Assessing survival benefits from lung transplantation

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Summary

Introduction. — Published studies used several methods to assess the impact of lung transplantation on patient survival. To interpret the results of these studies, a basic understanding of the models used and underlying hypotheses is required.

Current knowledge. — The most often used method consists in assessing the survival of waiting-list patients and measuring the impact of lung transplantation on the baseline hazard (instantaneous risk) for death, usually with a Cox proportional hazards model. This strategy involves strong assumptions about the link between the baseline hazard in waiting-list patients and lung transplant recipients. Whether these assumptions are true is extremely difficult to establish. Some studies compared predicted survival without transplantation to observed survival after transplantation. We recently reported a new method in which predicted survival without transplantation is compared to predicted survival after transplantation.

Perspectives. — All the methods described to date evaluate only the impact of transplantation on patient survival. The concomitant use of other markers such as respiratory function or quality of life would produce a more detailed picture of lung transplantation benefits.

Conclusion. — Evaluating the benefits of lung transplantation involves the use of complex statistical methods. The results should be considered with circumspection, and none of the methods described to date allows definitive conclusions.

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Introduction

Lung transplantation is an accepted treatment option in patients with end-stage respiratory failure\textsuperscript{[1]}. The primary goal of lung transplantation is to increase survival. Many studies have evaluated the impact of lung transplantation on the survival of patients treated for a variety of lung diseases. A number of discrepancies exist in the results of these studies. For instance, Liou et al. recently reported that lung transplantation failed to increase survival in the vast majority of children with cystic fibrosis\textsuperscript{[2]}, in contradiction to the results of a study done several years earlier\textsuperscript{[3]}. No randomized controlled trials are available. The only information about the impact of lung transplantation on
patient survival comes from studies based on complex statistical methods, whose interpretation is often unclear to clinicians. The objectives of this article are to describe these methods, to evaluate the underlying assumptions, and to discuss the limitations of each method. It is worth noting that this analysis of statistical methods applies also to other organ transplant procedures and, more generally, to comparisons of major surgical procedures with medical treatments.

The methods used to evaluate potential survival benefits from lung transplantation can be classified into two groups based on whether they compare the risk of death in waiting-list patients and lung transplant recipients or the observed survival in lung transplant recipients to the predicted survival without transplantation.

- No randomized studies of survival with and without lung transplantation are available. Two methods were used to evaluate the potential survival benefits of lung transplantation: either the risk of death was compared in waiting-list patients and transplant recipients or the predicted risk of death without transplantation was compared to the observed risk of death in transplant recipients.

**Methods based on survival in waiting-list patients**

**The naive approach**

Survival of nontransplanted patients counted from the day of inclusion on the transplant waiting list is compared to survival in transplanted patients counted from the day of lung transplantation. This method is biased, because the transplanted patients are not representative of the overall waiting-list population. Instead, they are selected based on their ability to survive until a transplant is available and, therefore, are probably at lower risk for death than the nontransplanted waiting-list patients. The naive approach is no longer used.

**Methods evaluating the impact of lung transplantation on hazard rates (instantaneous risk) for death**

These methods measure the change in the hazard rate (instantaneous risk) for death induced by lung transplantation. The hazard rate is defined in Table 1. In waiting-list patients, the hazard rate changes little over time. After transplantation, the hazard rate is multiplied by a factor known as the hazard ratio (HR), which reflects the effect of transplantation on the risk of death (in either direction). The Cox model [4], which is widely used in survival studies, can incorporate a time-dependent covariate that quantifies the impact of transplantation on the hazard rate of death. Using this model in a study of children with cystic fibrosis, Aurora et al. found that lung transplantation was associated with an HR of 0.31 (95% confidence interval [95%CI], 0.13–0.72) [3]. Thus, according to their model, the risk of death at any point in time after transplantation (i.e., irrespective of time since transplantation) was 69% lower (i.e., multiplied by 0.31) in the transplanted patients than in the patients who were still on the waiting list.

Advantages of the Cox model include simplicity, availability in most of the available statistical software packages, and use in many studies of potential benefits of lung transplantation in a variety of patient populations [2,3,5,6]. In contrast to the above-described naive approach, the Cox model accounts for prognostic differences between the patients who die while on the waiting list and those who survive to transplantation.

However, a major assumption made for the Cox model is that the hazard rate of death after transplantation is proportional to the hazard rate of death before transplantation (Fig. 1). In other terms, taking the example of the above-mentioned study by Aurora et al. [3], the model assumes that the hazard rate of death in transplant recipients is 69% lower than the hazard rate of death in the waiting-list patients, regardless of the time since transplantation. This assumption is not realistic. Although the hazard rate of death in waiting-list patients may be considered roughly stable over time, the hazard rate of death after transplantation varies over time, increasing sharply in the early postoperative period (with an about 10% mortality rate within the first month) and decreasing sharply beyond this period. This fact indicates that proportional hazards models (including the Cox model) are inappropriate (Table 2, Figs. 1 and 2). Thus, the continued use of proportional risk models to assess the potential benefits of lung transplantation is surprising. Modified Cox models that do not assume risk proportionality have been developed [7]. Although these modified Cox models may be more appropriate, they also make assumptions about the risk of death before and after transplantation. These assumptions, which are required to estimate the model parameters, are severely constraining, difficult to test, and possibly untrue.

