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"Who'll be the next in line?" The lung allocation score in patients with pulmonary arterial hypertension

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There was a time when the cartoon shown reflected the only hope of survival for patients with pulmonary arterial hypertension (PAH); even worse, the lines were long (Figure 1). This is no longer the case due to the development of multiple drugs over the last few decades; patients with PAH are living longer and have a better quality of life. In fact, because of these therapies, many patients have been removed from transplant lists, have had transplant evaluation deferred, or have not been offered transplant referral. However, the need for transplant still exists and may actually increase as the number of surviving PAH patients increases, disease awareness expands, survival rates improve, and lung transplant for patients $>$ 60 years of age gains acceptance. Thus, this seems a propitious time to evaluate the current transplant status of PAH patients. Using the article by Gomberg-Maitland et al in this issue,[1] as well as 3 other recent studies addressing similar topics,[2–4] we evaluate several aspects of lung transplant and the lung allocation score (LAS):

1. Does the current LAS accurately predict waitlist survival for PAH patients?
2. Does the current LAS effectively discriminate between those PAH patients who are most in need of transplant and those who can wait?
3. Has the current LAS improved outcome of PAH patients?

Does the current LAS score accurately predict waitlist survival for PAH patients?

Based on currently available data, especially studies by Gomberg-Maitland et al[1] and Benza et al,[2] the unequivocal answer is a resounding YES. Average survival for the cohort of PAH patients on the waitlist for lung transplant can be predicted with a very high level of accuracy.

Gomberg-Maitland et al and Benza et al examined waitlisted and "waitlistable" cohorts and compared expected survival based on the LAS formula to the Kaplan–Meier estimates. Without stratification, considering only the entire aggregate population, the LAS formula appears to be quite accurate. In contrast, a formula based only on cardiopulmonary hemodynamics at diagnosis did not accurately predict survival for the waitlisted cohort. It is critical to note, however, that the validity of a model depends on both calibration and discrimination. As such, it is possible for a model to be well calibrated (accurate on average) without being effective in discriminating between high- and low-risk patients. This potential deficiency in the model leads to the second question.

Does the current LAS effectively discriminate between those PAH patients most in need of transplant and those who can wait?

Based on currently available data, the unequivocal answer to this question is a resounding NO. If so, why is this the case? Patients with PAH are an unusual group—they appear much healthier on the outside (by appearance) than they are in the inside. As such, they are often assumed to be reasonably healthy, when in fact they are not. This has been demonstrated by the delay in receiving aggressive or advanced therapies when they are in fact deteriorating, with gaps in clinic visits under such conditions.[5] Thus, referral for transplant in PAH patients is often deferred until they are very ill (on the inside). Furthermore, the LAS does not include many of the factors known to portend a poor outcome for PAH patients. Thus, LAS appropriately designates those who fall into the middle of the group, but it does a very poor job of identifying those most ill.

The poor discrimination of the LAS waitlist model in PAH patients is demonstrated by the receiving operator characteristic (ROC) analyses by Gomberg-Maitland et al[1] and subgroup analyses by Benza et al.[2] It also likely influenced the relatively narrow range of LAS scores in PAH demonstrated by Chen et al.[3] Unfortunately, due to the

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Scuse Me Buddy, Is this the bread line or the lung transplant wait list?

Figure 1

absence of variables critical for PAH risk prediction in the data set used by Schaffer et al,[4] there was no opportunity to assess discrimination. The net effect of the good calibration and weak discrimination is that the cohort as a whole is appropriately placed in the middle of the line, but they are not spread out in a way such that the most deserving patients can move far enough up the line to actually receive a transplant. A proposal has been put forth to add some of the variables associated with higher risk (mean right arterial pressure and 6-minute walk distance); however, these are not yet part of the LAS equations, except for a cut-point for 6-minute walk distance (6MWD) that is so low that it applies to only very few patients.

Has the current LAS improved the outcome of PAH patients?

Based on currently available data, the unequivocal answer to this question is a resounding MAYBE, but not to the degree we would expect or that should be considered satisfactory. First, there is a marked difference in the PAH population pre- and post-LAS. Nowadays, patients are not referred for transplant unless they have had a poor response to currently available therapies, including systemic prostanoids. Lack of improvement with systemic prostanoids or the inability to use or tolerate them is, in itself, a poor prognostic sign[5]; thus, patients now referred for lung transplant evaluation are invariably FC IIIb or FC IV, have a poor outcome, and tend to have a biased LAS, because those factors that equate with poor prognosis, as noted previously, are not inclusive.

The mean 6MWD data in the study by Gomberg-Maitland et al[1] and the number of FC IV patients in the study by Schaffer et al[4] demonstrate that the post-2006 PAH waitlist cohort is much sicker than the pre-2006 PAH cohort. Gomberg-Maitland et al[1] also indicated that the current cohort includes more high-risk PAH patients; furthermore, these patients are often omitted from other analyses even though they are an increasing portion of the at-risk cohort. It is therefore not surprising that the sicker post-2006 cohort has a higher mortality.[1,3] Nevertheless, this conflicts with results for adjusted mortality described by Schaffer et al,[4] who described improved cumulative mortality in the propensity-matched analysis and neutral model-adjusted mortality in the Cox model. On balance, the shift in mortality post-LAS for those who remain on the transplant waitlist has been neutral at best.

The data that least match the other data include the findings by Schaffer et al,[4] suggesting that cumulative mortality may have declined; however, these analyses point to the importance of considering competing risk models. In a competing risk model, patients are assigned a zero-chance of waitlist mortality once they are transplanted. Without taking into account competing risks, they are censored and effectively assumed to have comparable outcomes to patients who continue to be followed. This explains some of the key differences between the conclusions by Gomberg-Maitland et al[1] and Schaffer et al,[4] but it also raises the philosophical question of which model is most appropriate for which question. Assessing risk to allow statistical discrimination between individual patients may require different statistical tools than the methods needed when assessing the effect of an intervention, such as introduction of the LAS, on a population.

It is clear that development of the LAS has been, by and large, positive. It provides an excellent framework with which to move forward. However, to be more relevant and inclusive to the PAH cohort, changes need to be instituted. Currently, the very sickest PAH patients are not as likely to receive transplants because their risk is underestimated, whereas the healthier PAH patients may be slightly more likely to receive a transplant than would be warranted by a strictly accurate risk assessment. Patients in the middle are often stuck there because the factors that shift their true risk do not translate to changes in score with sufficient urgency or

accuracy for them to be viable transplant candidates. Also, of extreme importance, it has become apparent that PAH patients often deteriorate very quickly[5]; thus, it is often very difficult to find the "sweet spot" for transplant, especially when the LAS lacks the critical markers of deterioration.

Differences between databases and possible data quality issues in these critically important databases are a concern raised by Gomberg-Maitland et al.[1] Given the total cost of a typical transplant, one wonders if the amount being spent on data quality is far too little. All 4 studies we have described in this commentary used very advanced statistical methods. Missing data problems can be overcome to some degree, but more important data quality issues, such as duplicate listings, can lead to bias in ways that are often hard to predict and overcome.

Thus, although we have clearly advanced the status of PAH patients in the "transplant line," we still have a ways to go to put them on equal footing with patients being considered for transplant due to other lung diseases. PAH patients deserve the same shot at the "loaf of bread" as anyone else waiting in line.

Disclosure statement

The authors have no conflicts of interest to disclose.

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