frailty is independently associated with prolonged hospital stays, de-listing from the transplant waitlist, and poorer posttransplant survival (8). Clearly, measuring patients' frailty is valuable for determining suitability for transplant candidacy, while also lending opportunity to optimize the patient in preparation for a potentially lengthy postoperative period. Currently, there is no standardized method to measure frailty among all transplant centers, but in our opinion, lower functional status provides evidence for worse physical frailty.

Our higher volume transplant center routinely evaluates and transplants sick and otherwise high-risk LTx candidates. A review of our transplant database yielded a total of 25 redo LTx procedures performed within the last 5 years. These patients had a mean LAS of 58.5 and mean KPS score of 53.2%. The mortality rate was 48% at the time of writing, with most deaths occurring within 2 years of the redo LTx procedure, similar to the present study. Despite extensive physical rehabilitation after redo LTx, many of our patients were readmitted frequently for post-operative pulmonary complications. Morbidity remains high in our series, evidenced by prolonged intensive care management, need for early tracheostomy, and development of critical illness myopathy. We have previously detailed our center's transplant experience with patients requiring inpatient evaluation secondary to rapid deterioration (9). These patients trended toward having the highest LAS, the lowest functional status at listing, a more complicated perioperative course, higher morbidity within the first posttransplant year, and higher cost of care. Although typically underrecognized, appropriate resource utilization deserves proper attention when discussing the value of redo LTx in such high acuity candidates likely to require prolonged posttransplant stays.

In our view, aided by the findings from the present study and related experiences shared in the literature (10), redo LTx is a procedure that should be considered in patients who are apt for the challenge. Meaning, when evaluating candidates, it is reasonable to place even more emphasis on patients' functional status and time from primary transplant. These factors, taken together, seem to discriminate between candidates that may or may not receive maximal benefit, measured by disease-oriented outcome measures, from a second transplant operation.

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