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Assessment of Different Threshold Preoperative Glomerular Filtration Rates as Markers of Outcomes in Lung Transplantation

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Abstract

Background—The evidence behind the widely used prelung transplant glomerular filtration rate (GFR) cutoff of 50 mL/min per 1.73 m² is limited. This study reviews data from a large cohort to assess outcomes associated with this historical cutoff and to estimate other possible cutoffs that might be appropriate in lung transplantation.

Methods—We conducted a retrospective cohort analysis of lung recipients at a single center. Recursive partitioning and receiver operating characteristics analysis were used to estimate other potential GFR cutoffs with 1-year mortality as the outcome. Postoperative outcomes around the various cutoffs, including survival, acute kidney injury, and dialysis, were assessed using χ^2 , Kaplan-Meier, and Cox regression methods.

Results—A total of 794 lung recipients met study inclusion criteria. Compared with 778 patients with GFR 50 mL/min per 1.73 m² or greater at time of transplant, 16 patients with GFR below this cutoff were older and more likely to have restrictive disease. One-year mortality below the cutoff was 31.3% compared with 15.1% above the cutoff ($p = 0.021$). Recursive partitioning estimated potential GFR cutoff values between 46 and 61 mL/min per 1.73 m². Patients with GFR below these cutoffs were at significantly higher risk for adverse outcomes ($p < 0.05$). Receiver operating characteristics analysis was less successful at identifying meaningful cutoff values with areas under the curve approximately 0.5.

Conclusions—Study results support the practice of requiring candidate GFR 50 mL/min per 1.73 m² or greater for lung transplantation. Future work should focus on reproducing the analysis in a larger cohort of patients including more individuals with low GFR.

Preoperative renal function is an important marker of postoperative outcomes in surgical populations [1–3]. Given the nephrotoxicity of immunosuppressive medications, stress of major surgery, and accompanying diuresis in the immediate postoperative period, there is heightened concern about renal function in lung recipients [4]. Indeed, several studies have

demonstrated the high incidence of acute and chronic renal failure after lung transplantation [4–6].

The original International Guidelines for the Selection of Lung Transplant Candidates [7] advocated for exclusion of certain candidates from transplantation based on creatinine clearance less than $50 \text{ mg} \cdot \text{mL}^{-1} \cdot \text{min}^{-1}$. While many US transplant centers exclude patients based on these recommendations, there is a paucity of objective data supporting this practice; the original guideline being based on findings from a single-center study that described the nephrotoxic effects of cyclosporine in 30 lung recipients [8]. Although more recent guidelines only recommend exclusion of patients with untreatable, advanced organ system dysfunction [9, 10], many centers still use renal function as a contraindication to transplantation and some centers, including ours, continue to exclude candidates based on glomerular filtration rates (GFR) less than $50 \text{ mL/min per } 1.73 \text{ m}^2$. However, some patients with pretransplant GFR less than $50 \text{ mL/min per } 1.73 \text{ m}^2$ have gone on to receive lung transplantation. These patients make up a key cohort in our analysis and the rationale behind their receiving organs despite having marginal renal function is outlined in the discussion.

The aim of the current study was to review data from a large cohort to assess outcomes associated with the $50 \text{ mL/min per } 1.73 \text{ m}^2$ GFR cutoff for lung transplantation. We tested the hypothesis that patients with GFR below $50 \text{ mL/min per } 1.73 \text{ m}^2$ at the time of transplant had worse outcomes than those with GFR above this cutoff. Authors provide the first formal evaluation of a renal function cutoff that has been used for many years as an independent disqualifier from lung transplantation.

Material and Methods

Study Design and Patient Selection

We conducted a retrospective cohort analysis of all lung recipients at a single center from January 1, 1996 to March 1, 2011 with follow-up data collection through March 2012. The study protocol was approved by the Institutional Review Board at Duke University Medical Center. All patients who received lung transplant prior to March 2011, with availability of 1-year mortality and preoperative serum creatinine data were included. Patients were excluded from the study if they were retransplant recipients, underwent multiorgan transplant, or were younger than 12 years of age at the time of transplant.

