Mortality Prediction After Kidney Transplantation: Comparative Clinical Use of 7 Comorbidity Indices

Jason Moore,1,3 Xiang He,2 Xiang Liu,2 Shazia Shabir,1 Simon Ball,1 Paul Cockwell,1 Nicholas Inston,1 Mark A. Little,1 Atholl Johnston,2 Richard Borrows1

Abstract

Objectives: Despite comorbidity associated with chronic kidney disease, little data exist applying comorbidity scoring systems to renal transplant recipients. This study compared the performance of 7 established comorbidity scores in predicting mortality after kidney transplantation.

Materials and Methods: We retrospectively analyzed prospectively collected data from 2033 incident renal transplant recipients. Comorbidity was assessed at baseline, and the following scores were derived: Recipient Risk Score, Charlson Comorbidity Index, Age-adjusted Charlson Comorbidity Index, Modified End-Stage Renal Disease Charlson Comorbidity Index, Foley Score, Wright-Khan Index, and Davies Index. Cox models investigated the association of each comorbidity score with mortality; performance characteristics were tested using receiver operating characteristic curve analysis.

Results: Age-stratified Cox analyses showed the Recipient Risk Score-based model displayed the best fit, and receiver operating characteristic curve analysis showed the Recipient Risk Score demonstrated greatest predictive use (5-year mortality c-statistic: 0.787). The independent effect of age on mortality was demonstrated after analysis of scores not containing age as a component (the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, the Davies Index). Addition of age to these scores improved fit.

Conclusions: Of the currently available comorbidity scores, the Recipient Risk Score demonstrated greatest use. This has implications for deceased-donor allocation algorithms, assessment of confounders in clinical research, and potentially, individual patient management.

Key words: Prediction, Recipient risk score

Introduction

Surprisingly, little evidence exists quantifying the importance of comorbidity in renal transplantation, despite the burden of comorbid conditions present in patients with kidney disease and the effect of these conditions on mortality and graft failure. Assessment of the prevalence and consequences of comorbid conditions has important implications for individual patient management, for clinical research where adjustment for comorbid confounders is necessary, and in developing organ allocation policies. With regard to the latter, organ allocation algorithms based on either pure utilitarian principles (designed to maximize allograft lifespan) or on “net lifetime survival benefit” (designed to maximize overall patient survival on the wait list) are critically dependent on incorporating comorbidity assessment.

Several comorbidity indices have been developed and validated in renal populations, the most notable and widely tested being the Charlson Comorbidity Index. The Charlson Comorbidity Index was initially developed in a cohort of general medical patients as both a pure weighted comorbidity score and also, as a score incorporating age (age-adjusted Charlson Comorbidity Index).1-3 Both the Charlson Comorbidity Index and the Age-adjusted Charlson...
Comorbidity Index have been validated in hemodialysis and peritoneal dialysis test populations. The initial Charlson Comorbidity Index has also been modified for use specifically in end-stage renal disease patients (Modified End-Stage Renal Disease Charlson Comorbidity Index).

Other validated indices include the Davies index (derived from peritoneal dialysis patients) and the Wright-Khan scoring system (derived from patients starting renal replacement therapy). The Foley score, a lesser known but clinically applicable prognostic scoring system (developed to aid in the prediction of death within 6 months of starting maintenance dialysis), has not been validated in a separate test population. More recently, the Recipient Risk Score has been developed as a practical system that when combined with a method to assess donor organ quality may improve deceased-donor kidney use. The Recipient Risk Score is the first comorbidity score developed specifically for renal transplant recipients.

Apart from this recent description of the Recipient Risk Score, only 2 previous studies have addressed the association between comorbidity scores and subsequent mortality in renal transplant recipients. The first showed an association between baseline the Charlson Comorbidity Index and mortality. The second study, from Jassal and associates, compared the performance of the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, the Davies Index, and the Wright-Khan Index simultaneously, concluding that the Charlson Comorbidity Index was the score best associated with subsequent mortality. However, this study did not assess the Age-adjusted Charlson Comorbidity Index, the Foley Score, or the more-recently developed Recipient Risk Score. In addition, the performance characteristics of the scores regarding their use in predicting subsequent mortality was not assessed. Therefore, the important task of translating the results from the level of the population to the level of the individual was not possible.

