Patient Selection for Lung Transplantation

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Isolated lung transplantation was first performed successfully as a unilateral graft in a patient with idiopathic pulmonary fibrosis in 1983. Beginning around 1990, as the number of transplant centers increased the number of lung transplants also increased rapidly. However, by 1996 the limit of the donor pool was reached and the number of transplants plateaued. Since then, the number of lung transplant operations performed throughout the world has averaged between 1300 and 1400 per year, with approximately 65% performed in the United States. Meanwhile, the United Network for Organ Sharing (UNOS) list of patients with various types of end-stage lung diseases who are awaiting transplantation has steadily grown, and now includes nearly 4000 names. This disparity means that most patients waiting for a lung graft will never receive one.

At the same time, favorable outcomes following lung transplantation have lagged behind those of other solid organs. The Registry for the International Society for Heart and Lung Transplantation (ISHLT), which is jointly sponsored by UNOS, reports that patients receiving a lung transplant can expect to have survival rates of approximately 75% at 1 year and 45% at 5 years. Over the past 12 years, these rates have improved only slightly.

With the limited availability of lung grafts and suboptimal recipient survival, the process of selection of surgical candidates becomes a critical factor. Appropriate candidates should be sufficiently ill to benefit from transplantation, yet well enough to survive the rigors of the procedure.

Selecting appropriate candidates for lung transplantation is difficult. Longitudinal epidemiologic studies involving large groups of patients with progressive, fatal pulmonary processes are necessary to identify prognostic factors, but such studies are difficult to perform and are few in number. In addition, an individual’s unique medical characteristics often influence disease progression, thereby making it difficult to apply statistical models to specific patients.

When International Guidelines for the Selection of Candidates for Lung Transplantation were published in 1998, one major study, by Kerem et al, had been published that identified prognostic factors in patients with cystic fibrosis (CF). This study identified FEV1 (and, to a lesser extent, several other parameters) as a useful marker for predicting survival; an FEV1 of less than 30% of the predicted value was associated with 2-year survival of approximately 50%. However, the study was limited by only including patients from 1 clinical center and, therefore, might have been flawed by biases related to the patient population or treatment practices of that particular center. For example, the patient population had a high rate of colonization with Burkholderia cepacia, an organism known to influence survival in patients with advanced pulmonary disease. Nevertheless, the International Guidelines Committee adopted criteria from the study by Kerem et al as the best available at that time for selection of patients with CF who are candidates for lung transplantation.

Several subsequent studies challenged the use of FEV1 as the major factor for predicting outcomes following lung transplantation for CF, although most included relatively small patient populations. Some studies used multivariable regression analysis to define significant variables associated with mortality and then applied these to develop models to predict survival more precisely in these patients. The model created by Liou et al is particularly appealing because it was developed using the largest collection of CF patient data available, the Cystic Fibrosis Foundation Patient Registry (CFFPR). The authors used data from more than 5800 registry patients to develop the 9-parameter model and then validated the model in a second similarly sized group of patients. After applying their model, the authors stratified patients into 5 categories based on predicted survival ranging from less than 30% to approaching 100%, and then asked whether the model would perform better than criteria used previously for choosing appropriate candidates for transplantation.

In this issue of THE JOURNAL, Liou and colleagues now attempt to answer that question. The authors obtained pretransplant clinical information from the CFFPR for 468 patients who had subsequently received lung transplants from 1992 through 1997 and compared their posttransplant survival over 5 years with predicted survival for 11,630 patients.
tients (controls) who had not undergone lung transplantation. The model showed that lung transplantation provided a survival advantage only for the group of patients with a predicted 5-year survival of less than 30%. In a secondary analysis assuming that the selection criteria was FEV1 30% of predicted (as suggested by the International Guidelines), the survival rate for patients with that level of FEV1 was greater than 70% at 2 years, and some patients with FEV1 values greater than 30% of predicted fell into the poorest survival group. Thus, a substantial number of patients with FEV1 values less than 30% of predicted had much better survival than would have been suggested by the criteria in the study by Kerem et al. Liou et al also estimate that if CF patients in the United States were selected for lung transplantation based on FEV1% alone, survival at 2.5 years would be better for nontransplanted controls with similar FEV1% values than for those who received a transplant.

This latter finding is at odds with published data from the ISHLT/UNOS Registry. In this study, Hosenpud et al used data from wait-listed and transplanted patients and derived a model with which they could determine the time when overall survival for remaining on the waiting list was equal to the overall survival after transplantation. This analysis, which involved 66+ CF patients and included patients listed for transplantation from 1992 through 1994, found that CF patients would need to survive only 182 days after transplantation to equal survival on the wait list. An explanation for the difference in risk of death while awaiting transplantation might be that other factors that are not considered in the Liou et al model—such as a rate of decrease of FEV1% or less quantifiable findings such as the patient’s mental status—had been used by centers to select patients for transplantation. Liou et al propose the survival advantage reported by Hosenpud et al is due to a survivor bias since patients surviving to transplantation might represent the least ill of those initially listed. That, of course, remains speculative because clinical data comparing the transplant group and the nontransplant group using the model of Liou et al or other mechanisms are not available. Whether the Liou et al model will prove superior in actual transplant candidate selection is unknown.

The results of the study by Liou et al that send 2 important and familiar messages. First, data from a single, possibly unique population might not be generalizable to a more diverse population. Second, a properly constructed multivariable model increases the precision of prediction of outcomes. As the authors acknowledge, more precise prediction of likely survival should help reduce the number of patients with CF placed on the transplant waiting lists, thereby ensuring that more patients who might derive survival benefits from lung transplants actually receive them.

A key remaining question is whether this model is simple enough to be used by clinicians in CF clinics. This factor is critical if this approach is to be used to identify the most appropriate candidates for lung transplantation. If the model is too complex or cumbersome, its value remains academic. Although the statistical nature of the model appears somewhat imposing, the information required is relatively simple: age, sex, FEV1%, weight-for-age z score, presence of pancreatic sufficiency, diabetes mellitus, Staphylococcus aureus or B cepacia infection, and the number of acute exacerbations requiring treatment. Clinicians wishing to use the model can obtain a worksheet from the authors, or can access a Web site (http://www.jhsp.edu/Publications/JEPI/liou.htm) to assist with making the calculations.

Application of prediction models such as this one by Liou et al that have been validated in large populations can be of great value to identify more precisely those patients who can optimally benefit from the limited number of donor organs available. The challenge now is for clinicians to test the model and determine whether it works as well prospectively as it seems to work retrospectively.

REFERENCES