cleavage from γ-secretase. Inhibiting MMP-1 (matrix metalloproteinase 1) and ADAM10 using a small-molecule inhibitor in an *in vitro* lung fibrosis assay decreased expression of α-smooth muscle actin, and this may be relevant because α-smooth muscle actin may contribute by further inducing contractile mechanical forces. ADAM10 and ADAM17 have a wide array of cell surface substrates, and *in vivo* effects of their inhibition require further study.

In summary, Wasnick and colleagues' findings support a role for Notch1 signaling in the reduced capacity for AEC2 regeneration and deficient surfactant production. Sustained broad Notch inhibition has been explored as a treatment for cancer, and its tolerability is limited primarily by gastrointestinal side effects (14). It remains to be seen whether the use of Notch1 inhibitors through an inhalational route of administration may be more effective and better tolerated or whether Notch1 signaling can be blocked *in vivo* by downstream inhibition of the Jak (Janus kinase)–Stat (signal transducer and activator of transcription) pathway, as suggested by Wasnick and colleagues (1), or by upstream modulation of HDAC6 (histone deacetylase 6) (15). ■

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Comparing the Incomparable: Identifying Common Themes Across a Diverse Landscape to Address Equity in Lung Allocation

Solid organ allocation policy in the United States has evolved significantly in the past two decades. Since the U.S. Department of Health and Human Services' issuance of its final rule in March 2000, priority has been placed on severity of illness of the transplant recipient, while limiting the impact of geographic location of the organ donor in the allocation algorithm (1). The lung allocation score (LAS) was developed to transition lung allocation away from accrued wait time toward a system that maximizes transplantation benefit. The LAS has met some of its stated goals, with reduction in wait list deaths and increases in transplantation rates (2).

Although the LAS has improved the efficiency of lung allocation, its impact has differed in specific candidate cohorts. The original modeling used for the development of the LAS demonstrated that patients with idiopathic pulmonary fibrosis (IPF) had the highest risk of wait list mortality and a substantially lower risk of post-transplantation mortality than patients with other diagnoses (3),

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leading to the prioritization of allocation for patients with IPF. The impact of the LAS on patients with pulmonary arterial hypertension (PAH) has been less dramatic. Studies have consistently shown a decrease in wait list mortality for patients with PAH under the LAS system (4, 5), but rates of transplantation still lagged behind those among patients with other diseases under the original LAS (5). In 2015, the Organ Procurement and Transplantation Network introduced modifications to the LAS, incorporating additional variables more reflective of disease progression in patients with PAH (6).

In this issue of the *Journal*, Kolaitis and colleagues (pp. 300–311) examine data from the Organ Procurement and Transplantation Network to determine the impact of these modifications (7). The authors compare the incidence of wait list mortality, rates of transplantation, and one-year post-transplantation survival in the pre- and postmodification eras for the overall study cohort as well as stratified by candidate disease type. They determine that patients with PAH experience the greatest increase in LAS and reduction in wait list mortality of all candidate cohorts in the amended system. They also observe the greatest increase in likelihood of transplantation in patients with PAH among all cohorts. However, patients with chronic obstructive pulmonary disease still experience a lower risk of wait list death and patients with cystic fibrosis trend toward a lower risk of wait list death in the postmodification era compared with those with PAH, whereas the likelihood of transplantation remains higher for patients with cystic fibrosis and IPF than for those with PAH. These findings lead the authors to conclude that postmodification allocation policy remains inequitable, unfairly placing patients with PAH at a comparative disadvantage in the allocation schema.

Addressing the issue of equity across lung transplantation candidate cohorts remains difficult, and the conclusions reached by the authors of this analysis highlight the ongoing challenges of prioritizing organ allocation. As with the original design of the LAS, the modifications to the system achieve their stated goals, with a decrease in wait list mortality and an increase in transplantation rates across the entire cohort, as well as specifically for patients with PAH, to whom many of the allocation changes are targeted. In this study, patients with PAH have a risk of wait list death similar to that of patients with IPF, the group initially given highest priority in the algorithm, after the 2015 modifications.

However, as the authors point out, patients with PAH still do not achieve substantial priority on the wait list until they experience significant clinical decline. Unfortunately, this circumstance is also experienced by the remainder of the diagnostic cohorts, for whom the development of group 3 pulmonary hypertension, significant supplemental oxygen requirements, and/or the need for mechanical circulatory support produce the most substantive changes to the LAS. The focus on affecting candidates with the highest urgency has prioritized transplantation for patients experiencing acute exacerbation or decompensation. LASs have thus not unexpectedly been increasing for wait list candidates over time (8), with substantive implications on outcomes. Liu and colleagues demonstrated that recipients with higher LASs experienced increased post-transplantation mortality rates (9), and Tsuang and colleagues showed that an acute change in LAS of 5 points or greater was associated with a significant decrease in post-transplantation survival (10).

