Comorbid Conditions in Kidney Transplantation: Association with Graft and Patient Survival

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Although the impact of comorbidity on outcomes in ESRD has been evaluated extensively, its contribution after kidney transplantation has not been well studied. It is believed that comorbidity assessment is critical to the informed interpretation of kidney transplant outcomes. In this study, the Charlson Comorbidity Index was used to assess the comorbid conditions of 715 patients who underwent kidney transplantation at the Starzl Transplant Institute between January 1998 and January 2003. The impact of pretransplantation comorbidity on the development of acute cellular rejection after transplantation and on patient and graft survival was examined. The most common comorbid conditions among our patient population were diabetes ($n = 217$, 30.3%) and heart failure ($n = 85$, 11.9%). It was found the number of patients with high comorbidity at the Starzl Transplant Institute has increased significantly over time ($P = 0.04$). In multivariate adjusted models, high comorbidity was associated with an increased risk for patient death, both in the perioperative period (hazard ratio 3.20, 95% confidence interval 1.32 to 7.78; $P = 0.01$) and >3 mo after transplantation (hazard ratio 2.63; 95% confidence interval 1.62 to 4.28; $P < 0.001$). The Charlson Comorbidity Index is a practical tool for the evaluation of comorbidity in the transplant population, which has an increasing burden of comorbid disease. Increased comorbidity affects both perioperative and long-term patient outcomes and carries significant implications not only for the development of individual patient therapeutic strategies but also for the interpretation of patient trials and the development of policies that govern distribution of donor organs.

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Kidney transplant recipients often have multiple comorbid conditions. Various comorbidity indices, such as the Index of Coexistent Disease (ICED), Khan, Davies, and Charlson, have been developed and applied to the ESRD population (1–4). Although a significant body of literature discussing the effects of comorbid conditions on patients with ESRD (3–12) and their access to kidney transplantation exists (11–13), the consequences of patient comorbidity on kidney transplant outcomes have not been well studied. A few reports have evaluated the effects of single comorbid conditions, such as diabetes or cardiovascular disease, on transplant outcomes (14,15). Baseline comorbidity is often considered in preoperative risk stratification (16,17); however, patient outcomes after kidney transplantation to date have focused on immunologically relevant donor, recipient, and also transplant procedure characteristics. It was suggested previously that nonimmunologic factors, including comorbid conditions and the complications of chronic kidney disease, are more predictive of patient mortality after kidney transplantation than immunologic and transplant-related factors (18,19).

We propose that a systematic assessment of baseline comorbidity is important in understanding the influence of variability among institutions and the impact of the changing demographics of the kidney transplant population to research studies that assess outcomes after kidney transplantation. Baseline comorbidity of kidney transplant patients likely varies among transplant institutions (20), and the inclusion of a comorbidity assessment may aid in assessing generalizability and determining center effects to allow a better comparison of results across institutions. Furthermore, the chronic kidney disease population is composed of patients with a heterogeneous background of underlying disorders. We believe that the ability of a comorbidity index to serve as a summary indicator of health status offers a potential advantage over the consideration of diseases individually in this patient population.

The demographics of the kidney transplant patient population are changing to include an increasing number of elderly patients, a population predicted to have a substantial burden of comorbid disease (21,22). As the number of kidney transplants being performed has grown from 8871 in 1998 to >15,000 in 2003, patients 65 yr and older have shown the largest percentage increase. Currently, >8000 patients who are older than 65 yr are on the waiting list and account for 13.6% of the patients who are awaiting a kidney (23). Given the evolving ESRD population that is being considered for transplantation and studies that demonstrate a survival advantage of transplantation over dialysis in the elderly (24,25), we hypothesized that patients with an increasing number of comorbid conditions are

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being considered for and are undergoing kidney transplantation. Baseline comorbidity will have an increasing impact on preoperative patient assessment and care as well as patient and graft survival after transplantation.

In this study, we abstracted data from the electronic medical record and used the Charlson Comorbidity Index (CCI) to assess and describe the comorbid conditions of 715 patients who underwent kidney transplantation at our institution between January 1998 and January 2003. The CCI is an index of medical comorbidity that has been validated as a predictor of survival and health status in numerous patient groups, including the chronic kidney disease population (3–6,21,26–28). We examined the impact on model fit of the CCI compared with using all comorbid conditions. We also examined the trend of baseline comorbidity across time at our institution, and we evaluated the association of pretransplantation comorbidity with acute cellular rejection, graft failure, and patient mortality.