This study sought to comprehensively assess and compare the use of 7 comorbidity scores in predicting mortality in renal transplant recipients.

Materials and Methods

Patient population
The Long-Term Efficacy and Safety Surveillance (LOTESS) database was interrogated for the analysis. The Long-Term Efficacy and Safety Surveillance is a pharmaceutical-industry–funded pharmacovigilance project that collects data on renal transplant recipients treated with microemulsion cyclosporine therapy. Long-Term Efficacy and Safety Surveillance is an open, observational cohort study, and is conducted according to the guidelines for the safety of marketed medicines, the design of which has been described in detail previously and has yielded valuable insight into renal transplant outcomes in previous analyses. Patients from 64 centers in the United Kingdom were recruited between 1995 and 1998 and followed prospectively for up to 7 years. Participating centers submitted anonymized data on a 3-month basis to the central medical information processing and statistics department; data were collected by trained professional study monitors operating to good clinical practice standards. Although the database is limited to patients treated with microemulsion cyclosporine, the use of alternative calcineurin inhibitors (ie, tacrolimus) was uncommon in the United Kingdom during the period of data collection, and therefore, is largely representative of the United Kingdom renal transplant population as a whole.

Data were analyzed for incident adult (age ≥ 16 years) renal transplant recipients who displayed a complete set of data for the clinical variables described below. The study conformed with the ethical guidelines of the 1975 Helsinki Declaration.

Primary variables of interest: mortality and comorbidity
The outcome measure of interest was patient mortality, assessed by survival from the time of transplant until death or study termination. As with most data sets, information regarding death after graft loss is incomplete, and therefore, the analysis focuses on death with graft function. The exploratory variables of interest were the various comorbidity scores measured at baseline (ie, at the time of transplant). Scores were selected for analysis based on relevance to the renal population or prior validation in renal patients, recent development, and practicality of use. Relevant recipient demographics were collected to derive results for the comorbidity scores (detailed in the appendix to this manuscript). The “raw” comorbidity data (a total of 1303 possible qualifiers as individually reported comorbidities) submitted by the transplant centers was hand-searched and assimilated into each score category by
both JM and RB, with disagreement resolved by
discussion. For example, cardiac failure, cardiac failure
chronic, cardiac failure congestive, left ventricular failure,
ventricular failure, were all classified as congestive
heart failure for the Charlson Comorbidity Index.

The analysis was not performed by merely
developing a single multiple regression model after a
selection process to identify the comorbidity score(s)
that were significant in the final model. Rather, and
to overcome the inherent colinearity between these
scores, separate models were built, each of which
contained only 1 comorbidity score along with other
relevant baseline covariates (see below). The
goodness of fit for each model was then compared
using methodology described in the “statistical
analysis” section below. Comorbidity indices
contained within each model were as follows, and are
detailed in the appendix:

Model 1: Recipient Risk Score11
Model 2: Age-adjusted Charlson Comorbidity
Index2-3
Model 3: Foley Score10
Model 4: Wright-Khan Index8,9
Model 5: Charlson Comorbidity Index1
Model 6: Modified End-Stage Renal Diseases
Charlson Comorbidity Index6
Model 7: Davies Index7

