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Evaluation of the lung allocation score in highly urgent and urgent lung transplant candidates in Eurotransplant

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BACKGROUND: The purpose of the study was to investigate the impact of the lung allocation score (LAS) on mortality among highly urgent (HU) and urgent (U) lung transplant (LTx) candidates in Eurotransplant (ET) and to identify useful additional parameters (LAS*plus*).

METHODS: All adult LTx candidates for whom a first request for HU or U status was made in 2008 in ET were included ($N = 317$). Patients were followed until LTx, death on the waiting list (WL), delisting, or closure date (i.e., January 10, 2010). The relationship between the LAS/LAS*plus* and waiting list, post-transplant, and overall mortality was assessed with a multivariate regression model. The LAS and LAS*plus* were decomposed into their basic waitlist and post-transplant components.

RESULTS: Waiting list mortality rate was 22% and 1-year post-transplant mortality rate was 34%. The waitlist component of the LAS*plus* was significantly associated with waiting list mortality (hazard ratio [HR] 1.91, $p = 0.021$), whereas the LAS was not ($p = 0.063$). The post-transplant components of both scores were significantly associated with 1-year post-transplant mortality (LAS: HR 2.69, $p = 0.005$; LAS*plus:* HR 2.55, $p = 0.004$). Both scores strongly predicted overall mortality (LAS: HR 1.65, $p = 0.008$; LAS*plus:* HR 1.72, $p = 0.005$).

CONCLUSION: LAS accurately predicts overall mortality in critically ill transplant candidates and should therefore be considered as the basis for a new lung allocation policy in ET. An adjustment of the original LAS may be indicated to accurately predict waiting list mortality.

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Because lung transplantation has become a generally accepted treatment option for patients with end-stage lung disease, the donor pool is inadequate to provide treatment for all candidates. As a result, 14.3% of the patients registered in Eurotransplant (ET) in the year 2008 died without receiving a lung transplant within their first year on the lung waiting list.[1] Designing and achieving a fair and just allocation policy is hence a necessary, albeit challenging endeavor.

The current lung allocation policy in ET is ruled by urgency and waiting time. Urgent patients are classified as either urgent (U) or highly urgent (HU). Both U and HU patients are hospitalized and too ill to be discharged before transplantation; the HU classified patients should have been admitted to an intensive care unit (ICU). Patients with HU status are prioritized over U and elective patients; within the same urgency tier (U or HU), the patient with the longest waiting time is the first to get the lung offer.[2]

Similar to the discussions held in the USA, the ET Thoracic Advisory Committee and several national scientific thoracic committees have expressed concern about this focus of the lung allocation policy on urgency and waiting time. A more objective system is needed that would still prioritize the sickest patients without jeopardizing long-term results.[3,4]

Since May 2005, lung transplant candidates in the USA who are ≥12 years of age are ranked according to a score, called the lung allocation score (LAS).[5] This LAS is composed out of "waitlist" and "post-transplant" components,

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both predicting survival, with the difference reflecting the transplant benefit.

The LAS has some major limitations that hamper its unmodified future use in ET. First, the database on which the LAS was built is more than 10 years old and may therefore not reflect the current state-of-the-art in lung transplantation. This is especially important for diseases with dynamic changes in disease progression and recent therapeutic advances, such as pulmonary arterial hypertension (PAH). Second, allocation by waiting time only in the USA prior to the implementation of the LAS in 2005, has led to a pre-selection of waiting list candidates.[6] Finally, data on candidates with extremely high waiting list mortality (e.g., ventilated patients) is sparse in the LAS database.[7] In contrast, in ET, with its urgency-tier system, ventilated patients were transplanted successfully during the past 15 years and its proportion is >10% in some centers.[8,9] With these restrictions in mind a new benefit score based on the LAS was proposed, called the LAS*plus*.

The aim of this study was to investigate in a subset of critically ill transplant candidates whether an allocation scheme based on LAS/LAS*plus* might be a viable alternative to the current urgency-tier system for allocating lungs in ET.