Materials and Methods

Patient Population

In this cohort study, we examined all 715 consecutive renal transplants at our institution between January 1998 and January 2003. We included multiple-organ and repeat kidney transplant recipients of both cadaveric and living-donor organs. Four patients received a repeat kidney transplant within 6 mo of their previous kidney transplant and were evaluated as a single case, using follow-up time points and baseline characteristics from their second transplant. The majority of patients were treated with an immunosuppression regimen that consisted of tacrolimus, steroids, and mycophenolate mofetil. A "tolerogenic" protocol, consisting of antibody induction and low-dose tacrolimus monotherapy as described previously (29,30), was introduced in July 2001, and 15% of the patients included in this study were treated with this regimen. Sirolimus was used in 8.5% and azathioprine in 1% of our patients. Immunosuppressive medications were routinely evaluated by frequent blood level determinations and adjusted accordingly.

Ethical Guidelines/Human Subjects Protection

Information used for our analyses was obtained through an honest broker system from prospectively recorded databases maintained by the University of Pittsburgh Medical Center and the Starzl Transplantation Institute, under the auspices of the Institutional Review Board guidelines at the University of Pittsburgh (Pittsburgh, PA). Research data were coded to prevent the identification of patients either directly or through linked identifiers.

A subset of patients provided written informed consent for participation in a research registry maintained by the Starzl Transplantation Institute, in accordance with the Institutional Review Board at the University of Pittsburgh. Access to the identifiable medical information of these patients was limited to physicians who were involved directly in the care of these patients.

Data Collection

Outpatient records and the Medical Archival Retrieval System (a free text search database of all patients who are cared for at the University of Pittsburgh Medical Center) were reviewed to determine demographic characteristics (age, gender, and race), cause of kidney failure (diabetes *versus* other), laboratory values, and baseline patient comorbidity. The Medical Archival Retrieval System database was used to obtain discharge summaries; emergency room, operating room, intensive care unit, and outpatient notes; radiology and pathology reports; and financial transactions related to patient care. Baseline comorbid conditions were defined as conditions that were present at the initiation of kidney transplantation and were assessed by searching electronic hospital medical billing records that encompassed the period 6 mo before and up to the time of kidney transplant admission for *International Classification of Diseases, Ninth Revision, Clinical Modification* codes, as defined and validated originally by Deyo *et al.* (31), to calculate an adjusted CCI. Because age is included separately in our multivariate model, we used a modified version of the CCI score that excluded age as a component. In addition, all patients received a minimum score of 2 points for presence of moderate or severe renal disease.

The primary outcome measures were graft failure and patient death. Graft failure was defined as loss of renal function requiring re-transplantation or initiation of long-term dialysis. Data were recorded into the transplant patient database by patient care coordinators. Follow-up data for patients who returned to dialysis because of graft failure were collected from outside nephrologists, dialysis units, patient families, and newspaper obituaries. Delayed graft function was defined by need for dialysis in the first week after kidney transplantation and was assessed by reviewing hospital billing codes.

Statistical Analyses

Baseline demographic, laboratory, and transplant factors are described as means (SD) for continuous variables and as frequency distributions for dichotomous variables. Statistical significance of the differences between groups was tested using two-sample t test or ANOVA for continuous variables and χ^2 tests for categorical variables. We created a multiple logistic regression model to identify factors that were associated independently with CCI. A backward stepwise selection of covariates was used. All covariates with $P < 0.2$ in univariate analysis were entered initially, and the model was re-estimated after removal of each covariate with a $P > 0.10$. A Cox proportional-hazards model was used to identify factors that were associated with patient outcomes. Covariates included patient demographics (age, gender, and race), clinical factors (cause of ESRD, previous transplant, and body mass index [BMI]), and laboratory values (liver function tests, cytomegalovirus [CMV] and hepatitis B and C status, and total cholesterol) as well as donor factors (living or deceased, age, and antigen matching) and transplant procedure characteristics (cold ischemia time and delayed graft function). We used the Cochran-Armitage Test to evaluate whether we could identify a trend toward increasing percentage of patients with high CCI (CCI $\geq$ 5) over time.

