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## Understanding lung transplant listing practices: Survival in lung transplant candidates who improve clinically to delisting



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### ABSTRACT

**Background:** Occasionally, lung transplant candidates improve to the point where they are removed from the transplant list. We sought to determine the characteristics and outcomes of lung transplant candidates who improved to delisting both before and after implementation of the lung allocation score.

**Methods:** Using the United Network for Organ Sharing database, we reviewed all adult patients listed for lung transplant between 1987 and 2012. The last permanent status change was classified into transplanted, improved to delisting (improved), or deteriorated to delisting (deteriorated). Survival time was calculated using the linked date of death from the Social Security Administration. Survival analysis was performed via the Kaplan-Meier method, and adjusted multivariable logistic regressions identified characteristics predicting improvement to delisting.

**Results:** Of 13,688 candidates, 12,188 (89.0%) were transplanted, 454 (3.3%) improved, and 1,046 (7.6%) deteriorated. The 5-year mortality was greater in improved (hazard ratio = 1.21 [1.07–1.38],  $P = .002$ ) and deteriorated (hazard ratio = 3.36 [3.11–3.64],  $P < .001$ ) candidates relative to those transplanted; however, 1-year survival was greater in improved versus transplanted candidates (75.9% vs 67.2%, log rank  $P < .001$ ). Older, female patients listed for primary pulmonary hypertension and retransplantation were more likely to improve to delisting. The proportion of improved patients varied by hospital quartile volume ( $P < .001$ ) and the United Network for Organ Sharing geographic region ( $P < .001$ ). The number of patients improving to delisting decreased after implementation of the lung allocation score.

**Conclusion:** Lung transplant candidates improving to delisting faced less short-term but greater long-term mortality relative to transplanted candidates. Given that the improved population decreased dramatically after implementation of the lung allocation score, redefining patient listing criteria appears to have improved patient appropriateness for transplant.

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### Introduction

Demand for lung transplantation continues to exceed the supply of donor organs.<sup>1,2</sup> Lung allocation was determined historically by waiting time until May of 2005, when consensus guidelines recommended calculation of a lung allocation score using

pretransplant clinical diagnostic factors associated with survival.<sup>3</sup> Guidelines for lung transplantation listing currently recommend that adults with end-stage lung disease meet 3 major criteria: >50% risk of death from lung disease within 2 years without transplantation, >80% likelihood of surviving a minimum of 3 months post-transplant, and > 80% likelihood of 5-year survival if graft function proves adequate.<sup>4</sup> Recent history of malignancy, intractable organ dysfunction, medical instability, and medical noncompliance remain as absolute contraindications.<sup>4</sup>

In addition to the well-described criteria for listing a patient for lung transplantation, experts acknowledge that the entire clinical condition of the patient—including psychologic and social factors—should be considered when evaluating an individual

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patient as a candidate for transplantation.<sup>4–6</sup> Theoretically, a decision to list conveys that the patient faces a limited life expectancy and that all viable treatment options have been exhausted.<sup>4</sup> Nonetheless, there exists a small population of patients listed initially for transplantation who subsequently improve medically and are delisted. Although other investigations have characterized heart transplant candidates who improve to delisting, the characteristics and fate of those being considered for lung transplantation remains ill-defined.<sup>7–10</sup>

Therefore, this study utilized a national registry database (the United Network for Organ Sharing [UNOS] registry) to characterize the demographics, comorbidities, and characteristics of the individual transplant center for patients listed initially for lung transplant but permanently delisted because of medical improvement. We also analyzed mortality outcomes for the population improving to delisting and compared them with those who underwent transplantation as well as those who deteriorated to delisting. We hope that an understanding of the characteristics and outcomes of patients who improve and are removed from the waiting list both before and after implementation of the lung allocation score will inform future decisions governing candidate listing for lung transplantation.

## Methods

This was a retrospective study of adult patients listed for lung transplantation between 1987 and 2012 in the national transplantation registry UNOS. The Death Master File from the Social Security Administration is linked to the UNOS database and allows for survival analysis of both transplanted patients and those listed but never transplanted. The interval between the date of removal from the final waiting list and of death was considered as survival time. The last permanent status change of candidates on the waiting list was tabulated using UNOS removal codes and categorized into transplantation, medical deterioration yielding delisting, and improvement yielding delisting. Patients less than 18 y of age at listing, those listed for or receiving multiple organs, those who refused transplant, those who died while listed, and those without a status classification on the waiting list were excluded.