Estimation of Glomerular Filtration Rate

Glomerular filtration rate was estimated using the original version of the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) equation which incorporates creatinine as the only serum marker of renal function. Cystatin c was not routinely collected in our patients, precluding the use of newer versions of this equation. The CKDEPI was selected over the Modified Diet in Renal Disease equation because of its documented superiority for estimating GFR in populations with broad ranges of renal function [11–13].

The main analysis was performed using CKDEPI GFR estimated using the last available serum creatinine value before transplant. A subgroup analysis was performed in patients with available creatinine data from time of listing.

Data Collection

Our institution maintains a data warehouse that contains administrative and clinical information generated during patient care [14]. This system was used to acquire patient demographic information, preexisting comorbidities, operative characteristics, postoperative complications, and survival information. These data were supplemented and validated with manual chart review as well as with data obtained from our institutional Database for Cardiovascular Disease and the United Network for Organ Sharing site-specific reports. Survival data were cross-referenced with the Social Security Death Index and tumor registries, which provided more complete and validated survival data.

Primary and Secondary Outcome Measures

One-year mortality was the primary outcome used to evaluate the traditional GFR cutoff and estimate other potential cutoff values. Secondary outcomes included acute kidney injury (AKI) and need for dialysis prior to discharge from the transplant hospitalization. Acute kidney injury was defined as serum creatinine greater than 3 mg/dL within the first week after transplant.

Subgroup Analysis

A subgroup analysis was performed in patients with available serum creatinine data from time of listing (compared with the main analysis, which is based on creatinine from time of transplant). For each patient in this subgroup, change in GFR between listing and transplantation was estimated and included in models as a potential predictor of outcomes.

Statistical Analysis

Overall survival for patients on either side of GFR cutoffs was estimated using the Kaplan-Meier method and compared by the log-rank test. Hazard ratios were estimated using Cox regression modeling. Similar comparisons were performed for secondary outcomes using χ^2 and logistic regression methods.

Recursive partitioning and receiver operating characteristics (ROC) were used to estimate additional GFR cutoffs for lung transplantation. In recursive partitioning, data on the predictor variable of interest are split at the value that maximizes differences in outcomes [15]. The goal is to create maximal difference in the distributions of outcomes when comparing groups on either side of the split value.

For ROC analyses, the ideal GFR cutoff was estimated at the value that maximizes the sum of sensitivity and specificity. The area under the curve (AUC), a measure of the overall sorting efficiency of a variable for predicting an outcome, and Mann-Whitney 95% confidence interval were calculated for each ROC curve.

Multivariable Cox and logistic regression models (controlling for recipient characteristics in Table 1 as well as donor age, gender, and race) assessed GFR at time of transplant as a predictor of overall survival, AKI, and dialysis. Variable inclusion in the final model was determined based on a backward selection algorithm. The GFR was included in models as individual values, deciles, and quartiles. Further models considered GFR over versus under

the historical cutoff of 50 mL/min per 1.73 m². Similar models were created in the subgroup of patients with available GFR at time of listing in order to assess change in GFR between listing and transplant as a predictor of outcomes.

Recursive partitioning was performed using JMP Pro v10 (SAS Institute Inc, Cary, NC). All other statistical analyses were carried out using SAS v9.2 (SAS Institute Inc).

Results

Overall Patient Characteristics

A total of 794 transplant recipients met the study criteria and were included in the analysis. Mean age for the entire sample was 51.9 ± 14.7 years and 41.3% of the patients were female; 85.1% of patients received bilateral lung transplantation. The average serum creatinine at time of transplant was 0.86 ± 0.25 mg/dL while the average GFR was 93.3 ± 24.3 mL/min per 1.73 m². The mean lung allocation score was 47.2 ± 16.5 [Table 1].