We examined model fit of CCI *versus* individual comorbidities comparing the Aikaike's Information Criterion, which rewards both model fit and parsimony. We also analyzed the Wald scores for the CCI and compared it with that of individual comorbid conditions alone.

Survival Analysis

We assessed the impact of higher CCI score on patient and graft survival using the Kaplan-Meier product limit estimate. Patients who were lost to follow-up and those who remained enrolled at the close of the study were censored at the time of those events. The magnitude of a factor's association with survival was estimated by the Wilcoxon statistic, a test of the null hypothesis that there is no association between the factor and survival. To adjust for baseline factors that may confound the relationship of comorbidity to subsequent outcomes, we entered into the Cox proportional hazards regression model baseline covariates that were associated significantly with comorbidity and other major demographic covariates that were thought to be associated with survival. We examined survival models using additional groups of variables to identify potential confounding. A fully adjusted model

(model 3) included comorbidity and factors that were associated significantly with either patient or graft survival, also including age, gender, race, BMI, living kidney donor, use of HMG-CoA reductase inhibitors, year of transplant, treatment under the tolerogenic protocol, delayed graft function, history of previous transplantation, and CMV IgG seropositivity.

All analyses were conducted using SAS software version 8.2 (SAS Institute Inc., Cary, NC). Data are presented as means ± SD and reported as significant when $P < 0.05$.

Results

Demographics

Figure 1 shows the distribution of CCI scores among the transplant recipients in our study. We divided our patients into two groups, which we defined as a high comorbidity group (CCI ≥ 5) and lower comorbidity group (CCI < 5) on the basis of the distribution of CCI scores and of visual inspection of Kaplan-Meier plots for patient and graft outcomes by CCI score. Baseline patient and donor characteristics are shown in Table 1. Patient and donor age, cause of ESRD, hepatitis C status, and liver transaminases measured on admission for transplant differed significantly between the two groups. Our institution did not have an extended criteria donor program in place during the time frame encompassed by this study.

The prevalence of comorbid conditions among the 715 kidney transplant recipients is shown in Table 2. The most common comorbid conditions among our patient population were diabetes without complications ($n = 93$, 13%), diabetes with end-organ damage ($n = 124$, 17.3%), and heart failure ($n = 85$, 11.9%). A significant trend toward an increased percentage of patients with CCI ≥ 5 over time was identified (12.9% in 1998, 10.3% in 1999, 20.8% in 2000, 20.67% in 2001, 17.8% in 2002; $P = 0.04$). The proportional hazards assumption was evaluated, and no violations were found using goodness of fit and time-dependent variables for the perioperative, long-term, and both time periods together.

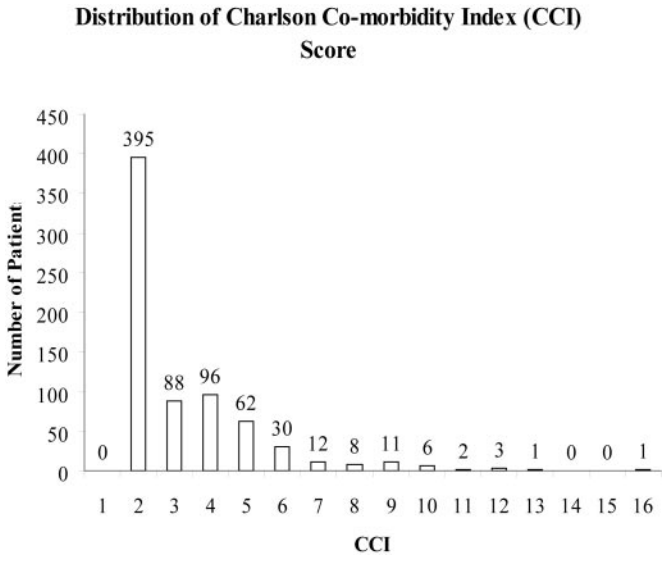

Figure 1. Distribution of Charlson Comorbidity Index (CCI) score.