Patients were stratified into 3 groups by status change on the waiting list: transplanted, improved to delisting (improved), or deteriorated to delisting (deteriorated). Secondary stratification was by time period divided into pre- versus post-introduction of the lung allocation score. The primary outcome was survival at 5 years. Secondary outcomes included predictive characteristics of improvement to delisting, as well as differences in status changes on the waiting list by transplant center volume and UNOS region. The diagnoses of type of lung diseases were divided into 6 categories: suppurative lung disease, restrictive lung disease and interstitial pulmonary fibrosis (IPF), obstructive lung disease and chronic obstructive pulmonary disease (COPD), primary pulmonary hypertension (PPH), retransplantation, and other diseases. Transplant centers were organized into volume quartiles with the 1st quartile consisting of <281 total transplants, 2nd quartile between 281 and 434 transplants, 3rd quartile between 434 and 733 transplants, and 4th quartile at >733 transplants since 1987.

Demographics and comorbidities were analyzed using the Kruskal-Wallis test for continuous variables and  $\chi^2$  analysis for categorical variables. Survival analysis was performed via the Kaplan-Meier method with censoring at 5 years. Multivariable Cox hazard models were utilized to adjust for differences in baseline characteristics and to identify the impact of delisting on 5-year mortality. Furthermore, a multivariable logistic regression was utilized to identify patient characteristics that predict improvement to delisting. Regressions were adjusted for the following patient demographics: age, sex, race, insurance coverage, and body mass index (BMI) and

comorbidities (lung disease diagnosis, mean primary arterial pressure [PAP]), oxygen requirement at listing, being maintained on extracorporeal membrane oxygenation (ECMO) and life support measures at listing, diabetes mellitus, and days on waiting list). In all comparisons, a  $P < .05$  was considered statistically significant. All statistical analyses were performed using STATA 14.2 (StataCorp LLC, College Station, TX). The study was deemed exempt by the Institutional Review Board at the University of California, Los Angeles.

## Results

Of 13,688 patients initially listed, 12,188 (89.0%) were transplanted, 454 (3.3%) improved, and 1,046 (7.6%) deteriorated to delisting (Table I). Patients who improved were on average slightly younger (48.5 years vs 50.9 years,  $P < .001$ ), more likely to be female (60.9% vs 45.4%,  $P < .001$ ), and had somewhat lower recorded systolic PAP (40.7 mmHg vs 43.6 mmHg,  $P < .001$ ) relative to those transplanted. Improved patients also were more likely to utilize mechanical ventilation (4.4% vs 1.5%,  $P < .001$ ) and extracorporeal lung support (1.3% vs 0.3%,  $P < .001$ ) at listing relative to transplanted patients. Improved patients were also more likely to be retransplant candidates (9.5% vs. 3.6%,  $P < .001$ ), with greater rates of PPH (9.5% vs 3.6%,  $P < .001$ ) but lesser rates of obstructive lung disease (38.3% vs 43.6%,  $P < .001$ ). In contrast, patients who deteriorated to delisting were on average slightly older (52.6 years vs 50.9 years,  $P < .001$ ), with somewhat greater mean systolic PAP (47.7 mmHg vs 43.6 mmHg,  $P < .001$ ) and greater rates of restrictive lung disease/IPF (40.3% vs 28.4%,  $P < .001$ ) relative to transplanted patients.

After adjustment for baseline differences, Cox hazards regression indicated that, compared with transplanted candidates, 5-year mortality was increased by 21% for improved candidates (hazard ratio [HR] = 1.21 [1.07–1.38],  $P = .002$ ) and by 236% (HR = 3.36 [3.11–3.64],  $P < .001$ ) for deteriorated candidates (Table II). Additional significant predictors of increased 5-year mortality included age >60 years (HR = 1.16 [1.07–1.27],  $P < .001$ ), Medicare coverage (HR = 1.08 [1.03–1.14],  $P = .002$ ), males (HR = 1.04 [1.00–1.04],  $P = .048$ ), use of life support at listing (HR = 1.30 [1.16–1.47],  $P < .001$ ), greater oxygen requirements at listing (HR = 1.05 [1.04–1.05],  $P < .001$ ), and retransplant candidates (HR = 1.59 [1.40–1.81],  $P < .001$ ).

