Lung Transplantation in Germany Since the Introduction of the Lung Allocation Score

A Retrospective Analysis

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SUMMARY

Background: The allocation of donor lungs for transplantation in Germany was changed on 10 December 2011 to a system based on the Lung Allocation Score (LAS). The aim of the present study is to determine whether this change has prolonged the survival of patients on the transplant waiting list and of those who have undergone lung transplantation (Ltx).

Method: We retrospectively compared data from the three-year periods before and after the change to an LAS-based allocation system (2009–2011 vs. 2012–2014).

Results: The number of patients on the active waiting list declined from 606 on 12/31/2011 to 432 on 12/31/2014, a 29% decrease. The number of patients who died while on the waiting list fell from 306 in 2009–2011 to 226 in 2012–2014 (−26%, p = 0.04). Waiting-list mortality declined across all disease groups. Meanwhile, the number of lung transplantation procedures per year increased by 21% over the period of observation, from 865 to 1045. During the period in which the LAS was used, the proportion of transplant recipients with restrictive lung disease (46% vs. 31%; p<0.001) surpassed the proportion of those with a diagnosis of obstructive lung disease (33% vs. 40%; p = 0.003). The percentage of transplantations in patients treated with mechanical ventilation or extracorporeal respiratory support before transplantation rose from 9% to 13%. The one-year survival rate after lung transplantation was 76% in 2009–2011 and 81% in 2012–2014.

Conclusion: The introduction of the LAS in Germany was associated with a decrease in the number of patients on the waiting list, and also in the number of deaths among patients on the waiting list. The distribution of primary diagnoses among transplant recipients shifted away from obstructive and toward restrictive lung diseases. In the future, additional parameters of patients on the waiting list should be considered to enable further improvement of the allocation model.


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cases) and to increased survival after lung transplantation (reflecting a shift toward those patients who benefit most from transplantation).

**Method**

We retrospectively analyzed the nationwide (German) data of Eurotransplant from the three-year periods before and after the introduction of the LAS.

**Study population**

All lung transplant candidates in Germany who were registered with Eurotransplant (ET) in the years 2009 to 2014 were included in the study. All lung transplantation procedures performed during this 6-year period were included in the analysis as well, and the survival status of the recipients was tracked until the end of 2015. The three-year periods 2009–2011 and 2012–2014 were compared. Even though the LAS was in fact introduced three weeks before the end of 2011 (on 10 December 2011), full-year periods were chosen in order to facilitate comparisons with the waiting-list and donor data of other Eurotransplant member countries. Heart-lung transplantations were excluded from the analysis because these were allocated according to the rules for heart transplantation.

**Diagnoses**

The patients were classified into 4 categories depending on their underlying disease: category A, obstructive airway diseases (e.g., chronic obstructive pulmonary disease [COPD]); category B, diseases of the pulmonary circulation (e.g., idiopathic pulmonary arterial hypertension); category C, suppurative lung diseases (e.g., cystic fibrosis [CF]); and category D, restrictive lung diseases (e.g., pulmonary fibrosis).

**Allocation scheme**

Before the LAS was introduced, donor lungs were allocated within the group of potential recipients of the appropriate body size and blood group in consideration of urgency above all, and then in consideration of the time already spent on the waiting list. The degree of urgency was classified as elective (T), urgent (U), or highly urgent (HU). Patients classified as not transplantable (NT) were not offered organ transplantation; only hospitalized patients were eligible for U or HU status. On discharge from the hospital, U and HU patients automatically reverted to status T. Assignments of U and HU status were made at Eurotransplant by three independent experts, after confirmation according to predefined criteria, upon the request of the transplant centers. In contrast, from 10 December 2011 onward, whenever more than one potential recipient of a suitable body size and blood group was available, donor lungs were allocated according to the LAS.

The LAS was calculated by Eurotransplant according to the guidelines of the German Medical Association (6), as described in the eBox. The LAS ranges from 0 to 100, with higher scores indicating higher urgency and greater likelihood of benefit.