Of relevance, the Recipient Risk Score, the Age-
adjusted Charlson Comorbidity Index, the Foley
Score, and the Wright-Khan Index incorporate age
scored equivalently to other comorbid disease,
whereas the Charlson Comorbidity Index, the
Modified End-Stage Renal Disease Charlson
Comorbidity Index, and the Davies Index are scored
by identifying only relevant comorbidities and do not
incorporate age (ie, “pure” comorbidity scores; see
appendix). The Charlson Comorbidity Index and the
Age-adjusted Charlson Comorbidity Index are
identically weighted scoring systems (with the sole
exception of age). Compared with the Charlson
Comorbidity Index, the Modified End-Stage Renal
Disease Charlson Comorbidity Index discards 4 of the
original comorbidities, assigns a lower weight to 2,
assigns a higher weight to an additional 6, leaving the
remaining 6 with the same weight. The Recipient Risk
Score can be fragmented into 4 “recipient grades” of
increasing comorbidity, and the Davies Index into 3
risk grades (see appendix).

Other data collection
To control for confounding factors in the analyses, the
following baseline variables (assessed at the time of
transplant) also were collected and entered into each
of the models: Donor demographics: age, sex, race, and
source (live- versus deceased-donor). Recipient
demographics: age, sex, race (white versus Indo-Asian
versus black versus other), duration of dialysis, dialysis
modality (hemodialysis versus peritoneal dialysis),
prior transplant, induction immunosuppression
(depleting antilymphocyte antibodies versus anti
CD25 monoclonal antibody versus none), use of
mycophenolate (versus azathioprine), and body mass
index.

Statistical analyses
The SAS software package for Windows (SAS
Institute Inc., Cary, NC, USA) was used for the
analyses. Summary statistics are shown as mean ±
standard deviation unless stated otherwise. Time to
event analyses was performed using the Cox model.
Factors showing an association with events on univariate analysis ($P < .15$) were entered into the
multiple regression models. The final model was
constructed by means of a forward conditional
stepwise selection process. In light of the colinearity
between the various comorbidity scores, an analysis
was not performed entering all the formulae as
covariates into a single analysis. Rather, separate
models were built, each containing 1 of the
comorbidity scores (ie, 7 models in all, each
containing 1 of the 7 comorbidity scores along with
the other independent variables). Goodness of fit for
the models was then compared using the Akaike
information criterion. The Akaike information
criterion is a statistical tool for ranking the models,
with a lower Akaike information criterion suggesting
a better fitting model.

A further challenge for the analysis was to
account for the effect of age, which was present as a
contributor to some, but not all, the comorbidity
scores, as discussed above. To overcome this, the time
to event analyses was performed in 3 stages. The first
analysis compared only those comorbidity scores
where age contributed to the score (the Recipient
Risk Score, the Age-adjusted Charlson Comorbidity
Index, the Wright-Khan Index, and the Foley Score).
In this analysis, age was removed as an independent
covariate from the statistical model, thereby
avoiding colinearity between age and the
comorbidity score. The second analysis compared only those comorbidity scores where age was not a contributor (the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index). In this analysis, age was assessed in the model as an independent covariate. Finally, all scores were simultaneously compared. For this final analysis, an age-stratified model was built to minimize the effect of age on the relation between comorbidity score and mortality.

The performance characteristics of the scores was tested by constructing receiver operating characteristic curves that assessed and compared the use of each comorbidity score in predicting mortality within the subsequent 3- and 5-year times. Area under the receiver operating characteristic curve, otherwise known as the c-statistic, was used to compare the discriminatory performance of the different comorbidity scores.

For all analyses, a type 1 error rate below 5% ($P < .05$) was considered significant.

**Results**

**Study group outcomes**

A total of 2033 adult (age ≥ 16 years) renal transplant recipients were available for analysis. Demographics of the group are shown in Table 1. All patients were treated with cyclosporine microemulsion, with 77% treated with adjunctive azathioprine and 4% with mycophenolate mofetil. Corticosteroids were administered to 91%. The values for the various comorbidity scores, assessed at the time of transplant, are shown in Table 2.

Mean follow-up for the cohort was 42 ± 20 months. Mortality at 1 and 2 years was 7.9% and 11.8%. Over the course of follow-up, 303 patients died resulting in a crude mortality rate of 14.9%. The cause of death was cardiovascular in 23%, infectious in 22%, and malignancy-related in 24%.