The overall 5-year Kaplan-Meier survival curve for all lung transplant candidates is presented in Figure 1. At 1 year after the status change on the waiting list, survival was 75.9% for patients improving to delisting but only 67.2% for transplanted patients and 25.1% for those deteriorating to delisting. By year 3, this short-term survival benefit disappeared—survival was 41.7% for transplanted patients and 40.0% for patients improving to delisting. By the end of year 4, survival for transplanted patients was 32.8%, which was greater than that of improved patients at 23.6%.

Of note, 415 (91.4%) of the candidates improving to delisting were listed in the pre-lung allocation score era. Implementation of the lung allocation score was associated with a decrease in the percentage of patients improving to delisting (4.3% vs 1.0%,  $P < .001$ ; Fig 2). In subgroup analysis, patients improving to delisting in the pre-lung allocation score era were associated with increased 5-year mortality (HR = 1.30 [1.16–1.47],  $P < .001$ ); whereas those improving in the post-lung allocation score era were not associated with increased mortality (HR = 1.17 [0.85–1.62],  $P = .338$ ).

The predictive characteristics of lung transplant candidates most likely to improve to delisting are presented in Table III. Patients >60 years were more likely to improve (odds ratio [OR] = 1.96 [1.26–3.05],  $P = .003$ ), as were patients listed for PPH (OR = 2.27 [1.13–4.56],  $P = .022$ ) or retransplantation (OR = 8.49 [4.52–15.94],  $P < .001$ ) relative to suppurative lung disease. Men were less likely to improve (OR = 0.72 [0.56–0.91],  $P = .007$ )