**Statistics**

A retrospective explorative analysis was performed without null hypotheses or multiple testing. The demographic data relating to donors, recipients, and transplants were displayed as overall numbers and percentages or, for metric variables, as medians with 25% and 75% quartiles. Category variables were compared with the χ² test, continuous variables with the Mann–Whitney U test. Survival rates after lung transplantation (LTx) were plotted by the Kaplan–Meier method and compared with the log-rank test.
Results

Number of patients on the waiting list

The number of LTx candidates newly entering the waiting list remained unchanged in the three years before introduction of the LAS and the three years thereafter (1389 and 1350, respectively). The percentage of patients admitted to the waiting list because of restrictive lung diseases was higher after the LAS was introduced: 548 (41%) vs. 450 (32%), p<0.001.

The number of active transplant candidates on the waiting list, i.e., those with a status other than NT at any given time, fell from 606 at the end of 2011 to 432 at the end of 2014; at these same times, the number of patients with status NT was 247 and 248, respectively. The median LAS of the active waiting-list cohort was 34 on 1 December 2014 (25% and 75% quartiles: 31 and 36), and the 90th percentile was 40. 2.6% of patients had LAS scores of 50 or above on 1 December 2014.

In 2009–2011, a total of 1271 patients left the waiting list: 865 of them received transplants (68%), 306 died while waiting for a transplant (24%), and the remainder were taken off the list (8%). In 2012–2014, a total of 1454 patients left the waiting list: 1045 received transplants (72%), 226 died (16%), and 170 were removed from the waiting list for other reasons (12%).

The hazard ratio for death within three years of entry to the waiting list, in a comparison of the period after the introduction of the LAS to the period before it, was 0.65.

Ninety-eight (32%) of the patients who died while on the waiting list in the period 2009–2011 were in status U or HU when they died, and 126 were in status NT (56%). Classified by category over the two periods, the number of patients in category D (mainly pulmonary fibrosis) who died while on the waiting list fell from 99 to 78; the number of deaths on the waiting list in category C (mainly cystic fibrosis) fell from 59 to 28, that in category B (pulmonary hypertension) fell from 33 to 21, and that in category A (typically COPD) fell from 106 to 98 (Figure 1).

Transplantations

865 lung transplants were performed in the 3 years before the introduction of the LAS (2009–2011), and 1045 in the 3 years after it (2012–2014): there was thus an increase of 20.8%. The overall number of organ donors fell by 29.5% in the second of these two periods, but the number of lung donors increased (Table).

After the introduction of the LAS, the percentage of patients in category D rose from 31% to 46%, while the percentage in category A fell from 40% to 33%, and the percentages in categories B and C remained roughly constant (from 5% to 4%, and from 19% to 17%, respectively) (Figure 2). The number of transplant recipients with alpha-1-antitrypsin deficiency fell from 53 (5.0%) before the introduction of the LAS to 19 (1.7%) afterward. Among all patients in category D, the number who had idiopathic pulmonary fibrosis (IPF) was 149 (17.2%) before the introduction of the LAS and 284 (27.2%) afterward. The number of patients with other interstitial lung diseases rose from 102 to 123, but the percentage remained constant (11.8% both before and after). The number of retransplants rose from 11 (1.3%) to 46 (4.4%), and the number of recipients with sarcoidosis rose from...
In 2009–2011, 127 transplant recipients received their transplants while in status U, and 468 while in status HU (combined percentage, 68.7%). The introduction of the LAS was associated with a decrease of the median waiting time for a transplant from 199 days to 84 days (p<0.001). 28% of transplant recipients in 2012–2014 had an LAS score of 50 or above; the median LAS score among transplant recipients was 41.

Patients being treated with mechanical respiratory support
The Eurotransplant data contained detailed information on mechanical respiratory support techniques, such as artificial ventilation and extracorporeal membrane oxygenation (ECMO), only from 2011 onward. The percentage of patients receiving mechanical support before transplantation increased from 9% (27/300) in 2011 to 13% (134/1045) in the three years after the introduction of the LAS (p = 0.072). The percentage of patients receiving extracorporeal respiratory support among all those receiving mechanical support rose from 67% (18/27) to 87% (117/134) (p = 0.008). In 2011–2014, the 1-year survival of transplant recipients receiving mechanical support was 56%, compared to 80% in those not receiving mechanical support (p<0.001). The percentage of patients receiving mechanical support among patients who died on the waiting list rose from 21% (22/107) in 2011 to 27% (62/227) in 2012–2014 (p = 0.184).

