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Determining eligibility for lung transplantation: A nationwide assessment of the cutoff glomerular filtration rate

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BACKGROUND: Historical concerns about lung transplantation in patients with a glomerular filtration rate (GFR) $\leq$ 50 ml/min/1.73 m^2 have not been validated. We hypothesize that a pre-transplant GFR $\leq$ 50 ml/min/1.73 m^2 represents a high mortality risk, especially in the setting of acute GFR decline. In addition, we explore the potential for improved risk stratification using a statistically derivable alternative cutoff.

METHODS: Adult, primary, lung recipients in the United Network for Organ Sharing database were analyzed (October 1987 to December 2011). Recursive partitioning identified the GFR value that provides maximal separation in 1-year mortality. Survival over/under the cutoffs was compared using stratified log-rank, Cox, and Kaplan-Meier methods, before and after 1:2 propensity score matching.

RESULTS: Median GFR at time of transplant for 19,425 study patients was 94.2 ml/min/1.73 m^2 (quartile 1–quartile, 2 76.9–105.9 ml/min/1.73 m^2). Recursive partitioning identified a GFR of 40.2 ml/min/1.73 m^2 as the ideal inflection point for predicting 1-year survival. Cutoffs demonstrated statistically significant effects on survival after 840 patients with a GFR $\leq$ 50 ml/min/1.73 m^2 (hazard ratio, 1.28; 95% confidence interval, 1.15–1.43) and 401 patients with a GFR $\leq$ 40.2 ml/min/1.73 m^2 (hazard ratio, 1.57; 95% confidence interval, 1.36–1.83) were matched with high GFR controls ($p < 0.001$). In 13,509 patients with available GFR at the time of listing and transplant, a pre-transplant GFR decline of $\geq$ 50% from baseline was associated with worse survival ($p < 0.001$).

CONCLUSIONS: A pre-transplant GFR $\leq$ 50 ml/min/1.73 m^2 is associated with decreased survival. However, patients with GFR between 40 and 50 ml/min/1.73 m^2 do not suffer excessive post-transplant mortality and should not be automatically excluded from listing. Notably, outcomes are worse in patients with poor renal function and concomitant pre-transplant GFR decline. Strategies should be devised to detect and manage interval renal deterioration before lung transplantation.

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Poor pre-operative renal function is associated with adverse outcomes after lung transplantation, including early death and long-term chronic kidney disease.[1–5] Historically, a minimum glomerular filtration rate (GFR) of 50 ml/min/1.73 m^2 has been required for lung transplantation. This value is

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based on recommendations from the initial version of the "International Guidelines for the Selection of Lung Transplant Candidates" published in 1998.[6] Although many transplant centers—including ours—continue to adhere to this recommendation, there is a paucity of data to support it.

Previous work from our center provided the first empiric evidence evaluating this cutoff. In an analysis of 794 lung recipients, we concluded that a GFR $\leq$ 50 ml/min/1.73 m^2 at transplant was associated with increased peri-operative mortality.[7] However, we also noted that some patients with GFR below this cutoff might have acceptable survival. Unfortunately, that analysis was underpowered to make strong recommendations involving other cutoffs between 40 and 50 ml/min/1.73 m^2 that may provide optimal risk stratification for lung transplant candidates.[7]

Therefore, the aim of the current study was to analyze data from a nationwide database to assess overall survival around the 50 ml/min/1.73 m^2 GFR cutoff for lung transplantation. We tested the hypothesis that a GFR $<$ 50 ml/min/1.73 m^2 at transplant is associated with worse survival for lung recipients. In addition, we estimated alternative GFR thresholds for lung transplantation, hypothesizing that a statistically derived cutoff would provide a more rigorous standard to guide candidate evaluation and eventual transplantation.

Methods

The study protocol was approved by the Duke University Institutional Review Board. Individual patient consent was not needed.

Study design and patient selection

The United Network for Organ Sharing (UNOS) national database was queried for all United States adult transplantations recorded between October 1987 and December 2011. The primary inclusion criterion was availability of serum creatinine data at the time of transplant. The study excluded patients who underwent multiorgan or repeat transplant, or were aged younger than 18 years at transplantation. The primary study outcome was overall survival.

Estimation of GFR

GFR was estimated using the original Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, which incorporates creatinine as the only serum marker of renal function. UNOS does not routinely collect cystatin C data, precluding the use of newer versions of this equation. CKD-EPI was used instead of the Modified Diet in Renal Disease equation because of its documented superiority for GFR estimation in cohorts with broad ranges of renal function.[8–10]

The primary analysis was performed using GFR estimated based on the last available serum creatinine before transplant. A sub-group analysis was performed in patients for whom creatinine data were also available from the time of listing for transplantation.

Recursive partitioning

Recursive partitioning methods 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.[11] The goal is to maximize differences in the distributions of outcomes when comparing patients on either side of the split value.

Propensity score matching

Patients with GFR below historical and partitioning established cutoffs were matched 1:2 with high GFR controls (i.e., patients with GFR above the cutoffs) using the propensity score method as previously applied in the lung transplantation literature.[12–16] This method examines and controls for difference in measured characteristics between cohorts. In this study, the propensity score itself reflects the probability of having GFR below either cutoff, based on underlying patient, donor, and transplant characteristics. Scores were estimated using logistic regression models with covariate retention based on a stepwise selection algorithm. Variables included in the baseline model are noted in Table 1.

After conventions for addressing missing data in the propensity score analyses,[15–17] an additional level was created for each categoric variable to indicate missing data. For continuous variables, a value of 0 was imputed into empty fields, with subsequent creation of a new, binary variable indicating whether the patient had missing information. Balance in characteristics between the matched cohorts was assessed using standardized difference, with values less than 0.2 indicating negligible variation.[18,19]

Primary analysis

Overall survival rates for matched and unmatched groups were estimated using the Kaplan-Meier method and compared by the log-rank test. Comparisons of matched samples were done using a stratified log-rank test with classification based on quartiles of the propensity score.[20] Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models controlling for strata of the propensity score.

Secondary analysis

A sub-group analysis was performed in patients with available serum creatinine data from the time of listing as distinguished from the main analysis, which was based on creatinine from the time of transplant. For each patient in this sub-group, the change in GFR between listing and transplantation was estimated and included in regression models as a potential predictor of outcomes. Log-rank methods estimated the effects on survival of having a major decline in GFR, defined as $\geq$ 50% drop from baseline. Additional analyses tested for confounding by including major GFR decline and GFR above vs below cutoffs in models as possible predictors of survival.

Statistical analysis

Recursive partitioning was performed using JMP Pro 10 software (SAS Institute Inc, Cary, NC). All other analyses were done using SAS 9.3 software (SAS Institute Inc).

Results

Patient characteristics

A total of 19,425 lung recipients (45% women) met criteria for inclusion in the study. Median age was 56 years (25th [quartile 1]–75th [quartile 3] percentiles [Q1–Q3], 45–61 years), and