**Table 1**  
Demographics and comorbidities by status change on the status change waiting list

|   | Transplanted (N = 12,188) | Improved (N = 454) | Deteriorated (N = 1,046) | P     |
|---|---------------------------|--------------------|--------------------------|-------|
| Age (y) <sup>*</sup>                                | 50.9 ± 12.6               | 48.5 ± 11.8        | 52.6 ± 12.8              | <.001 |
| Male  | 6,653 (54.6%)             | 178 (39.1%)        | 495 (47.1%)              | <.001 |
| Race  |                           |                    |                          | <.001 |
| White   | 10,815 (88.7%)            | 380 (83.7%)        | 869 (83.1%)              |       |
| Black   | 829 (6.8%)                | 47 (10.4%)         | 96 (9.2%)                |       |
| Hispanic  | 396 (3.3%)                | 14 (3.1%)          | 52 (5.0%)                |       |
| Asian   | 76 (0.6%)                 | 4 (0.9%)           | 19 (1.8%)                |       |
| Other   | 72 (0.6%)                 | 9 (2.0%)           | 10 (1.0%)                |       |
| Insurance   |                           |                    |                          | <.001 |
| Private   | 6,621 (54.3%)             | 289 (63.7%)        | 576 (55.1%)              |       |
| Medicaid  | 795 (6.5%)                | 46 (10.1%)         | 89 (8.5%)                |       |
| Medicare  | 2,619 (21.5%)             | 86 (18.9%)         | 297 (28.4%)              |       |
| Other   | 2,153 (17.7%)             | 33 (7.3%)          | 84 (8.0%)                |       |
| Lung disease  |                           |                    |                          | <.001 |
| Suppurative   | 1,251 (10.3%)             | 31 (6.8%)          | 100 (9.6%)               |       |
| Restrictive/IPF                                     | 3,462 (28.4%)             | 109 (24.0%)        | 421 (40.3%)              |       |
| Obstructive/COPD                                    | 5,316 (43.6%)             | 174 (38.3%)        | 315 (30.1%)              |       |
| PPH   | 422 (3.5%)                | 61 (13.4%)         | 67 (6.4%)                |       |
| Retransplant  | 435 (3.6%)                | 43 (9.5%)          | 87 (8.3%)                |       |
| Other   | 1,302 (10.7%)             | 36 (7.9%)          | 56 (5.4%)                |       |
| Cardiac output (L/min) <sup>*</sup>                 | 5.3 ± 1.4                 | 5.1 ± 1.5          | 5.3 ± 1.6                | .094  |
| Mean PAP (mmHg) <sup>*</sup>                        | 26.9 ± 11.0               | 30.9 ± 17.3        | 28.3 ± 12.5              | .001  |
| Systolic PAP (mmHg) <sup>*</sup>                    | 43.6 ± 20.1               | 40.7 ± 16.7        | 47.7 ± 25.8              | <.001 |
| PCWP (mmHg) <sup>*</sup>                            | 11.1 ± 5.8                | 11.8 ± 5.5         | 10.8 ± 5.6               | .024  |
| BMI (kg/m <sup>2</sup> ) <sup>*</sup>               | 24.5 ± 5.4                | 26.1 ± 5.5         | 25.2 ± 5.5               | <.001 |
| Creatinine (mg/dL) <sup>*</sup>                     | 0.88 ± 0.39               | 0.91 ± 0.31        | 0.88 ± 0.32              | .37   |
| Total serum albumin (g/dL) <sup>*</sup>             | 3.9 ± 0.6                 | 3.9 ± 0.7          | 3.8 ± 0.7                | <.001 |
| Diabetes mellitus                                   | 1,301 (12.5%)             | 50 (11.3%)         | 201 (20.1%)              | <.001 |
| Prior cardiac surgery                               | 239 (2.0%)                | 1 (0.2%)           | 33 (3.2%)                | .001  |
| Smoking history                                     | 6,307 (51.8%)             | 238 (52.4%)        | 569 (54.4%)              | .253  |
| Initial O <sub>2</sub> requirement (L) <sup>*</sup> | 2.6 ± 2.7                 | 1.9 ± 2.5          | 4.4 ± 4.9                | <.001 |
| Functional status                                   |                           |                    |                          | <.001 |
| Severe  | 322 (9.1%)                | 10 (18.9%)         | 154 (26.1%)              |       |
| Mild  | 1,859 (52.5%)             | 19 (35.9%)         | 234 (39.7%)              |       |
| Normal  | 1,359 (38.4%)             | 24 (45.3%)         | 202 (34.2%)              |       |
| Use of ECMO at time of listing                      | 40 (0.3%)                 | 6 (1.3%)           | 18 (1.7%)                | <.001 |
| Ventilator use at time of listing                   | 187 (1.5%)                | 20 (4.4%)          | 86 (8.2%)                | <.001 |
| Use of life support Measures at time of listing     | 349 (2.9%)                | 33 (7.3%)          | 112 (10.8%)              | <.001 |
| Previous lung transplant                            |                           |                    |                          | <.001 |
| 0   | 11,694 (96.0%)            | 400 (88.1%)        | 945 (90.3%)              |       |
| 1   | 476 (3.9%)                | 51 (11.2%)         | 97 (9.3%)                |       |
| 2+  | 18 (0.1%)                 | 3 (0.7%)           | 4 (0.4%)                 |       |
| Total days waiting <sup>*</sup>                     | 317 ± 384                 | 1,597 ± 1,193      | 419 ± 625                | <.001 |
| Year  |                           |                    |                          | <.001 |
| Pre-lung allocation score                           | 8,894 (91.1%)             | 415 (4.3%)         | 454 (4.7%)               |       |
| Post-lung allocation score                          | 3,294 (83.9%)             | 39 (1.0%)          | 592 (15.1%)              |       |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IPF, interstitial pulmonary fibrosis; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PPH, primary pulmonary hypertension.

\* Continuous variables are represented as averages ± SE.

relative to females. At listing, use of life support measures (OR = 3.63 [2.15–6.13],  $P < .001$ ) but decreased oxygen requirements (OR = 0.89 [0.83–0.95],  $P < .001$ ) were further predictive of improvement to delisting.

Figure 3 presents the trends in patient improvement or deterioration to delisting by hospital volume. Increasing hospital volume was associated with an increased proportion of patients improving to delisting ( $P < .001$ ), but increasing hospital volume was associated with decreases in the percentage of patients deteriorating to delisting ( $P = .044$ ). Figure 4 presents the differences in the percentage of patients improving or deteriorating to the point of delisting by UNOS geographic region. Regions 4 and 6 had the least rates of patient improvement to delisting, and region 8 had the greatest rate of improvement to delisting.