**Association between comorbidity and mortality: Cox model**

For the reasons described above, the initial analyses addressed separately those comorbidity scores that incorporate age (the Recipient Risk Score, the Age-adjusted Charlson Comorbidity Index, the Foley Score, and the Wright-Khan Index; models 1-4), and those that did not incorporate age (the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index; models 5-7). For models 1-4, recipient age was not entered as a separate explanatory variable during model building; for models 5-7, recipient age was entered as a covariate in the model building process. The final multiple regression models are shown in Tables 3 and 4. All comorbidity scores were significantly associated with mortality in their respective models ($P < .001$ for all). For the comparison of comorbidity scores that incorporated age (models 1-4), best fit (as assessed by Akaike information criterion) was seen for the Recipient Risk Score, followed by the Age-adjusted Charlson Comorbidity Index, the Foley Score, and the Wright-Khan Index (Table 3). For comparison of comorbidity scores that did not incorporate age (models 5-7), best fit was seen for the Charlson Comorbidity Index, followed by the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index (Table 4). Importantly, recipient age remained significant in the final multiple regression models 5-7 (ie, those not incorporating age; Table 4).
The final models are stratified into the following groups (years):

- Comorbidity Index, and the Davies Index.
- Age was modified for end-stage renal disease Charlson Comorbidity Index, the Foley Score, and the Wright-Khan Index to be compared with those that do not (the Charlson Comorbidity Index, the Davies Index).
- Limiting the influence of age in the analysis and allowing those comorbidity scores that incorporate age (the Recipient Risk Score, the Age-adjusted Charlson Comorbidity Index, the Foley Score, and the Wright-Khan Index) to be compared with those that do not (the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index).
- Age was stratified into the following groups (years): < 30, 31-40, 41-50, 51-60, > 60. The final models are shown in Table 5. With regard to model fit, the general "order" of the comorbidity scores was consistent with the previous analysis. Best model fit was seen with the Recipient Risk Score, followed by the Wright-Khan Index, which showed model fit similar to the Charlson Comorbidity Index and the Age-adjusted Charlson Comorbidity Index. No other baseline covariates were significant in any of the multiple regression models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% Confidence intervals</th>
<th>P value</th>
<th>Akaike Information criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Recipient Risk Score</td>
<td>4.92</td>
<td>3.43, 7.05</td>
<td>.0001</td>
<td>1389.10</td>
</tr>
<tr>
<td>2</td>
<td>Age-adjusted Charlson Comorbidity Index</td>
<td>1.70</td>
<td>1.52, 1.89</td>
<td>.0001</td>
<td>1413.27</td>
</tr>
<tr>
<td>3</td>
<td>Foley Score</td>
<td>1.74</td>
<td>1.51, 2.00</td>
<td>.0001</td>
<td>1435.56</td>
</tr>
<tr>
<td>4</td>
<td>Wright-Khan Index</td>
<td>3.18</td>
<td>2.29, 4.41</td>
<td>.0001</td>
<td>1442.36</td>
</tr>
</tbody>
</table>

For each model, only the comorbidity score(s) and age (and no other covariate) remained significant in the final multiple regression analysis for each model. Comparison is made between separate models (each containing a different comorbidity score) using Akaike information criteria. Improved model fit is associated with a lower Akaike information criterion.

- Effect per unit score.
- Effect per risk group.

For each model, only the comorbidity score and age (and no other covariate) remained significant in the final multiple regression analysis. Comparison is made between separate models (each containing a different comorbidity score) using Akaike information criteria. Improved model fit is associated with a lower Akaike information criterion.