Graft and Patient Survival

Unadjusted graft survival and patient survival by CCI are presented in Figures 2 and 3. Both graft and patient survival curves show a consistent survival advantage in patients who had a lower CCI score, which begins at the time of transplantation and persists through the duration of the study. Patients were followed for a mean of 40.15 mo (SD 19.48 mo), and graft function was followed for a mean of 35.01 mo (SD 20.78 mo). Patient time was greater than graft time as some patients were followed after graft failure and return to renal replacement therapy.

Age (hazard ratio [HR] 1.02; 95% confidence interval [CI], 1.01 to 1.04), year of transplant (HR, 1.32; 95% CI, 1.10 to 1.59), and nonparticipation in the tolerance protocol (HR, 2.06; 95% CI, 1.13 to 3.77) as significant factors were associated with having a CCI ≥ 5. After additional adjustment for age, gender, race, BMI, living kidney donor, use of HMG-CoA reductase inhibitors, year of transplant, treatment under the tolerogenic protocol, delayed graft function, history of previous transplantation, and CMV IgG seropositivity, patient death was associated significantly with CCI ≥ 5 (HR, 2.67; 95% CI, 1.75 to 4.08; $P < 0.001$). In our multivariate adjusted models, high comorbidity was associated with an increased risk for patient death, both in the perioperative period (HR, 3.20; 95% CI, 1.32 to 7.78; $P = 0.01$) and >3 mo after transplantation (HR, 2.63; 95% CI, 1.62 to 4.28; $P < 0.001$).

We examined model fit of CCI *versus* individual comorbidities comparing the Aikaike's Information Criterion, which rewards both model fit and parsimony. The model that used the CCI showed the best result (data not shown.) We also analyzed the Wald scores for the CCI and compared it with that of individual comorbid conditions alone. The results demonstrated that the CCI is the strongest predictor of patient outcome, more predictive than individual conditions such as diabetes and ischemic heart disease.

Information regarding cause of death was available for 82 of the 96 patients who died. The major causes of death were cardiovascular disease and infection. Cardiovascular disease was listed as a cause of death in 39% of deceased patients (31 [41%] of the CCI < 5 and 6 [30%] of the CCI ≥ 5 group), and infection was listed in 30% of patients (20 [26%] of the CCI < 5 and nine [45%] of the CCI ≥ 5 group). Because of the small numbers in each group, we could not detect a significant difference in cause of death between the groups. The P value for χ^2 test of difference between infection rates in the group with CCI < 5 compared with that of the group with CCI ≥ 5 was 0.1, suggestive of a trend.

CCI ≥ 5 was also associated with graft failure, although the adjusted risk did not reach statistical significance (HR, 1.36; 95% CI, 0.97 to 1.90; $P = 0.08$; Table 3). A total of 107 patients died. When censored for death, comorbidity in our adjusted model was not associated with graft survival (HR, 0.57; 95% CI, 0.30 to 1.10; $P = 0.10$). Looking across the adjusted models, the parameter estimates are relatively stable, suggesting little confounding between patient comorbidity index and other baseline covariates. Acute cellular rejection was not associated sig-

Table 1. Baseline patient, donor, and transplant procedure characteristics[a]