<table>
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<tr>
<th>Table 1</th>
<th>Hazard rate of death.</th>
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<tbody>
<tr>
<td>The hazard rate of death, usually denoted $\lambda$, is the probability of dying (Pr) within a specified time interval ($t$), among individuals who were alive at the beginning of the time interval (survival time [$T$] &gt; $t$), as follows: $\lambda (t) = \lim_{\Delta t \to 0} \frac{Pr(T = t + \Delta t</td>
<td>T &gt; t)}{\Delta t}$</td>
</tr>
<tr>
<td>The hazard rate is usually modeled over time. For instance, the hazard rate increases sharply just after a major surgical procedure then diminishes. The hazard rate for a patient cohort is the proportion of patients who die within one time unit (e.g., 1 day)</td>
<td></td>
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</table>
Benefits from lung transplantation

Figure 1. Hazard rate of death over time before lung transplantation (solid line) and after lung transplantation (broken line).
Panel A. Hazard rates of death according to the assumption of hazard proportionality. The Cox model makes the assumption that hazard rates of death with and without transplantation are proportional regardless of time since lung transplantation. The hazard rate is stable in waiting-list patients (solid line) and decreases after transplantation (broken line).
Panel B. Hazard rates of death before and after lung transplantation as observed in the US registry (UNOS). The hazard rate of death is stable in waiting-list patients (solid line). After transplantation (broken line), the hazard rate increases then diminishes slowly [13]. The hazard rates of death are clearly not proportional. Therefore, proportional hazards models (including the Cox model) are not appropriate for evaluating the potential benefits.

Methods comparing predicted survival without transplantation to observed survival with transplantation

The first step consists in modeling survival without transplantation, based on pre-established outcome predictors. Survival after a specified time interval (e.g., 5 years) can thus be predicted depending on variables related to the patient and/or disease. Many predictive models have been described in pulmonology journals, including models for idiopathic pulmonary fibrosis [8], cystic fibrosis [9], and chronic obstructive pulmonary disease (COPD) [10]. In the second step, observed survival in a group of lung transplant patients is compared to survival without transplantation predicted by the model. Liou et al. used this approach to evaluate the potential survival benefit of lung transplantation in patients with cystic fibrosis [11,12]. They used a North American cohort of 5820 patients with cystic fibrosis to model the probability of 5-year survival without transplantation then validated their model in a different cohort of 5810 patients [9]. This validation step is indispensable to establish the predictive performance of the model. Then, survival was measured in cystic fibrosis patients treated with lung transplantation, who were divided into two groups based on whether their predicted 5-year survival without transplantation was lower or greater than 50% [11]. The group with a predicted 5-year survival greater than 50% had a lower survival rate after transplantation, indicating that lung transplantation was not beneficial. This method rests on a simple concept but has several weaknesses. The main weakness is that the model for predicting survival without transplantation is applied to a population that differs noticeably from the population it was derived from. Indeed, cystic fibrosis patients treated with lung transplantation are not representative of the overall population of patients with cystic fibrosis. The model probably underestimates survival without transplantation. Another weakness is that survival without transplantation is compared directly to survival.

<table>
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<th>Table 2 Proportional hazards models.</th>
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<td>The equation for proportional hazards models is $\lambda(t) = \lambda_0(t) e^{\beta z}$</td>
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<td>where $\lambda_0(t)$ is the baseline hazard rate of death, $\beta$ the vector of the coefficients, and $Z$ the vector of the co-variables</td>
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<td>In the Cox model, the baseline hazard rate of death ($\lambda_0(t)$) is considered a nuisance parameter and is not estimated.</td>
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<td>The parameters are estimated by maximization of a likelihood function, known as the partial likelihood, which does not take $\lambda_0(t)$ into account. Thus, the Cox model is a semi-parametric model.</td>
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<td>In parametric proportional hazards models, the baseline hazard rate of death ($\lambda_0(t)$) is modeled.</td>
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<td>These models can be parameterized in many ways. A classic model is the two-parameter Weibull model, whose equation is $\lambda_0(t) = \gamma \lambda t^{\gamma - 1}$.</td>
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<tr>
<td>Fig. 2 illustrates the changes in the hazard rate of death over time depending on the value of $\gamma$.</td>
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• The naive approach comparing survival in waiting-list patients (including patients who have died and those who are still alive at the time of the study) to survival in transplant recipients is no longer used.
• Methods that evaluate the impact of transplantation on the hazard rate of death assume that the hazard rate of death after transplantation is proportional to the hazard rate of death before transplantation, which is far from always being true.

after transplantation. For instance, if lung transplantation is shown to increase survival in COPD patients with forced expiratory volume in 1 second (FEV₁) values lower than 20% of predicted, the appropriate conclusion is that the hazard rate in this group of COPD patients is lower with than without transplantation and not that all COPD patients with FEV₁ values less than 20% of predicted should be put on the lung transplant waiting list. Indeed, patients placed on the list may have to wait many months before receiving a transplant (about 18 months according to the United Network for Organ Sharing [UNOS], http://www.unos.org), and many of them die before transplantation, which diminishes the benefit of transplantation on survival. The extreme example is that of patients with very severe disease, who are both those most likely to benefit from lung transplantation and those most likely to die before receiving a transplant.