Characteristics Stratified by GFR Above or Under 50 mL/min per 1.73 m²

After stratification by GFR around the cutoff of 50 mL/min per 1.73 m², it was noted that compared with patients who had GFR 50 mL/min per 1.73 m² or greater (n = 778), patients with GFR less than 50 mL/min per 1.73 m² (n = 16) were older, more likely to have undergone transplantation for restrictive disease, and less likely for cystic fibrosis (*p* < 0.05). Notably, patients in the low GFR group spent an average of 29 ± 36 days on the waitlist, significantly lower than the average of 209 ± 433 days for the high GFR group (*p* < 0.001) (Table 1).

Serum tacrolimus levels up to 5 weeks after transplant were significantly higher for high GFR patients with median weekly average equal to 11.53 mg/dL versus 8.63 mg/dL for low GFR patients (*p* = 0.014). Of the 3 low GFR patients who required dialysis posttransplant, none survived past 1 year. All still had dialysis requirements at time of death. No patient in the low GFR group received kidney transplantation during the study dates.

Comparative Survival of Patients With GFR Above Versus Under the Cutoff of 50 mL/min per 1.73 m²

One-year mortality in patients with GFR less than 50 mL/min per 1.73 m² was 31.3% (n = 5 of 16) compared with 15.1% (n = 118 of 778) in the group with GFR greater than 50 mL/min per 1.73 m². Additionally, overall survival difference was statistically significant based on the Kaplan-Meier method (*p* = 0.021) [Fig 1A]. Unadjusted Cox regression analysis generated a hazard ratio of 2.18 (95% confidence interval [CI], 1.12 to 4.24) for patients with GFR below the cutoff compared with those with GFR above it. Multivariable Cox regression models demonstrated that GFR at time of transplant, considered as any of individual values, deciles, or quartiles, was not an independent predictor of overall survival (*p* > 0.05). The GFR over versus under the cutoff of 50 mL/min per 1.73 m² demonstrated a trend toward statistical significance for predicting survival (*p* = 0.086).

Cause of death for the 5 patients in the low GFR group included respiratory failure secondary to metastatic adenocarcinoma, cardiac arrest, septic shock (×2), and primary graft

dysfunction. There were no clear relationships between early mortality and age, race, or pretransplant diagnosis ($p > 0.05$).

Recursive Partitioning and ROC Analysis to Estimate GFR Cutoffs Based on Mortality at 1 Year

Recursive partitioning identified $\text{GFR} = 48.0 \text{ mL/min per } 1.73 \text{ m}^2$ as the value that maximized difference in 1-year survival when comparing patients with lower GFR to those with equal or higher GFR (Table 2). A total of 782 patients had GFR above this cutoff with 15.1% 1-year mortality ($n = 118$), compared with 12 patients below this cutoff who had a 41.7% mortality at 1 year ($n = 5$) (Table 3). The overall survival difference was statistically significant based on the Kaplan-Meier method ($p = 0.007$) (Fig 1B). Unadjusted Cox regression models generated a hazard ratio of 2.80 (95% CI, 1.32 to 5.93) for patients with GFR below $48.0 \text{ mL/min per } 1.73 \text{ m}^2$ compared with those above this value.

The ROC analysis examining GFR as a predictor of 1-year mortality generated an area AUC of 0.549 (95% CI, 0.493 to 0.605) (Fig 2) and identified a $\text{GFR} = 77.8 \text{ mL/min per } 1.73 \text{ m}^2$ as the value that maximizes the sum of sensitivity and specificity (Table 2). Sensitivity and specificity at this value were 0.33 and 0.78, respectively. A total of 596 patients had GFR above this value with 13.8% ($n = 82$) mortality at 1 year, compared with 198 patients below with 20.7% ($n = 41$) mortality (Table 3). There was no difference in unadjusted survival when comparing patients with GFR below this ROC-based cutoff to those with GFR above it ($p = 0.976$) (Fig 1C).

Reclassification into low versus high GFR based on the cutoff of $48 \text{ mL/min per } 1.73 \text{ m}^2$ identified by recursive partitioning changes the number of patients with GFR below the cutoff from 16 (2% of the total) to 12 (1.5%). The 4 patients reclassified into the normal GFR group survived beyond 1 year. None required dialysis prior to discharge and only 1 suffered from AKI.