## Discussion

Because the demand for lung transplantation exceeds the supply of donor organs, the criteria for listing of candidates are critical

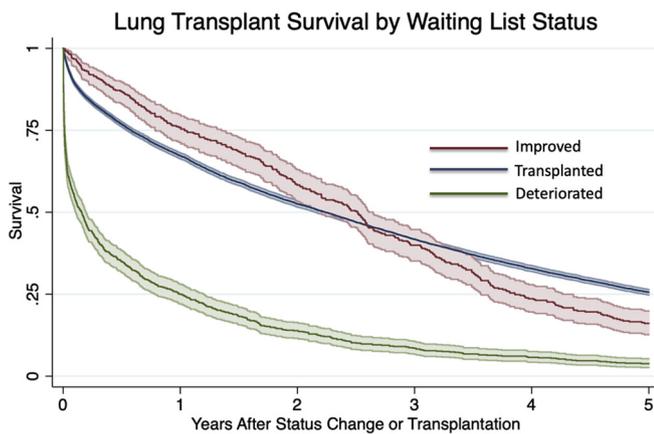
to optimizing outcomes. This study analyzed 13,688 lung transplant candidates who were listed between 1987 and 2012. We found that lung transplant candidates who improved and were removed from the waiting list sustained a survival benefit of 2 to 3 years but ultimately experienced greater 5-year mortality relative to transplanted patients. Of note, implementation of the lung allocation score and de-emphasis on lung allocation by duration of time on the waiting list has virtually eliminated this unique population of patients.

The early survival benefit of patients improving to delisting suggests that these patients do not represent those at the limits of optimal medical therapy and thus are not true, end-stage patients. The predominance of patients improving to delisting in the pre-lung allocation score era supports this conclusion and implies that many of these patients may have been listed for transplant inappropriately. Lung allocation before implementation of the lung allocation score was dependent on waiting time rather than on clinical diagnostic factors predicting survival.<sup>3</sup> This system created a perverse incentive to list patients as

**Table II**  
Cox regression predictions for 5-year survival by waiting list status

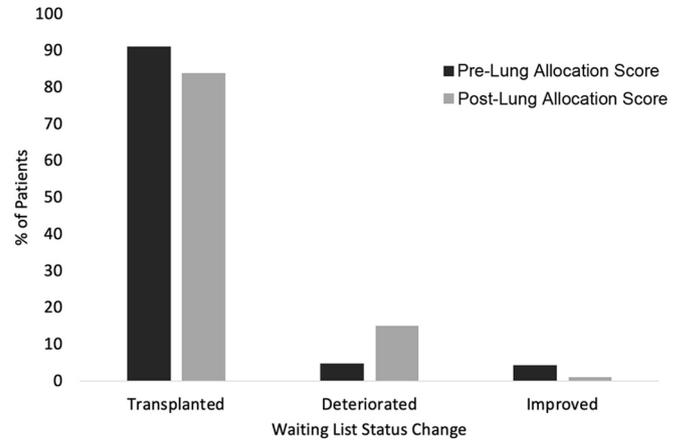
| Factor   | Hazard ratio [95% CI] | P     |
|--|-----------------------|-------|
| <b>Patient status</b>                              |                       |       |
| Transplanted                                       | Ref                   | Ref   |
| Improved, removed                                  | 1.21 [1.07–1.38]      | .002  |
| Deteriorated, removed                              | 3.36 [3.11–3.64]      | <.001 |
| <b>Age group (y)</b>                               |                       |       |
| <40  | Ref                   | Ref   |
| 40–50  | 0.97 [0.89–1.05]      | .465  |
| 50–60  | 0.92 [0.85–1.00]      | .048  |
| >60  | 1.16 [1.07–1.27]      | <.001 |
| Male   | 1.04 [1.00–1.09]      | .048  |
| <b>Race</b>  |                       |       |
| Caucasian  | Ref                   | Ref   |
| Black  | 1.03 [0.96–1.12]      | .404  |
| Hispanic   | 1.15 [1.03–1.29]      | .011  |
| Asian  | 1.11 [0.89–1.39]      | .349  |
| Other  | 0.95 [0.74–1.23]      | .710  |
| <b>Insurance</b>                                   |                       |       |
| Private  | Ref                   | Ref   |
| Medicaid   | 0.97 [0.89–1.05]      | .412  |
| Medicare   | 1.08 [1.03–1.14]      | .002  |
| Other  | 0.79 [0.74–0.84]      | <.001 |
| <b>Lung disease</b>                                |                       |       |
| Suppurative  | Ref                   | Ref   |
| Restrictive/IPF                                    | 1.06 [0.96–1.18]      | .247  |
| Obstructive/COPD                                   | 0.76 [0.69–0.84]      | <.001 |
| PPH  | 1.03 [0.89–1.19]      | .662  |
| Retransplant                                       | 1.59 [1.40–1.81]      | <.001 |
| Other  | 0.99 [0.89–1.11]      | .925  |
| BMI (kg/m <sup>2</sup> ) at listing                | 1.00 [1.00–1.01]      | .725  |
| Mean PAP at listing (mmHg)                         | 1.00 [1.00–1.01]      | .021  |
| Diabetes mellitus                                  | 1.13 [1.06–1.21]      | <.001 |
| Use of life support at time of listing             | 1.30 [1.16–1.47]      | <.001 |
| ECMO at time of listing                            | 1.35 [0.98–1.86]      | .062  |
| Initial O <sub>2</sub> requirements (L) at listing | 1.05 [1.04–1.05]      | <.001 |
| Days waiting                                       | 1.00 [1.00–1.00]      | <.001 |

