

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

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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

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Comorbidity Index have been validated in hemodialysis and peritoneal dialysis test populations.^{2, 4, 5} 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).⁶

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).⁷⁻⁹ 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.¹⁰ 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.^{11, 12} 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.¹³ The second study, from Jassal and associates,¹⁴ 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.^{15, 16}

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 previously¹⁷ and has yielded valuable insight into renal transplant outcomes in previous analyses.^{18, 19} 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 Index^{2,3}
- Model 3: Foley Score¹⁰
- Model 4: Wright-Khan Index^{8,9}
- Model 5: Charlson Comorbidity Index¹
- Model 6: Modified End-Stage Renal Disease 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 $\pm$ 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 covariable 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.

Table 1. Donor and patient demographics.

Donor	
Age (y)	41 $\pm$ 15
Sex (% male)	49.3
Live donor	9.5
Recipient	
Age (y)	44 $\pm$ 14
Sex (% male)	63.2
Prior transplant (%)	14.0
Race (%)	
White	91.3
Black	2.2
South Asian	5.2
Other	1.3
Total HLA mismatch (Ag)	1.82 $\pm$ 0.99
Major comorbidities (%)	
Diabetes	10.7
Ischemic heart disease	0.5
Myocardial infarction	0.3
Peripheral vascular disease	8.1

Table 2. Distribution of comorbidity scores.

	Mean	SD	median	range
Recipient risk score	2.37	0.70	2.11	0.880-4.070
Age-adjusted Charlson comorbidity index	2.92	1.17	2	2-9
Foley score	1.64	0.95	1	1-6
Charlson comorbidity index	2.40	0.81	2	2-7
Modified end-stage renal disease Charlson comorbidity index	0.51	1.11	0	0-7
Davies index	0.31	0.56	0	0-4
Wright-Khan index	low: 80.6%; medium: 18.7%; high: 0.7%			

Scores had a positively skewed distribution; results are shown as mean, standard deviation, median, and range. Wright-Khan index described in 3 ordinal risk groups (see appendix for criteria).

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).

Table 3. Multiple regression models describing association between comorbidity scores (containing age as a contributor) and mortality (Cox models).

Model	Variable	Hazard ratio	95% Confidence intervals	P value	Akaike information criterion
1	Recipient Risk Score ^a	4.92	3.43, 7.05	.0001	1389.10
2	Age-adjusted Charlson Comorbidity Index ^a	1.70	1.52, 1.89	.0001	1413.27
3	Foley Score ^a	1.74	1.51, 2.00	.0001	1435.56
4	Wright-Khan Index ^b	3.18	2.29, 4.41	.0001	1442.36

For each model, only the comorbidity score (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.

^aEffect per unit score.

^bEffect per risk group.

Table 4. Multiple regression models describing association between comorbidity scores (not containing age as a contributor) and mortality (Cox models).

Model	Variable	Hazard ratio	95% Confidence intervals	P value	Akaike information criterion
5	Charlson Comorbidity Index ^a	1.43	1.22, 1.68	.0001	1391.00
	Age ^b	1.07	1.05, 1.09	.0001	
6	Modified end-stage renal disease Charlson Comorbidity Index ^a	1.27	1.12, 1.42	.0001	1394.06
	Age ^b	1.07	1.05, 1.09	.0001	
7	Davies Index ^a	1.55	1.21, 1.99	.0006	1396.95
	Age ^b	1.07	1.05, 1.09	.0001	

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.

^aEffect per unit score

^bEffect per year

Otherwise, no other studied baseline demographic or clinical variables were associated with mortality in any of the final models.

Comparison of all comorbidity scores: Cox model stratified by age

To allow comparison of all comorbidity scores, a second model stratified for age was built, thereby 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 5. Multiple regression models describing association between all comorbidity scores and mortality in age-stratified Cox models.