Pediatric patients
In a comparison of the 3-year periods before and after the introduction of the LAS (2009–2011 vs. 2012–2014), the number of transplants among children under the age of 12 rose from 4 to 12, while that of transplants among adolescents aged 12 to 17 fell from 24 to 21.

Rescue allocation
The percentage of transplantation procedures that were performed after rescue allocation was 27.9% in 2009–2011, before introduction of the LAS, and 36.5% in the three years afterward. Of the 343 organs transplanted in 2014 after the introduction of the “extended allocation” method (eBox), 199 (58%) were allocated primarily by LAS, 42 (12%) by extended allocation, and 102 (30%) by another accelerated allocation method. In both time periods (before and after the introduction of the LAS), 57% of the beneficiaries of rescue allocation were in category A. Patients whose transplants had been allocated primarily by LAS had higher LAS scores (median 46.9; 25% and 75% quartiles 39.6 and 63.2; p<0.001) than the beneficiaries of extended allocation (36.3; 33.5 and 41.5) or other steps in rescue allocation (34.2; 32.6 and 37.7).

Applications for an exceptional Lung Allocation Score
Applications for an exceptional Lung Allocation Score (eLAS) were made on behalf of 54 patients in 2012–2014 (5% of the total number of transplants). One-third (n = 18) of these applications were for patients in category B, and another one-third (n = 18) for patients in category C. One-third (n = 18) of the applications were approved, although 56% of the exceptional LAS scores granted were lower than the ones originally requested.

Survival after lung transplantation
The rate of 1-year survival after lung transplantation was higher in 2012–2014 than in 2009–2011, even though more critically ill patients received transplants (Figure 3). Among patients in category A, the 1-year survival rates before and after the introduction of the LAS were 79.4% and 85.8% (p = 0.022). There were
fewer patients (only 90) in category B, in which a fall in the 1-year survival rate was observed (from 83% to 73%) but was not significant (p = 0.257); an apparent rise in 1-year survival among patients in category C (from 82.6% to 87.3%) was not significant either (p = 0.221). Among patients in category D, the introduction of the LAS was associated with a significant rise in 1-year survival from 67.4% to 78.3% (p = 0.001).

Discussion

In the first three years after the introduction of the Lung Allocation Score in Germany, the mortality of transplant candidates on the waiting list for lung transplantation decreased by one-quarter. Patients with obstructive airway diseases received transplants less often, and those with restrictive lung diseases received transplants more often (this was mainly true of patients with idiopathic pulmonary fibrosis). Survival after lung transplantation was also somewhat better after the introduction of the LAS.

Since the initial implementation of the LAS in the USA in May 2005, many reports have been published concerning its effects on the patients on the waiting list, transplantation activity, and the outcomes of transplantation (7–13). The positive American experience encouraged the decision-makers in Germany to replace the previous system of allocation by waiting time and urgency of transplantation with a system based on the LAS, which they did in 2011. In the USA as in Germany, the volume of transplantation was higher after the LAS was introduced, and fewer patients died in both countries while waiting for a transplant each year (13).

In Germany, before the introduction of the LAS, more than two-thirds of patients had either status U or status HU, with the result that, in effect, transplants were allocated by waiting time alone among the large group of patients whose status was urgent. A similar situation obtained in the USA; in both countries, this fact accounts for the decline in mortality after the introduction of the LAS. In Germany, where the maximal distances are shorter, nationwide allocation became possible once the LAS was introduced, while allocation in the USA remained local even under the LAS-based system. It has been found that 53% of the lungs transplanted in the USA were allocated locally (within one of 58 defined local areas), while, for each local allocation, there were at least 6 potential recipients with higher LAS scores in the wider surrounding region (of which 11 were defined, covering the whole country) (14). The relatively stronger reduction of mortality on the waiting list in Germany, as compared to the USA, after the introduction of the LAS can be accounted...
for by the German system of nationwide allocation. The median LAS of transplant recipients in Germany is somewhat higher than in the USA (41 vs. 40) (15). This difference may also be attributable to the primarily regional allocation of lung transplants in the USA (14).