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IPF, interstitial pulmonary fibrosis; PAP, pulmonary artery pressure; PPH, primary pulmonary hypertension.



**Fig 1.** Lung transplant survival by waiting list status. Transplant candidates who improve and are delisted had lesser 5-year survival relative to transplanted patients (log rank  $P < .001$ ).

early as possible to maximize the probability of receiving a transplant. In response, the Institute of Medicine published a report in 1997 re-focusing allocation criteria on medical urgency in an effort to decrease futile transplants, to ensure allocation to those in greatest need, and to broaden geographic sharing of organs.<sup>11</sup> As a result, the Lung Allocation Subcommittee was assembled to recommend changes to meet these goals.<sup>3</sup> The revised allocation system de-emphasized waiting time and



**Fig 2.** Waiting list status by era. The percentage of patients improving to delisting decreased precipitously between the pre- and post-lung allocation score eras ( $P < .001$ ).

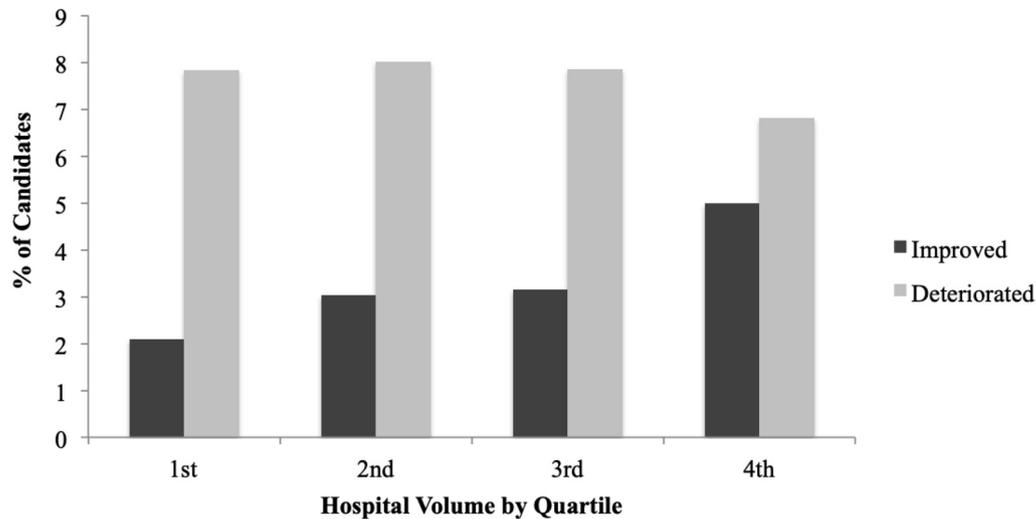
**Table III**  
Adjusted logistic regression results for likelihood of improvement to delisting