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<th>95% Confidence intervals</th>
<th>P value</th>
<th>Akaike Information criterion</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>Recipient Risk Score</td>
<td>4.42</td>
<td>2.45, 7.97</td>
<td>.0001</td>
<td>1078.81</td>
</tr>
<tr>
<td>2</td>
<td>Wright-Khan Index</td>
<td>2.27</td>
<td>1.60, 3.23</td>
<td>.0001</td>
<td>1082.48</td>
</tr>
<tr>
<td>3</td>
<td>Charlson Comorbidity Index</td>
<td>1.46</td>
<td>1.25, 1.72</td>
<td>.0001</td>
<td>1082.98</td>
</tr>
<tr>
<td>4</td>
<td>Age-adjusted Charlson Comorbidity Index</td>
<td>1.46</td>
<td>1.24, 1.72</td>
<td>.0001</td>
<td>1083.02</td>
</tr>
<tr>
<td>5</td>
<td>Modified end-stage renal disease Charlson Comorbidity Index</td>
<td>1.28</td>
<td>1.14, 1.44</td>
<td>.0001</td>
<td>1086.39</td>
</tr>
<tr>
<td>6</td>
<td>Davies Index</td>
<td>1.57</td>
<td>1.22, 2.03</td>
<td>.0004</td>
<td>1090.11</td>
</tr>
<tr>
<td>7</td>
<td>Foley Score</td>
<td>1.17</td>
<td>0.84, 1.65</td>
<td>.03</td>
<td>1100.09</td>
</tr>
</tbody>
</table>

For each model, only the comorbidity score (and no other covariate) remained significant in the final multiple regression analyses (with the exception of the Foley score). Comparison is made between separate models (each containing a different comorbidity score) using Akaike information criteria. Improved model fit is associated with a lower Akaike information criterion. Charlson Comorbidity Index denotes Charlson comorbidity index.

- Effect per unit score.
- Effect per risk group.

**Predictive performance of comorbidity scores: assessment and comparison**

While the above time to event analyses are informative in demonstrating the relation between comorbidity scores and mortality, they give little insight to the actual use of scores to discriminate between those patients dying and surviving. This was assessed by constructing a series of receiver operating characteristic curves. Figure 1 shows the results of the initial analysis, which compared all 7 comorbidity scores (in a univariate fashion), and demonstrated that the Recipient Risk Score best predicted mortality at both 3 and 5 years (Figures 1A and 1B). The area under the receiver operating characteristic curves (c-statistic) were 0.762 and 0.787 for the 3- and 5-year analyses, representing at least moderate use in predicting mortality. The results for the Recipient Risk Score were numerically superior to all other comorbidity scores, and with the exception of the Age-adjusted Charlson Comorbidity Index and the Foley Score, the result for the Recipient...
Risk Score also was statistically superior. Examination of the receiver operating characteristic curve revealed no obvious discriminatory cutoff value(s) of potential clinical relevance. Unsurprisingly, fragmentation of the Recipient Risk Score in the 4 grades proposed in the original report of the Recipient Risk Score (and described in the appendix to this manuscript) reduced the predictive performance slightly (area under receiver operating characteristic curve for 3- and 5-year mortality: 0.723 [95% CI: 0.666, 0.779] and 0.748 [95% CI: 0.690, 0.804]).

**Independent importance of recipient age in predicting mortality**

From the previous time to event analyses, it was clear that recipient age was associated with mortality in patients selected for transplant, and this effect was independent of comorbidity. The results of the receiver operating characteristic curve analyses also were consistent with this: Figures 1A and 1B show that comorbidity indices that incorporate age (Recipient Risk Score, Age-adjusted Charlson Comorbidity Index, Foley Score, and the Wright-Khan Index) displayed higher area under receiver operating characteristic curve values than those indices that not incorporate age (the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index).