Characteristics	Adjusted CCI <5 (n = 579)	Adjusted CCI ≥5 (n = 136)	All (n = 715)
Age at transplant (n = 715)[b]	49.0 ± 14.5	53.3 ± 11.8	49.8 ± 14.2
Male (%; n = 714)	61.7	65.4	62.4
Race (n = 711)			
white (%)	83.8	83.1	83.7
black (%)	14.1	14.7	14.2
other (%)	2.1	2.2	2.1
BMI (kg/m^2; n = 696)	25.6 ± 5.1	25.3 ± 4.7	25.5 ± 5.0
Cause of ESRD (%; n = 715)[b]			
diabetes	10.7	39.7	16.2
hypertension	19	13.2	17.9
other	57.9	43.4	55.1
unknown	12.4	3.7	10.8
Previous transplant (%; n = 715)	22.1	19.8	21.7
Panel reactive antibody (%; n = 686)	8.6 ± 19.5	7.8 ± 18.2	8.5 ± 19.2
Liver function			
AST (U/L; n = 628)[b]	21.7 ± 11.7	25.6 ± 16.4	22.5 ± 12.9
ALT (U/L; n = 630)[b]	26.5 ± 16.4	31.8 ± 25.7	27.6 ± 18.8
alkaline phosphatase (U/L; n = 627)[b]	104.9 ± 71.9	138.8 ± 137.9	111.9 ± 90.4
total bilirubin (mg/dl; n = 626)	0.55 ± 0.37	0.57 ± 0.32	0.56 ± 0.36
HbsAg positive (%; n = 715)	2.6	0	2.1
anti-HCV positive (%; n = 715)[b]	7.6	14	8.8
CMV IgG positive (%; n = 715)	78.4	83.1	79.3
total cholesterol (n = 506)	196.3 ± 56.2	189.7 ± 55.9	194.8 ± 56.2
creatinine at 3 mo (mg/dl; n = 652)	2.1 ± 1.6	1.9 ± 1.4	2.1 ± 1.6
Donor characteristics			
cadaveric (%; n = 715)	75.6	79.4	76.4
age (year; n = 693)[b]	37.0 ± 17.3	40.4 ± 17.5	37.6 ± 17.4
A antigen mismatch (%; n = 696)	22	26	22.7
B antigen mismatch (%; n = 701)	22	27.1	23
DR antigen mismatch (%; n = 697)	29.4	30.3	29.6
Transplant procedure characteristics			
cold ischemia time (min; n = 644)	1286.4 ± 739.4	1327.0 ± 756.2	1294.2 ± 742.2
delayed graft function (%; n = 715)	23.8	25	24.1
tolerance protocol (%; n = 715)	25	22.1	24.5

[a]CCI, Charlson Comorbidity Index; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; HbsAg, hepatitis B surface antigen; HCV, hepatitis C virus; CMV, cytomegalovirus.
[b]$P < 0.05$.

nificantly with comorbidity (HR, 0.94; 95% CI, 0.73 to 1.22; P = 0.66).

A separate validation of CCI scoring through chart review by two independent investigators, with a third investigator serving as arbitrator in instances in which discrepancies in scoring led to differential classification of a patient's comorbidity, was performed on a subset of 70 patients who previously signed informed consent to be included in a transplant research registry. The results of the chart review agreed with those obtained from billing records (P = 0.002).

Interactions

There were no significant interactions between CCI and age, gender, race, living donor, or tolerogenic protocol.

Discussion

To our knowledge, this is the first description and analysis of the impact of baseline comorbid conditions on kidney transplant outcomes using a simple comorbidity index. We present the comorbid conditions of 715 patients who underwent kidney transplantation at our institution between January 1998 and January 2003. The most common comorbidities among our patient population were diabetes without complications (n = 93, 13%), diabetes with end-organ damage (n = 124, 17.3%), and heart failure (n = 85, 11.9%). In addition, we found that, in accordance with the evolving ESRD population on the transplant waiting list, the number of patients who had high baseline comorbidity and received a transplant at our institution has

Table 2. Modified CCI and prevalence of comorbid conditions among 715 patients who underwent kidney transplantation

Comorbidity Score	Condition	*n* (%)
1	Myocardial infarction	54 (7.6)
	Heart failure	85 (11.9)
	Peripheral vascular disease	26 (3.6)
	Cerebrovascular disease	20 (2.8)
	Dementia	0
	Chronic pulmonary disease	67 (9.4)
	Connective tissue disorder	27 (3.8)
	Peptic ulcer disease	31 (4.3)
	Mild liver disease	31 (4.3)
	Diabetes	93 (13.0)
2	Hemiplegia	2 (0.3)
	Moderate or severe renal disease	715 (100)
	Diabetes with end-organ damage	124 (17.3)
	Any tumor, leukemia, lymphoma	37 (5.2)
3	Moderate or severe liver disease	26 (3.6)
6	Metastatic solid tumor	5 (0.7)
	AIDS	4 (0.6)