Despite these basic differences, another common trend was seen in Germany and the USA after the introduction of the LAS, namely toward more frequent lung transplantation in patients with restrictive lung diseases (12) and in critically ill recipients (9, 10, 16). In Germany, the median age of lung-transplant recipients rose by 2 years in the 3 years after the introduction of the LAS. In the USA, patients over age 65 are the most rapidly growing group of transplant recipients (12).

The declining numbers of new entries of patients onto the waiting list and the declining percentage of patients in category B among transplant recipients (most recently only about 5%), are both due to improvements in medical treatment (1). There was an earlier report of increased mortality on the waiting list among candidates with pulmonary hypertension (7), but an updated analysis of a larger cohort showed the opposite (11), as do the German data. Category B was the only one in which survival after lung transplantation was worse after the introduction of the LAS than before. This may reflect the increased use of extracorporeal techniques.

Over the period of observation, there has been an increase in the percentage of patients treated with mechanical ventilation and/or extracorporeal techniques. Most of this increase is accounted for by the extracorporeal techniques—a trend that has been observed in the USA as well (17). These patients have a poorer chance of survival after lung transplantation, but the LAS gives them preferential access to transplantation because of the more highly weighted consideration of the urgency of treatment. The outcomes of transplantation in patients receiving extracorporeal support in Germany seem to be markedly worse than in the USA. More than twice as many patients in this group received lung transplants in Germany (13% vs. 6.4%) (18).

The increasing use of rescue allocation methods and the rise of the median donor age from 46 to 50 after the introduction of the LAS are due to the extended criteria for donor lungs in the transplantation centers and are the main factors that account for the increasing numbers of transplant procedures carried out over the period of observation. In our view, this development is not related to the introduction of the LAS as such. The increasing number of donors from outside the country can also be explained by the expansion of donor criteria during the period after the introduction of the LAS.

The LAS has been in longer use in the USA than in Germany, and accordingly far more patients have been treated in the USA than in Germany since the introduction of the LAS. The opportunity to develop the LAS further (“LAS plus”[19]) will depend largely on the degree of reliability with which the transplantation centers record the additional patient-related parameters of the candidates on the waiting list.

### Overview

The implementation of the LAS-based allocation system in Germany has led to a decrease in mortality on the waiting list and to more transparency in the process of organ allocation. Survival after lung transplantation has improved. In the future, further patient-related parameters (e.g., cardiac index, bilirubin concentration, exacerbations) should be registered by the transplantation centers and analyzed so that the model can be optimized. There should also be improved quality assurance of the data that are recorded.

### Conflict of interest statement

Prof. Witt has received reimbursement of meeting participation fees and travel expenses from Astellas GmbH and research support (third-party funding) from Novartis. The other authors state that they have no conflict of interest.

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**Supplementary material**
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**CLINICAL SNAPSHOT**

**A Young Man With Dyspnea**

A 37-year-old man presented to the emergency room complaining of dyspnea of increasing severity over the last few days. He related having suffered a bout of acute pancreatitis a few months previously, probably due to high alcohol consumption; as far as he knew, he had no other illnesses. Ultrasonography revealed a large, anechoic left pleural effusion, in apparent continuity with a cyst-like fluid collection in the abdomen. Computerized tomography of the chest and abdomen revealed a pancreatic pseudocyst measuring 30 × 11 cm and a large accompanying left-sided pleural effusion, with atelectasis of the upper and lower lobes. No connection between the pseudocyst and the effusion was evident. There was no laboratory evidence of recurrent pancreatitis (the lipase and c-reactive protein [CRP] values were in the normal range). As the patient had no other known illnesses, a sympathetic pleural effusion in the aftermath of acute pancreatitis was diagnosed. The patient’s dyspnea rapidly improved after a chest tube was inserted and 2.5 liters of fluid were drained out of the left hemithorax. The pancreatic pseudocyst was drained as well, under ultrasonographic guidance, yielding a further 3 liters of fluid. The patient was asymptomatic on discharge from the hospital eight days after admission.

