Simulated waiting list prioritization for equitable allocation of donor lungs.


Journal of Heart and Lung Transplantation 2002; 21:797-803
Abstract:

Abstract:

**Background:** In lung transplantation (LTx), allocation of donor lungs is usually based on blood group, height and waiting time. Long waiting times favour patients with a slowly progressive end-stage lung disease and make the current allocation system subject of discussion. In order to try to equalize the chances for transplantation for every patient, irrespective of the diagnosis, we investigated the effect of diagnosis-dependent prioritization on the waiting list, using a simulation model.

**Methods:** For the main disease categories on the waiting list, relative risks of dying on the waiting list were calculated using the empirical data from the Dutch LTx program gathered over a period of 10 years. In a microsimulation model of the Dutch LTx program based on data from the real situation, patients with diagnoses associated with a statistically significant increased risk to die on the waiting list were prioritized by multiplying the waiting time on the waiting list with the relative risk.

**Results:** Relative risks of death on the waiting list were significantly increased in patients with cystic fibrosis, primary pulmonary hypertension and pulmonary fibrosis. Prioritization resulted in an increased chance of transplantation for the prioritized diagnoses and a decreased chance for the non-prioritized diagnoses. The distribution of diagnoses after LTx was almost equal to the distribution of diagnoses on the waiting list.

**Conclusion:** The simulated method of prioritization on the waiting list is a step forward to a more equitable allocation of donor lungs. Moreover, this method is clinically feasible, as long as the waiting list is frequently updated.
Introduction:

Long waiting lists for lung transplantation (LTx), caused by shortage of donor lungs, make equitable allocation of donor lungs subject of discussion. Usually, allocation of donor lungs is based on blood group, height and waiting time. However, the main types of end-stage lung diseases show considerable differences in the rate of disease progression. As a result of the long waiting lists, the chance to be transplanted depends on whether the patient has a slowly or a rapidly progressive disease.

This study was part of a cost-effectiveness study of the Dutch LTx program. The purpose of this specific part of the study was to create a situation, in which the distribution of diagnoses on the waiting list equals the distribution of diagnoses after lung transplantation. One possibility to improve the chance to be transplanted for the rapidly progressive diseases is a correction of the waiting time with a fixed number of days. Patients with an underlying disease that generally follows a rapidly progressive course are given a headstart on the waiting list. For instance, the United Network of Organ Sharing (UNOS) gives a priority of 90 days to patients with pulmonary fibrosis. Another possibility is to create a diagnosis-dependent correction factor for the waiting time. For patients with a rapidly progressive disease the waiting time will be artificially prolonged by multiplying it by a correction factor. These patients will rise faster on the waiting list than patients with a more favourable diagnosis.

It is ethically inadmissible to implement a new method in clinical practice without knowledge about the effects of such an implementation. Changes in waiting list policy may have great consequences with respect to the patients on the waiting list. Therefore, a simulation model is necessary to assess the effects of a system for prioritization in advance.

The aim of this study was to simulate the effect on the number of transplantations per diagnosis of a diagnosis-dependent prioritization method aimed at a more equitable, clinically feasible allocation system of donor organs.

Methods:

Patients/ actual program:

The lung transplantation program of the University Hospital Groningen is divided into different phases. The numbers of patients in the various phases of the program for the period July 1, 1990-April 1, 1999 are given in a flowchart in figure 1. After passing the final screening, patients were registered on the waiting list. Candidates for LTx were patients with irreversible, progressively disabling end-stage pulmonary disease whose life expectancy was considered to be maximally 12 to 18 months. Contraindications for LTx included evident and irreversible other vital organ involvement, active extrapulmonary infection, severe effects of systemic corticosteroids, ventilator-dependent respiratory failure, non-compliance with medical treatment, addiction to alcohol, drugs or tobacco and prior major surgery. Overweight or malnourishment, if severe and incorrectable, were also contraindications.