Analysis of Secondary Outcomes

The incidence of acute kidney injury (AKI) was 43.8% ($n = 7$) for patients with GFR below the historical cutoff of $50 \text{ mL/min per } 1.73 \text{ m}^2$ compared with 15.8% ($n = 123$) for patients with GFR above the cutoff ($p = 0.003$). For patients with GFR below the historical cutoff of $50 \text{ mL/min per } 1.73 \text{ m}^2$, 18.8% required hemodialysis prior to discharge, compared with only 7.3% of patients with GFR above the cutoff ($p = 0.087$).

Looking at AKI and dialysis as outcomes, recursive partitioning identified GFR values of $61.3 \text{ mL/min per } 1.73 \text{ m}^2$ and $46.1 \text{ mL/min per } 1.73 \text{ m}^2$, respectively, as ideal cutoffs for differentiating results. Suggested cutoffs by ROC analysis, as well as comparative outcomes around various cutoffs are reported in Tables 2 and 3.

Multivariable logistic regression models demonstrated that GFR decile at time of transplant is an independent predictor of AKI ($p < 0.01$; hazard ratio per unit decrease in decile, 1.18; 95% CI, 1.09 to 1.27). Transplant GFR was not an independent predictor of in-hospital dialysis requirement although this was an uncommon complication and likely not powered to be detected.

Subgroup Analyses in Patients With Serum Creatinine Data From Time of Listing

Four hundred sixty-five patients (58.5%) had available creatinine data from transplant listing and were included in the subgroup analysis. Patients in this subgroup were similar to the entire study population based on age (55.7 ± 13.2 years), gender make up (34.6% female), and procedure type (87.3% bilateral procedures). Additionally, average lung allocation scores (47.3 ± 16.5) and GFR (89.2 ± 21.0 mL/min per 1.73 m^2) were comparable. For the subgroup, average drop in GFR between listing and transplant was 2.6 ± 16.8 mL/min per 1.73 m^2 .

Twelve of the sixteen patients in the low GFR group (75%) had GFR greater than 50 mL/min per 1.73 m^2 at time of listing, up to several weeks prior to transplant. The average drop in GFR between listing and transplantation for the low GFR patients was 15.2 mL/min per 1.73 m^2 (compared with 2.12 mL/min per 1.73 m^2 in the high GFR cohort).

Multivariable Cox regression models demonstrated that change in GFR between time of listing and transplant, considered as any of individual values, deciles, quartiles, or yes or no for having GFR loss prior to transplant, was not an independent predictor of overall survival, acute kidney injury, or dialysis ($p > 0.05$).

Comment

Given the need for appropriate organ allocation, recipient selection is extremely important. In this study we demonstrate survival differences that are clinically and statistically significant when comparing patients on either side of a GFR inflection point around 50 mL/min per 1.73 m^2 . Using recursive partitioning methods, we estimated cutoffs based on 1-year mortality, acute kidney injury, and dialysis (48.0, 61.3, and 46.1 mL/min per 1.73 m^2 , respectively) that are remarkably similar to the historical exclusion value. This is notable, especially given the fact that the model for recursive partitioning was uninfluenced by the 50 mL/min per 1.73 m^2 cutoff. ROC analysis was less successful at estimating clinically relevant cutoffs, a finding that we attribute to the inadequacy of ROC models for predicting outcomes based on pretransplant GFR (evidenced by AUCs ~ 0.5). Additionally, analyses suggest that GFR decline from listing to transplant is not a predictor of negative posttransplant outcomes. Altogether, these findings indicate that it is appropriate for patients with preoperative GFR values less than 50 mL/min per 1.73 m^2 to be considered highrisk candidates for lung transplantation.

The observed relationship between low GFR and poor outcomes is driven by a combination of several factors. Globally, renal dysfunction is commonly an indicator of poor health, often accompanying comorbidities like diabetes mellitus and hypertension. With such risk profiles, patients with low GFR are likely to have poorer outcomes. Similarly, dialysis is a common eventuality for these patients and is itself associated with adverse outcomes. An additional consideration relates to the use of immunosuppressive medications in these patients. Our results suggest that serum levels, and likely dosing, of these drugs are lower for patients with significant renal dysfunction. Given the nephrotoxic effects of immunosuppressive treatment, such caution is appropriate. However, lower levels of immune modulation may contribute to deaths due to rejection and graft failure.