Model	Variable	Hazard ratio	95% Confidence intervals	P value	Akaike information criterion
1	Recipient Risk Score ^a	4.42	2.45, 7.97	.0001	1078.81
4	Wright-Khan Index ^b	2.27	1.60, 3.23	.0001	1082.48
5	Charlson Comorbidity Index ^a	1.46	1.25, 1.72	.0001	1082.98
2	Age-adjusted Charlson Comorbidity Index ^a	1.46	1.24, 1.72	.0001	1083.02
6	Modified end-stage renal disease Charlson Comorbidity Index ^a	1.28	1.14, 1.44	.0001	1086.39
7	Davies Index ^a	1.57	1.22, 2.03	.0004	1090.11
3	Foley Score ^a	1.17	0.84, 1.65	0.3	1100.09

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.

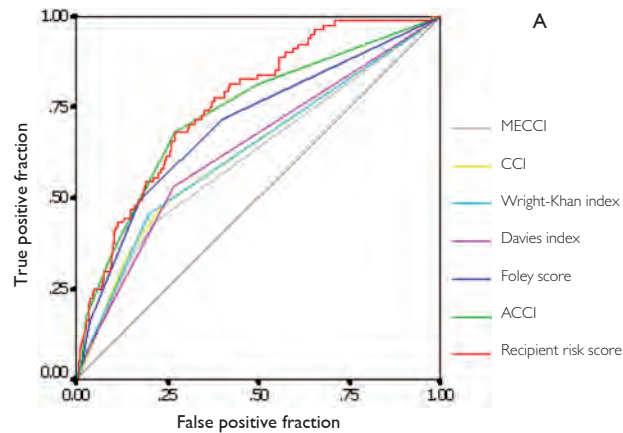
^aEffect per unit score.

^bEffect per risk group.

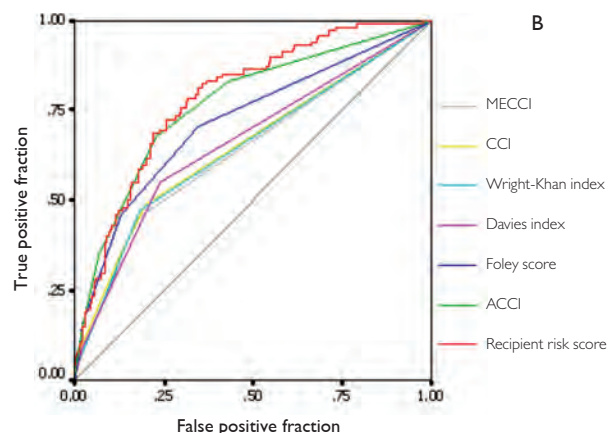
Predictive performance of comorbidity scores: assessment and comparison

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

Figure 1. Receiver operating characteristic curve analysis comparing predictive performance of 7 comorbidity scores. Figures 1A and 1B show results for all scores on and (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.



Comorbidity score	Area under receiver operating characteristic curve	95% CI
Recipient Risk Score	0.762	0.712, 0.812
Age-adjusted Charlson Comorbidity Index	0.734	0.674, 0.793
Foley Score	0.700	0.636, 0.763
Davies Index	0.634	0.568, 0.701
Wright-Khan Index	0.633	0.565, 0.701
Charlson Comorbidity Index	0.630	0.562, 0.698
Modified End-Stage Renal Disease Charlson Comorbidity Index	0.612	0.543, 0.681