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**Calculation of the Lung Allocation Score (LAS)**

The American LAS model of 1 January 2010 is used. The LAS is a composite of 17 variables (see below), which are given different weightings to estimate both the patient's likely survival time on the waiting list and the patient's likely survival time after lung transplantation. The complete computational model and an illustrative computation are given in the guideline (6). In Germany, unlike in the USA, there is no overarching regional allocation system. The LAS must be calculated for patients of other Eurotransplant (ET) member countries as well, in order to enable organ exchange across national borders. An LAS of 50 or above is called “high.” According to the Eurotransplant rules, lungs are first offered to patients with a high LAS in another ET member country that has a negative organ trade balance with respect to the country of the donor.

The LAS ranges from 0 to 100. Candidate recipients under age 12 are automatically given an LAS of 100. The LAS model has not been validated for this age group.

The LAS is calculated on the basis of the following parameters (6):

- Date of birth
- Height (cm)
- Weight (kg)
- Diagnosis of lung disease
- Functional status (without support, mild support, full support)
- Diabetes status (unknown, insulin-dependent, no diabetes, non-insulin-dependent)
- Mechanical ventilation (none, continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], continuous invasive, intermittent invasive)
- Oxygen treatment (none, at rest, only at night, only under stress)
- Oxygen requirement at rest (L/min or %)
- Forced vital capacity (% of norm)
- Systolic pulmonary arterial pressure (mmHg)
- Mean pulmonary arterial pressure (mmHg)
- Mean pulmonary capillary closing pressure (mmHg)
- Current carbon dioxide partial pressure (mmHg or kPa)
- Rise in carbon dioxide partial pressure (%) in relation to maximal carbon dioxide partial pressure (mmHg or kPa) and minimal carbon dioxide partial pressure (mmHg or kPa)
- 6-minute walking test (m)
- Current creatinine concentration (µmol/L or mg/dL).

The centers are required to update each patient's LAS every three months if the last LAS was below 50. For patients with an LAS of 50 or above, the LAS must be updated every 14 days. The LAS can be calculated on the Eurotransplant website (www.eurotransplant.org/cms/index.php?page=las_calculator).

In cases where donor lungs cannot be allocated according to the standard procedure (e.g., if the offer of an organ has already been declined by three or more different centers, or in case of impending organ loss because the donor is medically unstable), a provision has been made for a rescue allocation procedure, by which the organ in question can be offered to multiple transplantation centers in a short period of time. The candidates for transplantation via rescue allocation are determined by decision of the transplantation centers themselves. Since December 2013, “extended allocation” has been the first step in the rescue allocation procedure in cases where standard allocation is not successful. In the extended allocation procedure, multiple centers in the region of the coordinating center of the donor organ are allowed to name suitable candidates. Eurotransplant then offers the organ to the candidate with the highest LAS.
Exceptional cases

If, in the opinion of a transplantation center, a patient’s calculated LAS does not accurately reflect the urgency of transplantation and the likelihood of successful transplantation in the individual case, the center can apply for an exceptional LAS (eLAS). This is recommended, in particular, for transplant candidates in diagnosis category B (pulmonary hypertension) who would need a combined transplant (not including heart-lung transplantation), and for candidates with very rare diseases that are not well reflected in the LAS scheme. For patients on the transplant waiting list who are dependent on extracorporeal support (e.g., extracorporeal membrane oxygenation, ECMO), a rule has been introduced whereby the LAS is calculated on the basis of the last blood-gas values, ventilation status, and oxygen requirement just before installation of the support system. The presence of an extracorporeal support system is not itself taken as an LAS parameter. This rule prevents “pseudonormalization” of the LAS by extracorporeal systems. From 10 December 2011 onward, all lung-transplant candidates under age 12 have automatically been assigned an LAS of 100, and priority within the group of such patients has been assigned on the basis of waiting time. Organs from adolescent (age 12–18) and child donors (age under 12 years) are first allocated to recipients in these age groups. Children and adolescents can also receive organs from adult donors.