ORIGINAL ARTICLE

Modified Charlson Comorbidity Index for Predicting Survival After Liver Transplantation

Michael L. Volk,[1] **Jose C. Hernandez,**[2] **Anna S. Lok,**[1] **and Jorge A. Marrero**[1]
[1]*Department of Internal Medicine, Division of Gastroenterology, University of Michigan, Ann Arbor, MI;*
[2]*Department of Internal Medicine, University of California Los Angeles, Los Angeles, CA.*

The benefit of liver transplantation (LT) is determined not only by the severity of illness, but also by the likelihood of posttransplantation survival. Current models are unable to accurately predict which patients will have the best posttransplant survival. We hypothesized that the Charlson Comorbidity Index (CCI), which includes nine comorbidities, could be used to predict survival after LT. We performed a retrospective study of 624 patients undergoing LT, with a median follow-up time of 4.3 yr. Data on pretransplant comorbidities were collected, along with potential confounders such as age, gender, etiology, and severity of liver disease. Proportional hazards analysis was performed to determine the independent effect of each variable on posttransplantation survival, and to recalibrate the CCI for use in the liver transplant population. A total of 40% of patients had 1 or more comorbidities prior to transplantation. In the multivariate analysis, CCI was an independent predictor of posttransplantation survival (hazard ratio [HR] 1.21 per unit, $P < 0.001$). When the individual components of the CCI were analyzed, coronary disease (HR 2.33), diabetes (HR 1.38), chronic obstructive pulmonary disease (COPD) (HR 2.67), connective tissue disease (HR 2.32), and renal insufficiency (HR 1.61) were all independent predictors of posttransplant survival. The CCI was recalibrated using a simplified weighting system to create the CCI-orthotopic LT (OLT), which improved the likelihood ratio chi-squared value from 15 to 24 for predicting posttransplantation survival. In conclusion, survival after LT is diminished in patients with pretransplantation coronary disease, diabetes, COPD, connective tissue disease, and renal insufficiency. We demonstrate the usefulness of a modified comorbidity index, the CCI-OLT, for predicting posttransplantation survival. ***Liver Transpl 13:1515-1520, 2007.*** © **2007 AASLD.**

Received January 5, 2007; accepted February 23, 2007.

See Editorial on Page 1503

Transplantation is unique among all medical services, in that physicians are routinely forced to decide which patients will receive priority for limited resources. For patients with end-stage liver disease in the United States, this priority is determined by severity of illness. The Model for End-Stage Liver Disease (MELD) score accurately predicts mortality prior to liver transplantation (LT),[1] resulting in the allocation of organs according to those with the greatest need.[2] However, the survival benefit from a liver transplant is determined not only by reduction in the risk of death from end-stage liver disease, but also by the likelihood of posttransplantation survival.[3] From a societal and public health perspective, allocating limited organs according to the likelihood of benefit should lead to an increase in life-years gained for the transplant population as a whole.[4] Reflecting these concerns, the recently adopted Lung Allocation Score incorporates the likelihood of posttransplantation survival in addition to risk of death from lung disease when determining priority for lung allografts.[5]

In order to incorporate the likelihood of posttransplantation survival in liver allocation algorithms, one must be able to accurately predict posttransplantation outcomes using variables present prior to transplantation. Unfortunately, this has proven more difficult than

Abbreviations: LT, liver transplantation; CCI, Charlson comorbidity index; HR, hazard ratio; COPD, chronic obstructive pulmonary disease; OLT, orthotopic liver transplantation; MELD, Model for End-Stage Liver Disease; AUROC, area under the receiver-operating characteristic curve; CCI-OLT, CCI modified for OLT; HCC, hepatocellular carcinoma; SD, standard deviation; CI, confidence interval.

Supported in part by the Robert Wood Johnson Foundation and the Department of Veterans Affairs (to M.L.V.).