In this context, the authors emphasize in their analysis the late survival benefit that patients with PAH still experience, which is perhaps poorly emphasized in the assessment of net benefit of transplantation for patients with PAH. This point highlights the higher weighted impact of wait list mortality compared with post-transplantation outcomes in the current LAS system, as well as the focus on one-year survival as opposed to later-term survival assessment in lung allocation criteria.

Moreover, the authors identify regional differences as an important modifier of allocation for patients with PAH. The impact of regional characteristics such as the size of the waiting list, number of transplantation programs, and donor catchment area, as well as favored surgical procedure, can substantially affect wait times for lung transplantation candidates (11), and with the increasing acuity of lung transplant recipients, comfort with travel distance to donor facilities and mechanical circulatory support (12) are additional factors that can affect the likelihood of transplantation. The nearly uniform need to perform bilateral lung transplantation in patients with PAH exacerbates donor limitations for this cohort, magnifying the obstacles to transplantation for these candidates.

The authors also focus on the unique predictors of illness severity in PAH compared with other disease processes, underscoring the difficulties of developing an allocation process intended for patients with a wide variety of disease states with unique markers of severity (13). Thus, in emphasizing the limitations of organ allocation in patients with PAH, the authors bring to light substantial areas of opportunity in lung allocation policy more generally.

The upcoming transition to the continuous distribution allocation model (14), as noted by the authors, will attempt to address some of these opportunities for change, and we can look forward to a reassessment of equity in the allocation experience for patients with PAH as well as other diseases in the framework of this new model. ■

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Improved Survival for Patients with Systemic Sclerosis–associated Pulmonary Arterial Hypertension: For Real?

Previous studies in patients with systemic sclerosis (SSc) demonstrated that prognosis is substantially less favorable among patients who develop pulmonary arterial hypertension (PAH) compared with those without PAH (1). Indeed, screening programs for early detection of SSc–PAH are well established and now adapted into international expert consensus guidelines on the management of PAH (2). Importantly, patients with SSc may develop PAH at any time during the course of the disease and thus should undergo screening annually. Furthermore, the coexistence of interstitial lung disease and pulmonary hypertension (PH) is a particularly high-risk phenotype and is associated with a less favorable prognosis (3).

Over the past several decades, multiple therapeutic options have improved the prognosis of patients with PAH. The availability of standardized risk stratification methods has played a pivotal role and supported treatment decisions to improve survival of patients with PAH. Upfront combination therapy is strongly recommended on the basis of the results of the AMBITION (A Study of First-Line Ambrisentan and Tadalafil Combination Therapy in Subjects with Pulmonary Arterial Hypertension) and GRIPHON (Selexipag [ACT-293987] in Pulmonary Arterial Hypertension) studies in patients with PAH with low and intermediate risk scores (2). However, the implications of these therapies on outcomes of SSc–PAH remain unresolved. In the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) registry, for example, data focusing on patients with SSc–PAH suggest that adverse outcomes are elevated in this subgroup compared with patients with idiopathic PAH and PAH associated with connective tissue diseases (CTDs) other than SSc, despite pulmonary vasodilator therapy implementation (4). In turn, longitudinal data from a French registry suggest that survival in patients with SSc–PAH, overall, remains unchanged despite the availability of PAH therapy, although outcomes in patients <70 years old may have improved incrementally (5), whereas Khanna and colleagues reported improved survival of patients with SSc–PAH after reviewing data from various PH registries (6). The performance of the screening and treatment strategies among patients with SSc thus gains importance.

Hassan and colleagues (pp. 312–322) report in this issue of the *Journal* on the clinical, hemodynamic, and outcome profile associated with changes in mortality among patients with SSc–PAH evaluated at Johns Hopkins University (7). In this single-center retrospective analysis, two cohorts were evaluated: cohort A included patients diagnosed between October 1999 and September 2010, and cohort B included patients diagnosed between October 2010 and September 2021. To determine if outcome trends were different between these two cohorts, the investigators compared transplantation-free survival using time from initial diagnosis of PH. Furthermore, clinical and hemodynamic changes and possible parameters promoting any observed difference between cohorts were also assessed. Patients with similar clinical and hemodynamic characteristics were compared in terms of outcomes to avoid lead-time bias.

Among 628 patients with SSc screened, 504 had PH, with a mean pulmonary arterial pressure ⩾25 mm Hg. PAH was diagnosed in 246 patients in cohort A and 258 patients in cohort B. The 1-, 3-, and 5-year transplantation-free survival rates were 85%, 62%, and 37%, respectively, in cohort A with median survival of ∼4 years after diagnosis of PAH and 91%, 74%, and 60%, respectively, in cohort B with median survival after PAH diagnosis of ∼8 years. Furthermore, cohort B patients were *screened at an earlier stage* before becoming disabled, were more often characterized by *low risk stratification scores*, and were more often treated with *upfront combination therapy* compared with patients in cohort A. In contrast, survival, hemodynamic parameters, and functional status among patients with PH due to heart or lung disease (i.e., World Symposia on Pulmonary Hypertension groups 2 and 3, respectively, as opposed PAH) did not improve.

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