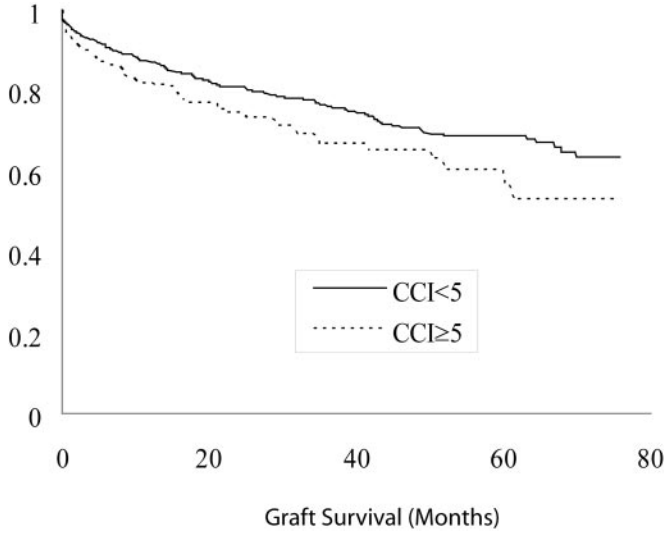

Figure 2. Comparison of graft survival for lower baseline patient comorbidity (CCI < 5) and high comorbidity (CCI ≥ 5). Crude hazard ratio (HR) for CCI ≥ 5 1.42; 95% confidence interval (CI), 1.02 to 1.97; $P = 0.04$.

increased over the past several years ($P = 0.04$). High patient comorbidity was associated with a 2.67-fold increased risk for patient death after kidney transplantation. We also observed a trend toward decreased graft survival in patients with high baseline comorbidity.

The CCI, developed in 1987 as a method for use in longitudinal studies to classify comorbid conditions that affect the risk for mortality (27), has been validated for numerous disease states (3,4,8,9,32,33). For example, in the ESRD population, the

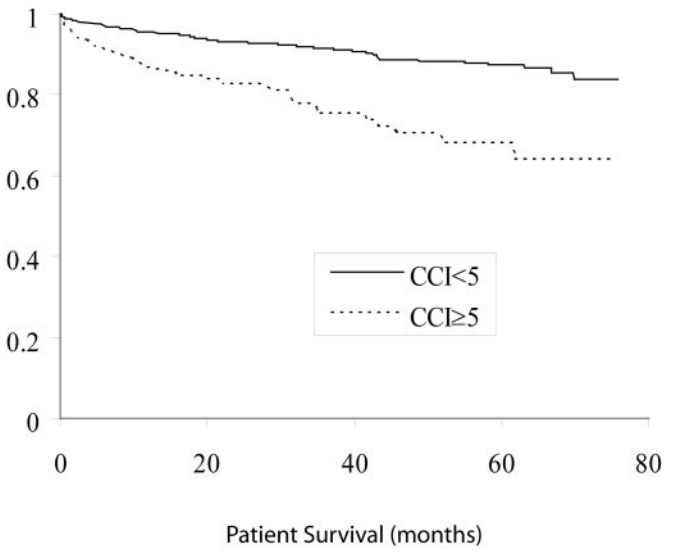

Figure 3. Comparison of patient survival for lower baseline patient comorbidity (CCI < 5) and high comorbidity (CCI ≥ 5). Crude HR for CCI ≥ 5 2.88; 95% CI, 1.90 to 4.37; $P < 0.001$.

CCI, when calculated from prospectively maintained databases or alternative methods of data acquisition such as patient surveys (34), has been associated significantly with a number of important outcomes, including mortality, readmissions and length of stay, hospital cost, and disability (5–9,32,33,35).

Among kidney transplant recipients, the consideration of baseline comorbidity has generally been limited to the assessment of operative risk (16,36). However, we found that patient comorbidity also has an impact on long-term survival. Higher comorbidity was associated with an increased risk for death both in patients who died <3 mo from transplantation and in those who survived >3 mo after transplant. Therefore, a comorbidity assessment may carry significant implications, not only for providing "surgical clearance" but also for optimizing individual patient therapeutic and monitoring strategies after surgery and interpreting the results of patient trials. Because comorbidity is not the sole determinant of transplant outcome, approaches such as the one detailed in a recent article by Krakauer *et al.* (20), which incorporate components such as psychologic factors, disability, and resource use in a more comprehensive model for clinical decision making, may be more appropriate in developing policies that govern distribution of donor organs. However, comorbid conditions are common in transplant recipients and have a significant impact on posttransplantation quality of life (37); thus, continued assessment of comorbidity provides an opportunity to identify issues that are essential for optimizing the continued care of kidney transplant recipients.