Address reprint requests to Michael L. Volk, 6312 Medical Science Building 1, 1150 W Medical Center Drive, Ann Arbor, MI 48109-0604. Telephone: (734) 647-4844; FAX: (734) 647-3301; E-mail: mvolk@med.umich.edu

DOI 10.1002/lt.21172
Published online in Wiley InterScience (www.interscience.wiley.com).

predicting death on the waiting list. The MELD score does not predict posttransplantation survival nearly as well as pretransplantation survival. This dichotomy is best illustrated in a study by Merion et al.,[6] which showed a nearly 300-fold increase in pretransplant mortality risk from the lowest MELD group to the highest, compared to a 2-fold increase in posttransplantation mortality from the lowest MELD group to the highest. A recent systematic review identified 5 multivariable prognostic models for posttransplantation survival.[7] Three of these models included donor or operative variables, which are not available prior to transplantation and thus could not be used for ranking patients on the waiting list. Of the other 2 models, one reports results for short-term (90-day and 1-yr) survival only.[8] If the goal is to maximize the use of scarce liver allografts, a model that predicts long-term survival would be more useful. To date, the only model predicting 5-yr survival using recipient characteristics: age, body mass index, creatinine, etiology of liver disease, United Network for Organ Sharing listing status, and race, had an area under the receiver-operating characteristic curve (AUROC) of 0.63.[9] However, this model relied heavily on the poor posttransplantation survival of patients with hepatocellular carcinoma in the pre-Milan criteria era. In addition, the United Network for Organ Sharing listing status in that model is no longer in use. Finally, since this model included race as a variable, using it to calculate survival benefit would mean that patients would be assigned different priorities for transplantation based on race. Thus, further improvement in posttransplantation prognostication is needed.

Little emphasis has been placed on medical comorbidities as predictors of survival after LT. Only diabetes and renal insufficiency have been evaluated, and each of these predicts decreased posttransplantation survival with hazard ratios (HRs) of 1.3[10] and 1.2-2.2,[11,12] respectively. It is unknown whether the effects of diabetes and renal insufficiency are independent of other comorbidities such as coronary disease. Additionally, no study has combined multiple comorbidities in an attempt to improve the prediction of survival after LT.

The use of comorbidities for prognostic assessment has been extensively studied in other fields of medicine. One of the most commonly used comorbidity models is the Charlson Comorbidity Index (CCI), which is based on comorbid conditions with varying assigned weights, resulting in a composite score. The CCI was originally derived in hospitalized general medicine patients,[13] and revised versions have since been validated in multiple patient populations including those undergoing hematopoietic stem cell transplantation[14] and renal transplantation.[15] The aim of this study was to determine if the pretransplant CCI predicts long-term survival after LT.

PATIENTS AND METHODS

Patients

The study population included all adults age 18 yr or more undergoing deceased donor LT at the University of Michigan Hospital between January 1, 1994 and December 31, 2005 (n = 710). This interval was chosen to achieve a median follow-up time of approximately 5 yr. Exclusion criteria were patients with acute liver failure, those receiving multiple organ transplants, recipients of partial or split organs, or patients with a history of LT prior to the study period. Patients with multiple liver transplants within the study period were analyzed from the time of their initial transplantation. Random samples of patients who were evaluated for transplantation but not accepted for listing (sample size = 55) and patients who died on the waiting list (sample size = 55) were also included in the study to compare the frequency of comorbidities in these populations. The study protocol was approved by the Institutional Review Board.

Data

The University of Michigan Hospital maintains an electronic database of all patients evaluated for solid organ transplantation since 1984. This includes survival data for all patients, clinical records since 1991, and laboratory data since 1997. This computerized medical record, supplemented by paper charts when needed, was retrospectively reviewed by 2 independent reviewers (M.V., J.H.). All variables were based on the most immediate pretransplantation data, and the primary outcome was posttransplantation survival. For patients who were no longer being followed at our center, survival status was verified using the Social Security Master Death File. Data were collected on demographics, including age and gender, clinical characteristics, including etiology of liver disease and the presence of hepatocellular carcinoma, and laboratory data for calculating the MELD and Child-Turcotte-Pugh scores. Since the aim of the study focused on pretransplantation predictors of posttransplantation outcome, data on donor or operative variables were not recorded.