| Variable  | Odds ratio [95% CI] | P     |
|---|---------------------|-------|
| <b>Age group (y)</b>                              |                     |       |
| <40   | Ref                 | Ref   |
| 40–50   | 0.97 [0.65–1.46]    | .885  |
| 50–60   | 1.21 [0.81–1.79]    | .357  |
| >60   | 1.96 [1.26–3.05]    | .003  |
| Male  | 0.72 [0.56–0.91]    | .007  |
| <b>Race</b>                                       |                     |       |
| Caucasian   | Ref                 | Ref   |
| Black   | 1.28 [0.85–1.95]    | .239  |
| Hispanic  | 0.93 [0.47–1.83]    | .835  |
| Asian   | 1.18 [0.30–4.63]    | .817  |
| Other   | 2.88 [1.12–7.45]    | .029  |
| <b>Insurance</b>                                  |                     |       |
| Private   | Ref                 | Ref   |
| Medicaid  | 1.15 [0.75–1.76]    | .530  |
| Medicare  | 0.92 [0.68–1.24]    | .596  |
| Other   | 0.31 [0.19–0.50]    | <.001 |
| <b>Lung disease</b>                               |                     |       |
| Suppurative                                       | Ref                 | Ref   |
| Restrictive/IPF                                   | 1.71 [0.92–3.16]    | .089  |
| Obstructive/COPD                                  | 1.32 [0.73–2.39]    | .355  |
| PPH   | 2.27 [1.13–4.56]    | .022  |
| Retransplant                                      | 8.49 [4.52–15.94]   | <.001 |
| Other   | 1.57 [0.79–3.13]    | .201  |
| BMI (kg/m <sup>2</sup> ) at listing               | 1.03 [1.01–1.05]    | .001  |
| Mean PAP at listing (mmHg)                        | 1.02 [1.01–1.03]    | .001  |
| Diabetes mellitus                                 | 1.09 [0.74–1.60]    | .674  |
| Use of life support at time of listing            | 3.63 [2.15–6.13]    | <.001 |
| ECMO at time of listing                           | 2.40 [0.83–6.97]    | .108  |
| Initial O <sub>2</sub> requirement (L) at listing | 0.89 [0.83–0.95]    | <.001 |
| Total days waiting                                | 1.00 [1.00–1.00]    | <.001 |

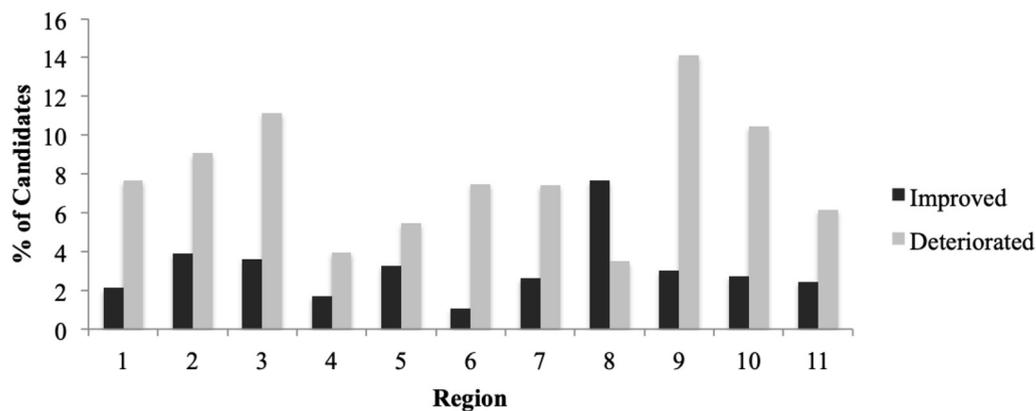
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; IPF, interstitial pulmonary fibrosis; PAP, pulmonary artery pressure; PPH, primary pulmonary hypertension.

instead combined geographic considerations with a calculation of both severity of illness and projected post-transplant survival time with the lung allocation score.<sup>12,13</sup>

By decreasing the incentives for early listing, adoption of the lung allocation score has decreased the size of the waiting list.<sup>12,14</sup> Conceivably, the loss of these incentives also decreased the size of the population improving to the point of delisting, because these patients were likely listed inappropriately early in an attempt to increase their probability of future transplantation. Our study supports this conclusion, because the



**Fig 3.** Percentage of candidates improving or deteriorating to delisting by hospital volume quartiles. Differences by hospital quartile volume are different for improved candidates ( $P < .001$ ) and for deteriorated patients ( $P = .044$ ).



**Fig 4.** Percentage of candidates improving or deteriorating to delisting by transplant center UNOS region. Differences by UNOS region are different for improved ( $P < .001$ ) and deteriorated ( $P < .001$ ) candidates.

population of patients improving to delisting dropped precipitously with the adoption of the lung allocation score. Given the continued gap between organ demand and supply, the lung allocation score appears successful in helping to ensure the allocation of lungs to those in greatest need.