Patients were delisted when they were transplanted, when they died on the waiting list or were rejected because of a newly occurring serious contraindication for transplantation. For all patients length of stay in all phases was registered. During the study period a total of 610 patients were referred to the program. After the inpatient screening 274 patients were put on the waiting list. From these 274 patients, 122 patients were transplanted, 16 patients were rejected because of serious contraindications, 78 patients died on the waiting list and 58 patients were still in the waiting list phase at the end of the study period.
Description of the simulation model:
A microsimulation model of the Dutch lung transplantation program was used. Characteristics of actual patients and donors were analysed and randomly assigned to simulated patients and donors, in modules of the model called the patient generator and the donor generator. Subsequently, patient histories were simulated based on data collected from actual patients.

The model was set to simulate a period of 15 years of constant inflow of donors and patients. The length of the simulation period was chosen to make sure that a steady state in the program is reached in which the numbers of patients in the phases before transplantation are stable.

Patient generator:
The patient generator simulates individual patients. Over the entire 15-year period of the simulation, 65 new patients were entered in the model each year, corresponding to the mean of the last 5 years in our actual program. Based on the overall distribution of characteristics in
the empirical data of patients from the LTx program, every simulated patient was assigned a value for age, underlying diagnosis, height, and blood group as described below.

- **Age**: The age in the simulation was determined with the formula:
  \[
  \text{Age} = \text{Mean age} \pm (\text{random factor} \times \text{standard deviation})
  \]
  With this formula the calculated ages randomly fluctuate around the mean age with the shape of a Z-distribution.

- **Underlying diagnosis**: The distribution of the diagnoses is based on the respective proportions in the actual population listed for LTx. The value of a randomly generated proportion for each simulated patient determined the diagnosis in the model.

- **Height**: The height was determined the same way as age, using the actual mean height as the center of the distribution.

- **Blood group**: The distribution of blood groups was based on empirical data and determined in the same way as the diagnosis.

- **Starting time in the program**: within the year of inflow, a random day was determined.

- **Type of transplantation**: For all diagnostic categories the empirical data on the percentages for bilateral, unilateral left or unilateral right transplantation were applied to the simulated patients. However, the type of transplantation was not taken into account in any further procedures in the simulation model.

**Donor generator:**

Donor characteristics were blood group, height, and date of availability of (a) donor lung(s). The distribution of characteristics was also based on empirical data of donors from our LTx program. The number of available donors in the model was set to 17 each year, again corresponding to the mean of the last 5 years in our program.

- Age and height were determined in a way similar to the methods used in the patient generator.

- **Blood group**: The distribution of blood groups based on empirical data in the general population.

- **Time of availability of the donor**: with the year of inflow, a random day was determined.

**Patient flow simulator:**

The patient flow simulator randomly simulates a course through the transplant program for every simulated patient. For each possible outcome of the phases of the LTx-program, a duration is simulated. The shortest duration determines the outcome. For instance, if for a patient on the waiting list the simulated number of days until transplantation, until rejection and until death is 200 days, 250 days and 300 days, respectively, this patient will be transplanted and enters the next phase of the program.

**Donor matching:**

The results of the patient generator and the donor generator are two lists of simulated persons. A recipient (patient) list sorted by date of placement on the waiting and a donor list sorted by date of availability of the donor. Matching of donor and recipient is based on the ranking order of the patients on the waiting list. Starting at the top of the patient list, a matching patient is sought for each donor. The patients with the longest waiting time are at the top of the list and have the best chance of being matched. For every patient on the waiting list the simulator checks:

- Which patient is on the waiting list at the moment of availability of the donor lung.

- Whether the height of the recipient deviates less than 5% from the donor’s height.
- If the blood group of the recipient is identical to the donor blood group. The first patient fulfilling these criteria proceeds to the transplantation phase and is removed from the waiting list. If none of the patients fulfil the above mentioned criteria, another matching attempt is made with a maximum deviation in height of 8% between donor and recipient.