Our data suggest that the CCI is a simple tool for the evaluation of comorbidity and that increased preoperative patient comorbidity increases the risk for patient death after kidney transplantation. Although the suggestion that higher comorbidity leads to decreased patient survival may seem intuitive, we believe that its assessment in potential kidney transplant recip-

Table 3. Association of comorbidities with patient survival, graft survival, and time to ACR[a]

	Patient Death	Graft Failure	ACR
Crude: CCI ≥ 5	2.88 (1.90 to 4.37) $P < 0.001$	1.42 (1.02 to 1.97) $P = 0.04$	0.94 (0.73 to 1.21) $P = 0.63$
Adjusted model 1: +Age/gender/race	2.60 (1.71 to 3.94) $P < 0.001$	1.39 (1.00 to 1.94) $P = 0.05$	0.97 (0.75 to 1.25) $P = 0.80$
Adjusted model 2: Model 1 + BMI	2.65 (1.74 to 4.04) $P < 0.001$	1.36 (0.97 to 1.90) $P = 0.07$	0.97 (0.75 to 1.25) $P = 0.81$
Adjusted model 3: Model 2 + donor type, statin use, year of transplantation, tolerance, delayed graft function, previous transplant, CMV IgG+	2.67 (1.75 to 4.08) $P < 0.001$	1.36 (0.97 to 1.90) $P = 0.08$	0.94 (0.73 to 1.22) $P = 0.66$

[a]ACR, acute cellular rejection.

ients is important for a number of reasons. The level of patient comorbidity almost certainly varies among transplant institutions. Therefore, the inclusion of a comorbidity assessment is necessary to allow a reasonable assessment of generalizability and to permit the informed comparison of results across institutions from studies involving transplant patients. In addition, we show that the demographics of the kidney transplant patient population in our program are changing to include a greater percentage of patients with a substantial burden of comorbid disease, increasing the importance of a comorbidity assessment when reporting patient and graft survival after transplantation.

The use of a disease index provides a method of assessing and summarizing the health status of patients who may present with a combination of comorbid conditions and offers a means to include and compare patients who have less common but significant comorbidities such as HIV infection. We also show that patient comorbidity not only affects perioperative risk but also significantly influences patient survival >3 mo after transplantation and may be important both for developing an appropriate therapeutic strategy for the ESRD patient and for the long-term maintenance care of transplant recipients.

Our results must be interpreted in light of several limitations. Our data are obtained from a single center with a predominantly white patient base. However, our transplant center serves a wide geographic community and a medically diverse patient population that, for example, includes a number of non–kidney organ transplant recipients, as well as HIV-positive patients. The relatively small sample size of our study limits our ability to examine the separate contributions of specific comorbid conditions or immunosuppression drug protocols, and further studies are needed to determine the potential interactions between specific drug regimens and the presence of specific comorbid diseases on transplant patient outcomes. In addition, some of the comorbid conditions in the CCI lack the precision of using more detailed indices that might, for example, separate claudication from amputation rather than grouping them under peripheral vascular disease. However, there exists a balance between precision and practical implementation of an index. Our method of assessing comorbidity using hospital billing codes is easily applicable and has been validated in other populations, including the ESRD population (5,38–44).

In conclusion, many nephrologists and kidney transplant centers are being asked to evaluate for kidney transplantation an increasing number of patients with significant comorbidity, often with multiple comorbid conditions. Those with an increased burden of comorbid disease are more likely to die and may be more likely to lose their graft function. Comorbidity data should be used to identify and stratify patients into groups that require more frequent medical assessment and intervention in both the preoperative and the postoperative periods. Future studies could include a comparison of comorbidity assessments obtained from different sources such as patient report, medical records, and billing data. In addition, further studies are needed to define the relative contribution of specific comorbid conditions and the importance of including conditions that may be specific to the kidney transplant population. Nonetheless, the kidney transplant community should not overlook this important tool for assessing clinical outcomes and its potential applications for improving patient care.

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