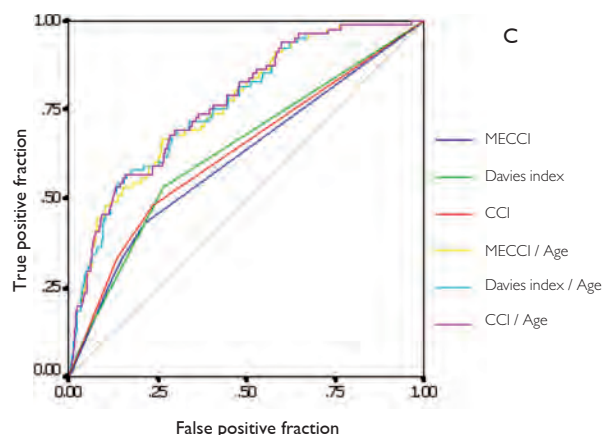
Comorbidity score	Area under receiver operating characteristic curve	95% CI
Recipient Risk Score	0.787	0.735, 0.840
Age-adjusted Charlson Comorbidity Index	0.769	0.712, 0.827
Foley Score	0.717	0.654, 0.780
Davies Index	0.658	0.592, 0.725
Charlson Comorbidity Index	0.651	0.584, 0.719
Wright-Khan Index	0.645	0.577, 0.713
Modified End-Stage Renal Disease Charlson Comorbidity Index	0.638	0.570, 0.707

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]).

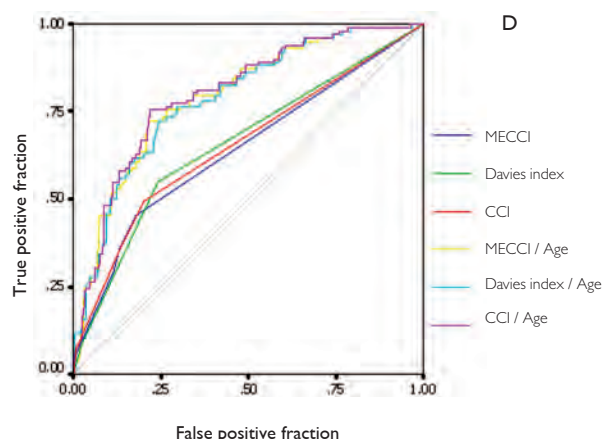
Independent importance of recipient age in predicting mortality

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



Comorbidity score	Area under receiver operating characteristic curve	95% CI
Modified End-Stage Renal Disease		
Charlson Comorbidity Index	0.612	0.543, 0.681
Charlson Comorbidity Index	0.630	0.562, 0.698
Davies Index	0.634	0.568, 0.701
Modified End-Stage Renal Disease		
Charlson Comorbidity Index / Age	0.763	0.710, 0.815
Davies Index / Age	0.764	0.711, 0.817
Charlson Comorbidity Index / Age	0.769	0.717, 0.820



Comorbidity score	Area under receiver operating characteristic curve	95% CI
Modified End-Stage Renal Disease		
Charlson Comorbidity Index	0.638	0.570, 0.707
Charlson Comorbidity Index	0.651	0.584, 0.719
Davies Index	0.658	0.592, 0.725
Davies Index / Age	0.789	0.737, 0.842
Modified End-Stage Renal Disease		
Disease Charlson Comorbidity Index / Age	0.796	0.743, 0.848
Charlson Comorbidity Index / Age	0.802	0.750, 0.853

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 mortality¹⁴; 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.”^{11, 12, 20} 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 generalizable to other populations. Indeed, this study confirms the association between Recipient Risk Score and outcome shown in North American registry data set analysis.¹¹ 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 Score¹¹

A weighted continuous score calculated as follows:

History of diabetes mellitus	(1.816 points +
[age in decades to 1 decimal place × 0.448 points])	
No history of diabetes mellitus	(Age in decades to
1 decimal × 0.213 points)	
Time on dialysis therapy ≤ 1 year	(0.159 points)
Time on dialysis therapy > 1 year	(0.407 points)
History of angina	(0.303 points)

Stratification into recipient grade (RG):

RG1 = ≤ 2.555; RG2 = 2.556-3.308;

RG3 = 3.309-3.802; RG4 = > 3.802

(2) Charlson Comorbidity Index¹

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:

Myocardial infarct	(1 point)
Congestive heart failure	(1 point)
Peripheral vascular disease	(1 point)

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 Index^{2,3}

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)

Ventilated and/or comatose	(4 points)
Sepsis and/or hepatic failure	(4 points)

(6) Wright-Khan comorbidity Index^{8,9}

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.

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