**Prioritization:**
Based on our own empirical data of 274 patients on the waiting list, Kaplan-Meier survival functions were calculated for the main diagnoses: emphysema, \(\alpha_1\)-antitrypsin-deficiency, primary pulmonary hypertension, secondary pulmonary hypertension, cystic fibrosis, pulmonary fibrosis and bronchiectasies. Rejected patients and transplanted patients were censored in this survival analysis. Cox regression analysis was performed to calculate relative risks of dying on the waiting list for patients with different underlying diseases in comparison with a reference group of emphysema patients. This patient category was chosen as the reference group because of the relatively good survival and the relatively high number of patients on the waiting list, which increases the reliability of the data. For diagnoses with a statistically significant increased risk to die on the waiting list, the relative risk was used as the priority factor.

**Microsimulation model with and without prioritization:**
On the simulated waiting list, patients were ranked according to the date of placement. In order to be able to calculate the influence of the priority factor on the waiting time for every single donor-recipient combination, which depended on the difference between the date of placement of the patient and the date of availability of the donor, a selection of possible recipients was made consisting of only patients who were on the waiting list at the moment of availability of the donor. Subsequently, the waiting time for every recipient could be calculated. First, the simulation model was run without prioritization to show the similarity of the distribution of diagnoses before and after LTx between the model and the actual program. Next, a second simulation was performed with prioritization. Patients with diagnoses with a statistically significant increased risk to die on the waiting list were prioritized. This was done by multiplying the waiting time by the relative risk, after which the waiting list was sorted in the order of prioritized waiting time. Starting at the top of the patient list, a matching patient was sought. For each donor possible recipients were selected and ranked according to the procedure described above.

**Results:**
The actual waiting list survival for the rapidly progressive end-stage respiratory diseases is given in figure 2. The actual waiting list survival for the slowly progressive end-stage respiratory diseases is given in figure 3.
Figure 2: The actual waiting list survival for the rapidly progressive end-stage respiratory diseases.

Figure 3: The actual waiting list survival for the slowly progressive end-stage respiratory diseases.
Chapter 2

The difference in survival on the waiting list between the slowly and rapidly progressive end-stage respiratory diseases was statistically significant (chi-square p<0.04). The relative risks to die on the waiting list for the main end-stage pulmonary diseases compared to the reference group, consisting of patients with emphysema with or without α1 AT-deficiency, are presented in table 1. Diagnoses with a significant increased risk to die on the waiting list compared to the reference group were primary pulmonary hypertension (p=0.002), cystic fibrosis (p=0.0005), and pulmonary fibrosis (p=0.003). For these diagnoses, the relative risks were 3.29, 3.00, and 3.43, respectively. These factors were used for prioritization in the simulation model.

Table 1: The calculated relative risk to die on the waiting list compared to the reference group emphysema/α1-antitrypsin deficiency.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Relative risk death on waiting list</th>
<th>95% confidence interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic Fibrosis versus Emph*/AT**</td>
<td>3.00</td>
<td>1.61 - 5.57</td>
<td>0.0005***</td>
</tr>
<tr>
<td>Primary Pulm. Hypertension versus Emph/AT</td>
<td>3.29</td>
<td>1.53 - 7.02</td>
<td>0.002***</td>
</tr>
<tr>
<td>Secondary Pulm. Hypertension versus Emph/AT</td>
<td>2.03</td>
<td>0.86 - 4.76</td>
<td>0.1044</td>
</tr>
<tr>
<td>Pulmonary fibrosis versus Emph/AT</td>
<td>3.43</td>
<td>1.59 - 7.74</td>
<td>0.0031***</td>
</tr>
<tr>
<td>Bronchiectasies versus Emph/AT</td>
<td>1.67</td>
<td>0.56 - 5.00</td>
<td>0.36</td>
</tr>
<tr>
<td>Other versus Emph/AT</td>
<td>2.81</td>
<td>0.63 - 12.41</td>
<td>0.1737</td>
</tr>
<tr>
<td>Emph versus AT</td>
<td>1.13</td>
<td>0.42 - 3.04</td>
<td>0.8085</td>
</tr>
</tbody>
</table>