Methods comparing predicted survival without transplantation and predicted survival with transplantation

We developed a new method involving numerical simulations to assess the potential survival benefits from lung transplantation in COPD patients and the factors associated with any such benefits [13]. We built two models, one for predicting survival without transplantation (while on the waiting list) and the other for predicting survival after lung transplantation. We used data from the UNOS registry including nearly 9000 patients with COPD. Both models are fully parametric and provide a very simple means of computing the mean or median expected survival of a patient with known characteristics, as well as the survival time distribution of a patient cohort of a given size. With these models, a random sample can be taken from the survival time distributions to obtain virtual patient cohorts. Fig. 3 describes the simulation procedure. We obtain virtual cohorts, each containing 100,000 patients, with all patients in the same cohort having the same values for the prognostic variables. Each patient is assigned a survival time without transplantation, a survival time after transplantation, and a time spent on the waiting list. Survival time without transplantation is taken at random from the waiting-list survival time distribution given by the model predicting the survival of waiting-list patients (Weibull model). Survival time after transplantation is taken at random from the posttransplantation survival time distribution given by the model predicting posttransplantation survival. We use a modified Weibull model for posttransplantation survival. In this model, whose equation is supplied in Appendix A, the hazard rate decreases sharply after transplantation then increases over time. The time spent on the waiting list is taken from a log-normal distribution replicating the waiting-list times in the UNOS registry.

This method provides an evaluation of median spontaneous survival (without transplantation) and of median survival when transplantation is planned. The difference between these two median values reflects the impact of transplantation (which may be favorable or unfavorable) (Fig. 3). In addition, the proportion of patients who die while on the waiting list can be estimated.
The results of these simulations are available online at http://www.copdtransplant.fr. This method has many advantages. First, prognostic factors that differ between pretransplantation and posttransplantation survival are easy to introduce. Second, the method involves no assumptions regarding the ratio of the preoperative and postoperative hazard rates of death. Third, several waiting-list times can be simulated and the percentage of patients who die before obtaining a transplant can then be computed as the proportion of patients whose survival while on the waiting list is shorter than their survival after transplantation. On the other hand, this method is considerably more complex to implement than the previously described methods and, as with all exploratory methods, the results require replication by other groups before they can be accepted.

**Conclusion**

Evaluating the benefits of lung transplantation is of crucial importance for all those involved in this procedure. At present, the potential benefits of lung transplantation are evaluated using complex statistical models. The users of these models may not be aware of the underlying assumptions, whose violations may bias the results. The results obtained using these models should therefore be viewed with circumspection, and none of the methods described to date can provide definitive conclusions.

**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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**KEYPOINTS**

- Studies of the impact of lung transplantation on survival have produced a number of discordant results.
- Methods based on transplantation-induced changes in the hazard rate of death are either methodologically flawed or burdensome to use.
- One problem in survival studies is sample homogeneity: thus, the patients who receive lung transplants are not representative of the overall population of patients with that disease.
- Methods comparing predicted survival without transplantation to predicted survival after transplantation provide an evaluation of median survival in both situations. The difference between these two median values reflects the impact of transplantation, which may be beneficial or detrimental.

**Appendix A. Weibull model used in [13]**

\[
\lambda(t) = e^{\alpha t} = [\lambda y(\lambda t)^{-\alpha} + \alpha] 
\]

**Panel.** Does lung transplantation improve survival in children with cystic fibrosis?

A study by Liou et al. published in 2007 in the *New England Journal of Medicine* suggested that lung transplantation produced clear survival gains in only five of 514 children who were on the waiting list over a 10-year period. The impact of lung transplantation on survival was estimated using a proportional hazards model. The model included age and presence or absence of diabetes and *Staphylococcus aureus* colonization. For each patient, the hazard ratio was computed based on the values for these three covariates.

This study has several weaknesses:

- the proportional hazards model is appropriate neither for lung transplantation nor for any other form of organ transplantation. When used in situations where the underlying assumptions are violated, the proportional hazards model substantially underestimates the impact of lung transplantation on patient survival;
- in this cohort of children in the US, survival after lung transplantation was shorter than currently observed in Europe, leading to underestimation of currently expected benefits from lung transplantation [14];
- interpreting the study results in terms of the number of patients who clearly benefited from lung transplantation is a source of confusion. The validity of this number depends on the precision with which the study parameters were estimated and therefore on the power of the
study, and not on the true impact of lung transplantation on patient survival.

References