Methods

Study population

All lung-only transplant candidates, aged >14 years, for whom a first HU or U request was submitted to Eurotransplant in the period January 1, 2008, until December 31, 2008, were included. All patients were followed up from time of request until transplantation, death on the waiting list or closure date (January 10, 2010), whichever came first.

Definitions

General and disease-specific criteria for HU and U status have been agreed upon by all seven countries that participate in ET.[1] In general, patients in both groups must be hospitalized before transplantation, while HU patients must be admitted to the ICU. Actual assignment of the HU and U status is performed by a team of three independent transplant experts, who decide by majority vote, with guidance by the HU/U criteria, whether a patient can be upgraded and/or can remain in his current urgency tier. Transplant centers can submit HU and U requests by fax to ET on any listed candidates. The information contained in these HU/U request forms was used as data source for calculating the scores. Missing data were replaced with the normal physiologic value.

LAS and LAS*plus*

LAS was calculated according to the published literature.[10] Based on clinical expertise and literature an adapted lung allocation score (LAS*plus*) was designed. In contrast to the original LAS, detailed information on ventilation settings, extracorporeal support and comorbidity were integrated into this scoring system (Table 1). The LAS*plus* encompassed the following additional items: mean pulmonary artery pressure (PAPm); systolic right ventricular pressure (RVPsys); current pneumothorax with drainage; recent hemoptysis with bronchial artery embolization; extracorporeal support; end-saturation in the 6-minute walk test (6-MWT); bilirubin; non-invasive ventilation (NIV); intravenous (IV) prostanoids; and coagulopathy.

Similar to the LAS, the raw score is the difference between the factors predicting waiting list and transplant mortality, whereas LAS*plus* is obtained by recalibrating the raw score as follows: LAS*plus* = 100 × ((raw score + 120)/180).

Statistics

Both scores were decomposed into their two original sub-scores: that is, the waitlist and the post-transplant components (Table 2). To have a complete 1-year follow-up, the post-transplant cohort was restricted to transplants performed prior to January 10, 2009 (N = 277).

The relationships between the LAS and LAS*plus* components and the actual waitlist and post-transplant mortality as well as the association between the LAS and LAS*plus* and overall mortality were analyzed in separate Cox regression models.

Waiting list time was counted from the date of the first HU or U request. Patients were classified into a high or low waitlist component group, where the median values of these raw sub-scores were used as cut-off values (319 for LAS, 8 for LAS*plus*). The probability of waiting list mortality within 1 year after HU/U request was calculated for patients with a high and low waitlist component and then subjected to Wald's test.[11]

To study the transplant components of the LAS/LAS*plus*, patients were again classified into a high vs low transplant component group; cut-off values for the raw sub-scores were 302 for LAS and 1 for LAS*plus*. The estimates of 1-year post-transplant survival rates for all groups were calculated using Kaplan–Meier curves and assessed by log-rank test.

Overall mortality refers to the probability of dying pre- or post-transplant, from the time of the first HU/U request until the study evaluation time-point. The association between the LAS and LAS*plus* high vs low score (dichotomized at the medians of 35 and 71, respectively) and the overall mortality was tested in a Cox model.

Transplant effect was defined as the comparative mortality risk after listing and after transplantation. The effect of the LTx on the risk of dying was assessed by using a time-dependent Cox regression model.[12] The effect of transplantation in the LAS and LAS*plus* high vs low score group was tested by incorporating an interaction factor between the factors "LTx" and the score.

Results

Study cohort

For a total of 361 patients, a request for a first HU or U lung transplant status was submitted to Eurotransplant in the year 2008 (Figure 1). Patients listed for a combined heart and lung transplant (N = 32) and children <15 years of age (N = 9) were excluded, yielding a study cohort of 317 transplant candidates. Of these, 70 (22%) died while waiting for a lung to become available, 232 (73%) received their lung allograft, 4 (1.3%) were delisted (with all 4 still alive at time of evaluation), and 11 (3.5%) patients were still waiting for a transplant. Notably, 18% of the candidates were ventilated and 7% were on extracorporeal support