Our center has maintained a policy of using a GFR of less than 50 mL/min per 1.73 m² as a relative contraindication to transplantation. In fact, only 2% of our recipients had GFR less than 50 mL/min per 1.73 m² at the time of transplant, and most of those (75%) were listed at a higher GFR but subsequently had a marginal loss of GFR before transplant. The occurrence of changes in GFR suggests that routine follow-up of GFR while on the waitlist might be beneficial in patients awaiting lung transplantation, even though deterioration in GFR itself for the entire cohort was not identified as a predictor of outcomes. Other patient populations transplanted with marginal renal function but otherwise ideal candidacy (ie, minimal comorbidities, young age, and relative functional independence) include patients with established potential living kidney donors in the event that end-stage renal disease develops after transplantation. In principle, patients with a diagnosis of pulmonary hypertension may suffer from impaired renal function due to poor forward flow and resulting poor renal perfusion. Therefore, this group of patients theoretically stands to recover some renal function after lung transplantation.

In the current study our results support the practice of using a candidate's GFR as a relative exclusion criterion. Results demonstrate notable superiority in outcomes for lung candidates with better renal function. In fact, with a hazard ratio nearly threefold of baseline, a pretransplant GFR less than 48 mL/min per 1.73 m² (estimated with recursive partitioning) remains more predictive for 1-year mortality posttransplant than any other recipient characteristics included in the lung allocation score calculation. It is important to note that recursive partitioning provides mathematic separation based upon the outcome of interest, generating a cutoff value that may or may not be the best option in clinical practice. Additionally, our single-center analysis remains preliminary, particularly given the small number of patients in the low GFR group. Analyses in larger cohorts will be required to make definitive recommendations about adjusting the current GFR cutoff for lung transplantation. In the interim, individual transplant programs will need to decide how to incorporate these new data into their candidate evaluation process.

Our study has a few limitations. First, we consider only patients who ultimately received lung transplantation, potentially creating a selection bias in our population. Many candidates were denied transplantation in part or solely due to low GFR and patients with borderline renal function who did undergo lung transplantation were otherwise ideal candidates. Thus, patients in our study who received lung transplantation despite having GFR less than 50 mL/min per 1.73 m² are not likely representative of the entire population of lung transplant candidates with borderline renal function. A second limitation is our estimation of GFR based on the CKDEPI equation, even though decisions about exclusion from transplantation can be made using a variety of other direct or indirect GFR measurements, at our center this typically includes a nuclear GFR assay. Benefits of performing our analysis using the CKDEPI equation included increased study power, generalizability of values, and application beyond our center. Moreover, the CKDEPI equation has been shown to be a good estimator of renal function [11, 12]. Finally, it should be noted that most of the low GFR patients suffered a drop, albeit modest, in GFR between listing and transplant. This raises a question of applicability to recipients with chronic kidney disease that is stable.

In conclusion, this study evaluated the GFR cutoff of 50 mL/min per 1.73 m² that has historically been used as an independent exclusion criterion from lung transplantation. Results suggest that this cutoff appropriately identifies patients who are at high risk for adverse outcomes posttransplant. Findings are supported by the fact that alternative cutoffs, identified using independent statistical analyses, are very similar to the historical value. Future work will reproduce this analysis in a larger cohort of patients, facilitating the establishment of definitive guidelines for acceptable GFR in lung transplantation.

DISCUSSION

DR MARK S. SLAUGHTER (Louisville, KY): In the patients that predominantly had primary pulmonary hypertension and presumably their renal function deteriorated while on the list and was presumably from low output, are they put on inotropic support or anything to “try and improve” forward flow and document that it’s easily reversible, or is it treated afterwards to see what happens?

MR OSHO: That’s a great question, and actually speaking to that point, the four patients with pulmonary hypertension on our list didn’t drop their GFR very much between listing and actual transplantation. They were actually in the group that had moderately bad GFR but moderately preserved between listing and transplantation.