Because there is an early survival benefit of the improving population, the approach of prioritizing the patients with the greatest acuity of illness rather than those listed for the greatest time, appears to have optimized outcomes for both medically and surgically managed candidates. Lung transplantation, although an effective therapy for end-stage lung disease, remains a highly invasive procedure requiring a baseline resistance to physiologic stressors.<sup>15,16</sup> Lung transplant patients face greater mortality within the first year, driven primarily by infection, primary graft failure, and acute cellular rejection.<sup>17,18</sup> Thus, candidates not at imminent risk of mortality may enjoy improved survival with medical management, particularly if they have increased age, a history of cardiac or lung surgery, poorer functional status, or greater frailty scores.<sup>17,19,20</sup>

Given the degree of subjectivity in listing decisions, it is no surprise that characteristics of the transplant centers were associated historically with the percentage of patients who improved or deteriorated to delisting. Transplant centers in the greatest quartile

for volume had a greater proportion of patients removed for medical improvement relative to those in the lowest quartile. Perhaps this trend suggests more liberal listing practices at institutions with greater organ allocation.<sup>21,22</sup> Patient percentages also varied by UNOS geographic region, perhaps further indicating differences in the culture of various regions of transplant centers, access to organs, and philosophy on practices of patient listing.<sup>23–25</sup> The implementation of the lung allocation score served to assuage these disparities by encouraging geographic organ sharing and decreasing the incentives for early listing.<sup>1</sup>

Our study is the first to characterize this unique population of lung transplant candidates improving to delisting. Patients likely to improve are younger and more often female, with diagnoses related to underlying autoimmune conditions like PPH. The association of younger age and increased likelihood of medical improvement has also been observed among heart transplant candidates.<sup>9,10</sup> Of note, these patients are also more likely to be retransplant candidates. Although retransplant candidates must meet the same criteria for untreatable severe lung allograft dysfunction to qualify for retransplantation, perhaps some candidates are relisted after an exacerbation of primary graft dysfunction or bronchiolitis obliterans syndrome that subsequently slows course.<sup>26–28</sup> Understanding the characteristics of candidates listed

in a putatively terminal state, yet improved medically to delisting, can inform future candidate selection criteria.

Although this study was the first to characterize lung transplant candidates who improved to delisting, other studies of similar candidates delisted from heart transplantation support this finding. An institutional analysis found that survival was initially greater in improved patients relative to transplanted patients but declined after 30 months.<sup>9</sup> Another institutional study verified the early survival benefit of medical improvement to delisting, observing a 100% survival rate at 3 years in 18 former heart transplant candidates.<sup>10</sup> Our study suggests that a similar pattern of early survival but increased long-term mortality is observed in lung transplant candidates improving to delisting.

This analysis has several limitations to this analysis including the inherent challenges of a retrospective multicenter design. Cause of death could not be evaluated across status changes in the waiting list, because UNOS only records cause of death for transplanted candidates. Furthermore, this analysis only compared the fates of transplanted patients relative to those who were deliberately delisted for either medical improvement or deterioration; however, the additional end points excluded from this analysis, including wait-list deaths and refusal of transplant, would only change the relative percentages of patients in each category. Finally, because most patients who improved to delisting were in the pre-lung allocation score era, the 1- and 5-year mortality rates are greater than what would be expected in the post-lung allocation score era. Improved survival rates in recent years for transplanted patients would likely decrease the duration of the short-term survival benefit observed for the improved to delisting population. Although the improved to delisting population would still be expected to sustain a short-term survival benefit given the persistent early mortality observed after lung transplantation, a greater survival rate for transplant recipients would likely decrease the duration of this superior survival. Future studies could explore the extent of change in characteristics of the transplanted population before and after adoption of the lung allocation score, as well as factors governing decisions to delist transplant candidates.

In conclusion, lung transplant candidates who improve medically to delisting sustain an early survival benefit but ultimately experience greater 5-year mortality relative to transplanted candidates. The pre-lung allocation score era encompassed the vast majority of this population, demonstrating that the lung allocation score decreased the perverse incentive of early and inappropriate listing for transplantation. Understanding that medically borderline lung transplant candidates sustain a short-term survival benefit and analyzing the characteristics of the population likely to improve to delisting allow for evaluation and optimization of the listing criteria for lung transplant candidates.

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