Receiver operating characteristic curve analysis was then repeated for the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index; scores that do not incorporate age as a contributor to the overall comorbidity score. The previous regression analysis showed that both comorbidity and age were independently associated with mortality in the models based on the Charlson Comorbidity Index, the Modified End-Stage Renal Disease Charlson Comorbidity Index, and the Davies Index. Output from the regression model was used to create receiver operating characteristic curves that represented the combined effect of age coupled with comorbidity. Figures 1C and 1D show that a numeric and statistically significant increase in the area under the receiver operating characteristic curve was evident when age and comorbidity were combined in this way, when compared with the use of the corresponding comorbidity score in isolation. The

### Table: Receiver Operating Characteristic Curve Analysis

<table>
<thead>
<tr>
<th>Comorbidity Score</th>
<th>Area under receiver operating characteristic curve</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient Risk Score</td>
<td>0.768</td>
<td>0.712, 0.812</td>
</tr>
<tr>
<td>Age-adjusted Charlson Comorbidity Index</td>
<td>0.724</td>
<td>0.674, 0.793</td>
</tr>
<tr>
<td>Foley Score</td>
<td>0.701</td>
<td>0.636, 0.763</td>
</tr>
<tr>
<td>Davies Index</td>
<td>0.643</td>
<td>0.586, 0.701</td>
</tr>
<tr>
<td>Wright-Khan Index</td>
<td>0.663</td>
<td>0.565, 0.701</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.630</td>
<td>0.562, 0.698</td>
</tr>
<tr>
<td>Modified End-Stage Renal Disease Charlson Comorbidity Index</td>
<td>0.612</td>
<td>0.543, 0.681</td>
</tr>
</tbody>
</table>

### Table: Receiver Operating Characteristic Curve Analysis (Continued)

<table>
<thead>
<tr>
<th>Comorbidity Score</th>
<th>Area under receiver operating characteristic curve</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient Risk Score</td>
<td>0.787</td>
<td>0.735, 0.840</td>
</tr>
<tr>
<td>Age-adjusted Charlson Comorbidity Index</td>
<td>0.729</td>
<td>0.712, 0.827</td>
</tr>
<tr>
<td>Foley Score</td>
<td>0.711</td>
<td>0.654, 0.780</td>
</tr>
<tr>
<td>Davies Index</td>
<td>0.658</td>
<td>0.592, 0.725</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>0.651</td>
<td>0.584, 0.719</td>
</tr>
<tr>
<td>Wright-Khan Index</td>
<td>0.645</td>
<td>0.577, 0.713</td>
</tr>
<tr>
<td>Modified End-Stage Renal Disease Charlson Comorbidity Index</td>
<td>0.638</td>
<td>0.570, 0.707</td>
</tr>
</tbody>
</table>

### Figure 1.

Receiver operating characteristic curve analysis comparing predictive performance of 7 comorbidity scores. Figures 1A and 1B show results for all scores on (A) 3-year mortality and (B) 5-year mortality. Figures 1C and 1D demonstrate the effect of the addition of age to 3 “pure” comorbidity scores (ie, initially derived without age as a contributor) on the predictive performance for (C) 3-year mortality, and (D) 5-year mortality.
predictive performance of the combination of comorbidity and age was numerically similar to, and not statistically different from, that of the Recipient Risk Score.

**Discussion**

This study represents a comprehensive analysis of the association of comorbidity with mortality in renal transplant recipients. It highlights the independent importance of comorbidity in this high-risk population, and is the first analysis to assess and compare use of these comorbidity scores in predicting mortality. The study results suggest that mortality after transplantation is best predicted by the recently developed recipient Risk Score, and question the current literature which identifies the Charlson Comorbidity Index to be most tightly associated with mortality. A previous study demonstrated the Charlson Comorbidity Index to be most tightly associated with mortality; however, this study was conducted before description of the Recipient Risk Score. The Recipient Risk Score also benefits from its ease of calculation and requirement for a limited number of clinical variables.