I am going to call on Matt Hartwig, our senior here, to speak to the inotrope use.

DR SLAUGHTER: We have the same problem with hearts and VADs and it’s a very sticky wicket, because the idea is to maintain the flow postop. You generally still have to have a high CVP [central venous pressure] to maintain your cardiac output. So therefore you intrinsically are going to have continued renal dysfunction or if you try and diurese them, then, once again, their creatinine just goes up.

DR MATTHEW G. HARTWIG (Durham, NC): Thanks, Asishana, for a wonderful talk. These patients, at least in this series, were not in the hospital and not on inotropes during that time. In fact, we did not notice a significant deterioration in the pulmonary hypertensives’ renal function between listing and the time of transplant and these were not on inotropic support.

DR DAVIS: There has been shift. Obviously they’re on PH [pulmonary hypertension] drugs and for the most part they are on triple-agent therapy. We’re starting to use ambulatory ECMO [extracorporeal membrane oxygenation] strategies on these folks. It’s combination VV/VA [Veno-venous/Veno-arterial] where we cannulate the axillary and we use the Avalon’s and kind of adjust the flows.

Our listing conferences can be quite contentious depending how much our pulmonary group has fallen in love with the patient and they are convinced that it’s all going to get better once you transplant him. Anyone who does lung transplant knows this is the absolute worst population. You have a PH who is end-stage, the belly is out to here; it looks like they have got twins or triplets. They’re not exactly going to immediately bounce back after you put lungs in them. Now, if they’re young enough, usually you can ride out the storm, but it’s not

that they're magically going to right the ship. And those are the patients that I would say are most likely to have a spin on the dialysis circuit before they actually get better. But they can get better, and it's difficult decision-making that I think we all struggle with.

The idea that we got 16 of them when we were not supposed to was kind of an interesting phenomenon as it is. But it's the same deal. Somehow they got transplanted, so we thought one way or another that they were transplantable. I think the UNOS [United Network for Organ Sharing] data set is going to be very interesting to see if we get a very similar cutoff or not with respect to GFR and outcomes.

It's on both sides of the LAS [lung allocation score] calculator; it's both a predictor of mortality on the wait list and it's a predictor of mortality after transplant. We have had some discussions, what is too much? Is a 30% mortality rate at one year too much? You are held to your center's outcomes as reported by SRTR [Scientific Registry for Transplant Recipients]. Therefore it may be too much, but can you take a few of these patients on and bury them in a bunch of other people who have good outcomes? Those are decisions to be made by centers.

But if you took a patient perspective, if they're looking at an IPF [idiopathic pulmonary fibrosis] diagnosis and they have got a 50-plus percent mortality, I know what most of them sign up for. The question is how many can you actually take on?

DR MICHAEL J. DIMAIO (Dallas, TX): Excellent work, nice presentation. You did a great job explaining the statistics. It's my lack of understanding of some of it. But with 16 patients, how much confidence do you have in this data to be able to go forward and utilize it in such a manner? Number two, have you done that? I heard Duane mention about the different contentious discussions in the committees, but have you begun to use this data moving forward in your selection process and changed anything?

MR OSHO: I will start with the second question, which is the easier one to answer. We haven't changed anything. At our center we still use the 50 as a cutoff, and even in the setting of this data we continue to do that.

To speak to the first question, 16 patients is, as you mentioned, a limitation, a very small number, and it certainly doesn't give us the confidence to change policy based on that. We are hoping to continue this analysis using the UNOS data set and larger sets, and I think that will give us much, much larger power.

DR DIMAIO: Were you or the attending surprised that 16 was the number? I would have thought it would have been a greater number. You have been so aggressive that you would have had more patients than 16 that would qualify.

DR DAVIS: But this is only the first count. So it excludes all the retransplants that are much more likely.

Now what it does do, so you have somebody who has got borderline renal function. We know that they are at risk. If they get below 30 or they are on dialysis, the kidney doctors

will give up the cadaveric kidney and you can go ahead and list them for a lung/kidney, and that's a good point.

