studies might support the use of certoparin or dalteparin, although experimental data tend to suggest that most LMWHs share anticancer activity.

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Testing Lung Function Decline to Time Lung Transplantation

To the Editor:

Timing of referral for lung transplantation for patients with end-stage lung disease from cystic fibrosis (CF) remains a difficult issue. The recent publication by Rosenbluth et al.1 proposes a method for timing referral of patients for wait listing. Using at least 4 years of previously measured percentage of predicted FEV1 (FEV1%), Rosenbluth et al suggest using a linear regression model to predict when FEV1% drops to < 30% in 2001. Unfortunately, there was no correlation between predicted and actual changes in FEV1% (Fig 1). For patients predicted to have an FEV1% < 30%, 45% of the actual FEV1% values in 2001 were > 30% (Fig 2). As we have shown previously, this is due to the low predictive power of linear regression to predict future FEV1%.

Second, of all patients identified by Rosenbluth et al.1 as good candidates for lung transplantation using FEV1% < 30%, only 15% would have predicted improved survival, while 22% would have predicted unchanged survival, and 63% would have predicted reduced survival based on their 5-year predicted survivals (Fig 2). In fact, even if we restrict attention to those 55% of patients who actually have FEV1% < 30% in 2001, fully half of those patients selected are not appropriate candidates for transplantation. We base these conclusions on our previous finding that using FEV1% by itself cannot identify a group of patients that has survival benefits from transplantation. In contrast, our 5-year predicted survival model does identify a group that triples its survival due to transplantation (Liou et al, Figure panels A and F).

Rosenbluth et al.2 have cited our work3 as justification for using FEV1% < 30% as a criterion for lung transplantation because those who had benefit from the procedure also had a mean FEV1% < 30%. Although the group that we chose for transplantation in our work had an FEV1% of 23% (calculated from Table 1).

Figure 1. The actual changes in FEV1% between 1999 and 2001 for 5,408 patients are compared to the predicted changes in FEV1%. Predictions were derived by linear regression from FEV1% values from 1996 through 1999. The dashed line shows the expected relationship between predicted and actual changes.
et al would be quite complex to implement in practice. First, it requires multiple years of high-quality data. Second, it requires choosing appropriate time windows over which to evaluate the decline in FEV\(_1\). Rosenbluth et al, in their Figure 2 and accompanying text, present no objective method for selecting the correct data points for application of linear regression. Finally, for transplant referral centers that do not have direct access to a patient’s past data, it increases the difficulty to corroborate the transplant decision. In contrast, while our 5-year predicted survival model requires multiple variables, they are all obtained as part of routine CF care and can be collected during a single clinic visit. A work sheet is published that makes calculation of 5-year predicted survival straightforward (aje.oupjournals.org/cgi/content/full/153/4/345/DC1).

The method proposed by Rosenbluth et al\(^1\) for selecting patients for lung transplantation is not simple and will lead to no survival benefit. However, there is a validated method\(^2\) that identified patients for whom lung transplantation clearly increased survival.\(^4\) Although rate of decline of lung function may prove useful in the future to further improve patient selection, clinical variables with a current demonstrated ability to improve selection should be utilized first.

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REFERENCES


To the Editor:

Liou et al raised the following two issues regarding our article (August 2004): (1) the linear regression model was not validated; and (2) eliminating late referrals will not help identify patients who could benefit from lung transplantation. We agree that the model we proposed was not validated, in the sense that it was not applied to a separate patient population or used to predict outcome and then compared to an actual outcome in our own patient population. Such studies would require access to data outside of our center or the performance of a longitudinal follow-up study. We would
agree that the results should be replicated in a larger patient population from multiple centers before they are adopted as being definitely valid, as is true for all clinical studies from a single center.