* Emph = emphysema **AT= α1-antitrypsin deficiency, *** significant

The distributions of diagnoses in the actual situation (on the waiting list and after transplantation), in the simulated situation without prioritization (on the waiting list and after transplantation) and in the simulated situation with prioritization are given in table 2. For some diagnoses, the actual situation shows large differences between the proportion of patients on the waiting list and the proportion of transplanted patients. For the slowly progressive diseases like α1 AT-deficiency, COPD/emphysema and bronchiectasies the actual proportions after transplantation are higher than on the waiting list. For the rapidly progressive diseases, like cystic fibrosis, primary pulmonary hypertension, and pulmonary fibrosis, on the other hand, the proportions of transplanted patients are lower than on the waiting list. This is also reflected in the simulation without prioritization. The last column of table 2 presents the results of the simulation with prioritization, demonstrating a marked shift in the distribution of diagnoses after transplantation. As a result of prioritization, patients with a rapidly progressive disease have a better chance to become eligible for LTx before they die on the waiting list. For the prioritized diagnoses primary pulmonary hypertension, cystic fibrosis, and pulmonary fibrosis the proportions of transplanted patients were +0.6%, +3.1% and +1.8% higher, respectively, than without prioritization. For the non-prioritized diagnoses α1 AT-deficiency, COPD/emphysema and bronchiectasies, on the other hand, less patients were transplanted. Their respective proportions among the transplanted patients decreased by -2.0%, -3.3% and -0.2%. The proportion of transplanted patients with secondary pulmonary hypertension remained stable.
Table 2: Distribution of diagnoses on the waiting list and after transplantation, with and without prioritization.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Waiting list (%)</th>
<th>After transplantation (%)</th>
<th>After transplantation prioritized (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual situation</td>
<td>simulation model</td>
<td>actual situation</td>
</tr>
<tr>
<td>α1 AT-deficiency</td>
<td>20,9</td>
<td>22,1</td>
<td>29,5</td>
</tr>
<tr>
<td>COPD/Emphysema</td>
<td>17,6</td>
<td>17,2</td>
<td>20,5</td>
</tr>
<tr>
<td>Bronchiectasies</td>
<td>6,2</td>
<td>6,3</td>
<td>9,0</td>
</tr>
<tr>
<td>Primary Pulm. Hypertension</td>
<td>11,4</td>
<td>10,7</td>
<td>9,0</td>
</tr>
<tr>
<td>Secondary Pulm. Hypertension</td>
<td>9,2</td>
<td>9,2</td>
<td>3,3</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>21,6</td>
<td>21,1</td>
<td>17,2</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>11,4</td>
<td>11,6</td>
<td>11,5</td>
</tr>
</tbody>
</table>

The category ‘other’ is not mentioned in this table because in this category no transplantation has been performed.

Discussion:

The results of the present study suggest that a more equitable allocation of donor organs is possible using a diagnosis dependent correction factor on the waiting list. In many centres waiting time plays an important role in the allocation of donor lungs. With increasing waiting times caused by donor organ shortage, this will result in a strong bias in favour of patients who best survive on the waiting list. In the Dutch lung transplantation program mainly the patients with emphysema or α1 AT-deficiency take advantage of the allocation system based on blood group, height and waiting time. In our program, calculated over the period 1990-1999, the proportion of patients with emphysema or α1 AT-deficiency amounted to 49.5% after LTx compared to 38.5% on the waiting list. International figures show the same trend. Although emphysema is debilitating, mortality from this disorder may not be as high as from other indications for lung transplantation. On the other hand, although these patients usually gain a limited survival benefit by LTx, their quality of life increases substantially.