What do you do in the gray zone from 30 to 50? And this actually helps from the standpoint programatically we were saying, all right, you want to take these on. You have got to identify a living donor to be in the wings that is suitable both from an HLA [human lymphocyte antigen], et cetera, match, and is physiologically sufficient to donate. So that if you get into the dialysis hell, you have got an exit point.

And we have struggled with our kidney team actually working them up. This gives us a little more leverage to say, yes, please continue; this is the reason to do this. If it's somebody we think may be a salvageable lung transplant, here is another strategy to be able to get them an acceptable outcome.

DR SLAUGHTER: One more quick question. Do you have an idea, though, also of why those patients died? Are they dying of renal-related complications or from modifying the immunosuppression that subsequently results in transplant-related issues? Is there a way to balance it to even maybe achieve a better outcome; ie, just start early dialysis if they are dying of renal complications and still give them full immunosuppression or vice versa?

MR OSHO: For the five patients with low GFR who died, two were septic shock, one was cardiac arrest, one was primary graft dysfunction, and then the last one had a pulmonary malignancy that caused respiratory dysfunction. All seemed pretty unrelated, well the graft dysfunction maybe, but all seemed pretty unrelated to renal dysfunction.

DR DAVIS: Well, I would say the infection most likely goes with it. I mean, the idea that you have got a wet lung that you can't dry out often leads to it.

We have all been there. It's the spiral of you don't have a great lung, therefore they're on the ventilator longer, they have got lines in them longer. You're just waiting for the infection. They die from infection because you had them in the hospital for God knows how long.

DR SIMON MALTAIS (Nashville, TN): Do you have to use a heart-lung machine more on these transplants? Let's say you want to remove fluid.

DR DAVIS: There is surgeon variation. I would say that by and large our group is an off-pump group. You use pump when you need to. Now, a PH patient is much more likely to end up on a pump. Again, we're probably doing more ECMO-related avenues of support for transplant. So, yes, these patients are more likely to have that. It gets more into all of the lowering of the immunosuppression, et cetera.

One of the interesting things that Dr Hartwig was looking at, we were expecting to see an injury pattern between 50 and 70. It didn't happen, because we lowered the immunosuppression enough that we actually keep the kidneys going. It doesn't have a short-term effect; it may have a longer-term effect. But on the short term, there was no mortality risk in that group. It actually started getting worse, outside of the range we thought we were safe in.

So it became that, what was it, 85, somewhere in there, 70 to 85, and you're thinking, oh, that's not a problem child. Yes, it turns out it is probably a problem child because it's not normal kidney function.

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Fig. 1.

Kaplan-Meier analysis of survival to 2 years, stratified by GFR above or below specified cutoffs. (A) Cutoff, 50.0 mL/min per 1.73 m² (historical); (B) Cutoff, 48.0 mL/min per 1.73 m² (recursive); (C) Cutoff, 77.8 mL/min per 1.73 m² (receiver operating characteristic, ROC). We observed significant differences in mortality on either side of the historic and recursive partitioning cutoffs. The ROC established cutoff did not generate groups with differing mortality. (CI = confidence interval; HR = hazard ratio.)

Fig. 2.

Receiver operating characteristics (ROC) curves displaying the sorting efficiency of Chronic Kidney Disease Epidemiology Collaboration glomerular filtration rate (GFR) for predicting post-lung transplant mortality at 1 year. The GFR value that maximizes the sum of sensitivity and specificity (ie, the ideal cutoff GFR values by the receiver operating characteristics method) is reported along with area under the curve (AUC). (CI = confidence interval.)