Liou et al then go on to present data that seemingly respond to this need by interrogating the Cystic Fibrosis Foundation Patient Registry and conclude that our model was useless in predicting actual changes in FEV\textsubscript{1} percent predicted (Fig I in their letter). We are reluctant to engage in a dispute about the meaning of their results because in a letter to the editor too little information is available about the methods employed. For instance, legitimate concerns about data quality are raised by Liou et al themselves in their letter. Furthermore, at the very least, it would be important to exactly replicate the methods used in our study before concluding that there were or were not meaningful differences. We have real concerns that Liou et al did not do this. For instance, in our study, 54% of the patients were in the “slow group” showing pulmonary function decline (ie, the rate of decline for each patient was less than the group mean \( + 2 \) SEs).

The coefficient of determination for the linear regressions in this group averaged only 0.44 \( \pm 0.30 \). Clearly, linear regressions in such patients cannot predict future events (in this case, for instance, the FEV\textsubscript{1} percent predicted for the next year) with great confidence. Of course, by definition, these patients show little change in their pulmonary function, and therefore, with all other things being equal, they would not be likely candidates for lung transplantation referral. We never implied that such patients do not require close clinical observation and follow-up. If circumstances change, the clinician must adapt accordingly.

In contrast, 35% of the patients were in the “rapidly declining” group. In these patients, the mean coefficient of determination was a startling 0.9 \( \pm 0.1 \). These results would suggest that for these patients the model should be highly predictive. Our conclusion regarding the referral for lung transplantation for these patients is that with this knowledge referrals could have occurred at an earlier time, potentially saving lives.

It is no surprise then that when Liou et al simply lump all the data in the Cystic Fibrosis Foundation Registry together (Fig I in their letter) the strategy that we proposed appears to be of little use; but we discount the value of such an analysis. This concern is relevant to both of the issues raised by Liou et al. Nevertheless, we urge Liou et al to submit their analyses of the complete registry database for publication so that their methods and analytic strategies can be properly peer-reviewed.

Liou et al also have mischaracterized and inappropriately applied our regression model to their data set. The regression model is not used to “predict when the FEV\textsubscript{1} percent predicted reaches 20%.” We agree that the decision to proceed with transplantation should not be based solely on a patient’s FEV\textsubscript{1} percent predicted and only assert in our article that this model may be utilized in timing the referral for lung transplantation.

Finally, we dispute the contention that our proposed method is not simple. It is of course trivially simple to analyze the four best points (per annum) of FEV\textsubscript{1} percent predicted data by linear regression! Whether, for example, the data have been obtained by accepted standards or the referral center would have access to the required prior data are issues that can be addressed in a straightforward manner if and when others corroborate our proposed approach in future studies.

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Reference

Value of Fiberoptic Bronchoscopy in Patients Undergoing Surgery for Solitary Pulmonary Nodules

To the Editor:

The American College of Chest Physicians evidence-based guidelines on the diagnosis and management of lung cancer do not recommend preoperative fiberoptic bronchoscopy (FB) in patients undergoing surgery for solitary pulmonary nodules (SPNs), qualifying the level of evidence as Good, None, D.1 Based on experience with real patients, we disagree. Preoperative FB is able to avoid serious mistakes on account of any of the not-so-unusual findings, as follow:

1. FB can detect subclinical disorders in vocal cords related to inferior laryngeal nerve compromise, changing staging and therapy.

2. Unexpected variations in bronchial anatomy could lead to difficult intraoperative situations (ie, double right-upper-lobe bronchial and vessels branching).

3. Subtle extrinsic compression of the bronchial wall, usually undetectable by CT scan, could change strategy. Endobronchial ultrasonography can be useful to guide histologic diagnosis.

4. Simultaneous central endobronchial lesions could be diagnosed. Dramatic changes in surgical approach could be necessary. Autofluorescence bronchoscopy can be useful when available.

5. Fluoroscopy-guided BF, even when not obtaining a cytologic or histologic diagnosis, is extremely important in localizing the segment where the SPN is placed in case it is not palpable during surgery. This can lead to an adequate “blind” segmental resection instead of a useless operation.

Randomized trials to base these kinds of observations on evidence could be unachievable. However, clinical mistakes can be cumbersome when a safe procedure such as FB is missing in the individual patient

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