The predictive characteristics of the 7 established comorbidity indices were broadly consistent across all analyses. Firstly, when comparing baseline comorbidity scores that incorporate age separately from those not incorporating age, the results suggest that the models based on the Recipient Risk Score and the Charlson Comorbidity Index showed the best fit. Secondly, comparing all scores together in a similar model, but this time stratifying for age, the superiority of the Recipient Risk Score-based model was demonstrated. Thirdly, receiver operating characteristic curve analysis demonstrated the Recipient Risk Score to have the greatest discriminatory use of all comorbidity scores studied for mortality at both 3 and 5 years after transplantation, with an area under the receiver operating characteristic curve of 0.762 and 0.787. Therefore, the Recipient Risk Score correctly discriminates between patients surviving and dying approximately 75% of the time. Receiver operating characteristic curves are best used for continuous covariates, and therefore it can be argued that scores such as the Wright-Khan Index and the Davies index (which were divided into only 3 and 4 categories) are not best suited to this type of analysis. However, consistency of results across the different analytic methods lends support to the robustness of the conclusion.

The superiority of the Recipient Risk Score most likely reflects the method of derivation, having been...
developed specifically for assessing renal transplant recipients. The other indices were developed in different populations, and comprise certain individual comorbidities of questionable relevance to transplantation. Dialysis duration (comorbidity unique to transplant recipients) is incorporated into the Recipient Risk Score and is not included in the other tested scoring systems. Furthermore, in addition to the use of age and diabetes as score components, the “synergistic” interaction between these 2 variables in construction of the score (see appendix) may be important, and give insight into the particular relevance of these factors (over and above other comorbidities encountered in patients selected for renal transplant) in determining outcome.

Identifying the optimal baseline comorbidity score for renal transplant recipients has implications for organ allocation policy. Of particular interest, it has been suggested that matching recipient to graft survival may improve the use of donated organs, and assessment of this has been conducted previously, with a focus on using the Recipient Risk Score in conjunction with a “deceased donor score.”

Aside from a pure “utilitarian” approach, recent revisions in allocation policies focus on maximizing “quality-adjusted net lifetime survival benefit” to the recipient (or “life years from transplant”); these also require accurate comorbidity assessment. The Recipient Risk Score itself may prove its use as allocation algorithms are continually refined. No attempt has been made in the current study to address whether matching donor and recipient characteristics might optimize either organ or recipient lifespan: larger datasets are required for this. Rather, the purpose of the analysis was to define the optimal comorbidity score, and the results suggest that there is currently no better alternative to the Recipient Risk Score in predicting subsequent mortality, so supporting its role in optimizing the overall use of a limited donor organ pool. Importantly, the current study validates the Recipient Risk Score in a population separate to that in which the score was initially derived.

In addition to the potential value for allocation strategies, use of the optimal comorbidity index in future studies of transplanted and wait-listed populations could allow simpler and potentially more-accurate assessment of comorbidity as a confounder. Furthermore, the moderate-to-good-predictive performance of the best-performing scores (area under receiver operating characteristic curve 0.7-0.8) suggests they may have some role to play in decision-making and counseling at the level of the individual patient, although their effect on decision-making will necessarily depend on the specific clinical scenario. Certainly, the decision to transplant or not to transplant a patient based solely on their comorbidity is not supported by this study.

It is acknowledged that the studied population is characterized by relatively low numbers of live-donor transplant recipients, low numbers of diabetic and ethnic minority recipients, and well HLA-matched grafts. Despite this, we believe that the results are likely to be generalizeable to other populations. Indeed, this study confirms the association between Recipient Risk Score and outcome shown in North American registry data set analysis. We also recognize the retrospective nature of the study accrues the potential for biases associated with such investigations.

In summary, this analysis confirms the importance of comorbidity in renal transplant, and extends current understanding of the performance of currently available comorbidity scores. We propose the Recipient Risk Score to be a simple and effective tool for assessing comorbidity.