Table 1

Patient Characteristics

Characteristic	Entire Sample n (%) or Mean (SD)	GFR ≥ 50 mL/min per 1.73 m ² n (%) or Mean (SD)	GFR < 50 mL/min per 1.73 m ² n (%) or Mean (SD)	<i>p</i> Value ^a χ^2 or <i>t</i> test
Number of patients	794 (100)	778 (100)	16 (100)	
Age recipient, years	51.9 (14.7)	51.7 (14.8)	61.6 (9.6)	0.008 ^b
Female gender	328 (41.3)	321 (41.3)	7 (43.8)	0.841
White ethnicity	704 (88.7)	690 (88.7)	14 (87.5)	0.882
Body mass index (n = 712)	23.6 (4.1)	23.6 (4.1)	25.3 (3.3)	0.098
Serum creatinine at time of transplant, mg/dL	0.86 (0.25)	0.85 (0.23)	1.54 (0.29)	0.001 ^b
Highest serum creatinine within the first week after transplant, mg/dL	1.87 (1.03)	1.85 (1.02)	2.92 (1.00)	0.001 ^b
CKDEPI GFR at time of transplant, mL/min per 1.73 m ²	93.3 (24.3)	94.3 (23.5)	43.9 (5.4)	0.001 ^b
Diagnosis				
Obstructive disease	257 (32.4)	252 (32.4)	5 (31.3)	0.007 ^b
Restrictive disease	339 (42.7)	330 (42.4)	9 (56.3)	
Cystic fibrosis/bronchiectasis	148 (18.6)	148 (19.0)	0 (0.0)	
Primary pulmonary hypertension	15 (1.9)	13 (1.7)	2 (12.5)	
Other	35 (4.4)	35 (4.5)	0 (0.0)	
Wait list time, days	205 (429)	209 (433)	29 (36)	0.001 ^b
Bilateral transplant	676 (85.1)	663 (85.2)	13 (81.3)	0.659
Age of donor, years (n = 776)	34.8 (15.4)	35.0 (15.4)	27.4 (13.6)	0.051
Female donor	276 (38.8)	273 (39.2)	3 (18.8)	0.097
Cold ischemic time, hours (n = 619)	6.6 (1.9)	6.6 (1.9)	7.5 (1.8)	0.086
Lung allocation score (n = 438)	47.2 (16.5)	47.1 (16.4)	14 (19.5)	0.633

CKDEPI = Chronic Kidney Disease Epidemiology Collaboration; GFR = glomerular filtration rate.

^a Student *t* test for continuous variables; χ^2 for categorical variables.

^b Statistically significant at alpha = 0.05.

Table 2

Estimated GFR Cutoffs for Excluding Patients From Lung Transplantation

Analysis Method	GFR (mL/min per 1.73 m ²)
Mortality at 1 year	
Recursive partitioning	48.0
ROC analysis	77.8
AKI ^a	
Recursive partitioning	61.3
ROC analysis	77.4
Dialysis prior to discharge	
Recursive partitioning	46.1
ROC analysis	85.9

AKI = acute kidney injury; GFR = glomerular filtration rate; ROC = receiver operating characteristics.

^a AKI is defined as serum creatinine greater than 3mg/dL within the first week after transplant.

Table 3

Comparative Outcomes for Patients With GFR Above and Below the Cutoffs

Variable	1 Year Mortality	AKI	Dialysis
Traditional cutoff (mL/min per 1.73 m ²)	50.0	50.0	50.0
Risk below cutoff (%)	31.3	43.8	18.8
Risk above cutoff (%)	15.2	15.8	7.3
Relative rate	2.1	2.8	2.6
<i>p</i> value (log-rank or χ^2) ^a	0.021	0.003	0.087
Recursive partitioning cutoff (mL/min per 1.73 m ²)	48.0	61.3	46.1
Risk below cutoff (%)	41.7	36.5	33.3
Risk above cutoff (%)	15.1	14.6	7.3
Relative rate	2.8	2.5	4.6
<i>p</i> value (log-rank or χ^2) ^a	0.007	0.001	0.003
ROC analysis cutoff (mL/min per 1.73 m ²)	77.8	77.4	85.9
Risk below cutoff (%)	20.7	25.3	10.3
Risk above cutoff (%)	13.8	13.5	5.8
Relative rate	1.5	1.9	1.7
<i>p</i> value (log-rank or χ^2) ^a	0.976	0.001	0.018

AKI = acute kidney injury; GFR = glomerular filtration rate; ROC = receiver operating characteristics.

^aLog-rank for mortality; χ^2 for AKI, dialysis.