Conversely, patients with rapidly progressive diagnoses like cystic fibrosis, primary pulmonary hypertension and pulmonary fibrosis represent a combined percentage of only 37.7% after transplantation compared to 44.4% on the waiting list. These patients nevertheless have the highest survival benefit by LTx. Because of this imbalance, we explored the possibilities of prioritization of patients with the most life threatening diseases in a simulation model.

Although the simulation model is moulded to reality as much as possible, the model has a distribution of diagnoses on the waiting list and after transplantation (without prioritization) which differs slightly from the actual numbers from the Dutch LTx program. The observed difference between model and reality concerning the diagnoses of transplanted patients has a number of possible explanations. First, the simulated transplantation program spans a greater number of years than the actual program has done so far. Second, the model works with strict algorithms, which cannot account for changes in clinical policy or diagnose-specific changes that determine the chance of transplantation, such as the influence of lung volume reduction surgery for COPD/emphysema and prostacyclin for the treatment of pulmonary hypertension. This may explain the different percentages of patients with pulmonary
hypertension in our actual program and the simulation model, both on the waiting list and after transplantation.

Although a number of criteria are applied to determine whether a patient should be placed on the waiting list, some of these criteria leave room for interpretation. Therefore, one might argue that an allocation system based on waiting time could be manipulated by placing certain patients or patient groups on the waiting list in an earlier phase of the disease. However, although listing patients in an earlier phase will increase the chance of lung transplantation for these patients, the survival gain from transplantation will decrease. From a cost-effectiveness perspective, this is an undesirable development. Moreover, the length of the waiting list will increase, with an inherent number of practical bottlenecks.

In setting criteria for placement on the waiting list, a major problem with the present predictors of mortality is that they seem to take little account of the rate of deterioration in the months up to listing for transplantation. Patients with the same diagnoses have often a quite variable natural history. For instance, patients with idiopathic pulmonary fibrosis may deteriorate and die within just a few months and others may live for many years with an indolent course. The optimal timing to place a patient on the waiting list is therefore very difficult. Although the model has some limitations, a mathematical approach as presented here seems a fair option because in this approach all diagnosis categories fulfil the criteria for placement on the waiting list and have an equal chance for transplantation.

The decision whether a patient is listed for unilateral or bilateral transplant depends on the original lung disease and the presence of recurrent infections. In the simulation model, the type of transplantation was not taken into account because this would not influence the principle and the results of the simulation in the Dutch situation. However, in practice the type of transplantation is of importance and would influence the results if two recipients were transplanted with lungs from one donor.

The operational simulation of waiting list priorities which has been developed showed the desired effect of an increase of the number of transplantations in the prioritized diagnoses and a decrease in the non-prioritized diagnoses. It is possible to extrapolate these effects to the actual situation. Moreover, it is clinically feasible as long as the waiting list is frequently updated.

After implementation of prioritization factors, it is of importance to keep an eye on the distribution of diagnoses both on the waiting list and after transplantation. This distribution could change in time for instance because of new therapies for patients on the waiting list. The proposed simulation model is also applicable to other lung transplantation programs. Therefore, the survival and relative risks on the waiting list for the different diagnosis categories have to be calculated based on their own empirical data have to be calculated and applied to the simulation model.

Although there are also ethical aspects to prioritization, the current situation is unequitable and therefore justifies intervention. Prioritization is aimed at improving the equitable distribution of donor organs, but overcorrection should be avoided.

Within the framework of our cost-effectiveness study, prioritization of diagnoses with a rapid progression also has a positive effect on the cost-effectiveness of lung transplantation. The cost-effectiveness will improve since the survival gain of the patients with prioritized diagnoses is larger than for patients with non-prioritized diagnoses.
Conclusion:
The simulated system of diagnosis dependent prioritization is a clinically feasible method resulting in a more equitable distribution of transplantations for elective patients on the waiting list. Although there are also ethical aspects to prioritization, some intervention in the current situation seems justified.

Acknowledgements: We want to thank the National Steering Group Lung Transplantation for their input in the study.

References:
3. www.eurotransplant.nl
4. www.unos.org Allocation of donor lungs 3.7.8