Appendix

(1) Recipient Risk Score

A weighted continuous score calculated as follows:

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes mellitus</td>
<td>1.816</td>
</tr>
<tr>
<td>Age in decades to 1 decimal place</td>
<td>0.448</td>
</tr>
<tr>
<td>No history of diabetes mellitus</td>
<td>0.213</td>
</tr>
<tr>
<td>Time on dialysis therapy ≤ 1 year</td>
<td>0.159</td>
</tr>
<tr>
<td>Time on dialysis therapy &gt;1 year</td>
<td>0.407</td>
</tr>
<tr>
<td>History of angina</td>
<td>0.303</td>
</tr>
</tbody>
</table>

Stratification into recipient grade (RG):

- RG1 = ≤ 2.555
- RG2 = 2.556-3.308
- RG3 = 3.309-3.802
- RG4 = > 3.802

(2) Charlson Comorbidity Index

A weighted score, ranging from 0 to 37. (All patients score a minimum of 2 owing to the universal presence of renal failure in our population) calculated as follows:

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarct</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
</tr>
</tbody>
</table>
Cerebrovascular disease (1 point)
Dementia (1 point)
Chronic pulmonary disease (1 point)
Connective tissue disease (1 point)
Ulcer disease (1 point)
Mild liver disease (1 point)
Diabetes (1 point)
Hemiplegia (2 points)
Moderate or severe renal disease (2 points)
Diabetes with end-organ damage (2 points)
Any tumor (2 points)
Leukemia (2 points)
Lymphoma (2 points)
Moderate or severe liver disease (3 points)
Metastatic solid tumor (6 points)
Acquired immunodeficiency syndrome (6 points)

(3) Modified End-Stage Renal Disease Charlson Comorbidity Index6

A weighted score, ranging from 0 to 33, calculated as follows:

Myocardial infarction (2 points)
Congestive heart failure (2 points)
Peripheral vascular disease (1 point)
Cerebral vascular disease (2 points)
Dementia (1 point)
Chronic lung disease (1 point)
Rheumatologic (1 point)
Peptic ulcer disease (1 point)
Diabetes (2 points)
Diabetes with complications (1 point)
Moderate/severe liver disease (2 points)
Metastatic disease (10 points)
Leukemia (2 points)
Lymphoma (5 points)

(4) Age-adjusted Charlson Comorbidity Index2,3

Identical to the original Charlson Comorbidity Index, with the exception that 1 point is added for each decade of age over 40 years.

(5) Foley Score10

A weighted score, with range from 1 to 22, calculated as follows:

Age ≤ 50 y (1 point)
Age 51-60 y (2 points)
Age 61-70 y (3 points)
Age > 70 y (4 points)
Moderate cardiac failure (1 points)
Severe cardiac failure (2 points)
Moderate ischemic heart disease (1 point)
Severe ischemic heart disease (2 points)
Dysrhythmia requiring therapy (2 points)
Severe peripheral vascular disease (2 points)
Advanced neoplasia (2 points)

(6) Wright-Khan comorbidity Index6, 9

Patients graded low-, medium-, or high-risk as follows:

Age < 70 years and no comorbid illness (low-risk)

Age 70-80 years with any one of the following:
Angina
Previous myocardial infarction
Cardiac failure
Chronic obstructive airways disease (medium-risk)
Pulmonary fibrosis
Liver disease (cirrhosis, chronic hepatitis)
OR
Age < 70 y with diabetes mellitus

Age > 80 y

OR
Any age with 2 or more organ dysfunctions in addition to end-stage kidney disease
OR (high-risk)
Any age with diabetes AND cardiopulmonary disease

OR
Any age with visceral malignancy

(7) Davies Index7

A nonweighted score, ranging from 0 to 7, calculated as follows:

Malignancy (1 point)
Ischemic heart disease (1 point)
Peripheral vascular disease (1 point)
Left ventricular dysfunction (1 point)
Diabetes mellitus (1 point)
Systemic collagen vascular disease (1 point)
Other significant pathology (1 point)

Stratification into grades: grade 0 (low-risk) is score 0; grade 1 (medium-risk) is a score of 1-2; grade 2 (high-risk) a cumulative score of 3.

References


17. The Long-Term Efficacy and Safety Surveillance study, Study Plan, Renal transplant recipients,. Novartis UK, 1995