Comorbidities

A total of 9 comorbidities comprising the CCI described in the renal transplant population were analyzed.[15] Each of the comorbidities was prospectively defined prior to the chart review as follows: 1) congestive heart failure—documented decreased left ventricular function or mean pulmonary artery pressure >25 mm Hg as determined by stress echocardiography, including patients with portopulmonary hypertension. 2) Coronary artery disease—documented history of myocardial infarction, or coronary disease on angiography. All men above age 40 yr and all women above age 50 yr, as well as patients of any age with risk factors for coronary artery disease underwent a stress test. Patients with a positive stress test but negative angiography were not considered as having coronary artery disease. 3) Diabetes mellitus—chronic hyperglycemia requiring outpatient medications at any time during the month preceding transplantation. 4) Peripheral vascular disease—documented arterial disease by angiography or ankle-

brachial index. 5) Cerebral vascular accident—history of stroke with residual neurological deficit. 6) Chronic obstructive pulmonary disease (COPD)—chronic lung disease with requirement for medications, documented forced expiratory volume in 1 second <1.5 L, or a history of intubation for respiratory failure. 7) Connective tissue disease—diagnosis by a rheumatologist of systemic lupus, rheumatoid arthritis, scleroderma, or seronegative spondyloarthropathy. Patients with osteoarthritis, or arthralgias without objective evidence of inflammatory arthritis, were not considered as having connective tissue disease. 8) Renal insufficiency—serum creatinine of 1.5 mg/dL or greater on most recent pretransplantation testing, or a history of renal transplantation. 9) Malignancy—history of malignancy, excluding nonmelanoma skin cancer and hepatocellular carcinoma. The CCI was calculated by assigning a weight of 2 to diabetes, stroke, renal insufficiency, and malignancy, and a weight of 1 to the other comorbidities, as previously described.[15] When each comorbidity was examined individually, no weighting was used.

Statistical Analysis

The mean CCI scores between the patients who received a transplant, died on the waiting list, or declined listing were compared using analysis of variance. Patient and graft survival were estimated using the Kaplan-Meier method. Pearson correlation was used to analyze the association between the number of comorbidities and year of transplantation. Unadjusted and multivariate adjusted analyses to determine factors that predict patient and graft survival were performed using Cox proportional hazards modeling.[8] The unadjusted analysis included the CCI as well as potential confounders such as age, gender, viral etiology of liver disease, hepatocellular carcinoma, and severity of liver disease as determined by MELD and Child-Turcotte-Pugh scores. All variables with $P < 0.1$ on unadjusted analysis were entered into the multivariate analysis. In addition, age was included since it has been shown in multiple prior studies to predict posttransplantation survival.[12,16,17]

To determine which components of the CCI provide the most prognostic power, and to recalibrate the CCI for use in the liver transplant population, all of the individual comorbidities were analyzed in a multivariate fashion using Cox regression. The comorbidities with $P < 0.05$ were then assigned simplified weights by rounding to the closest integer, to generate a revised CCI for orthotopic LT (OLT), designated "CCI-OLT." The prognostic power of the CCI-OLT was determined by the AUROC, and compared with that of the CCI using the Cox likelihood ratio chi-squared test with 1 degree of freedom.[18] The CCI-OLT was analyzed as a continuous variable, and as categorical variables to allow for analysis of the effects of higher CCI-OLT scores relative to a CCI-OLT score of 0. Statistical analysis was performed using STATA v9.2 (Stata Corp, College Station, TX).

TABLE 1. Characteristics of 624 Patients Transplanted in Our Center

	n (%)	Median (range)
Age at transplant (yr)		51 (18–71)
Transplant yr		2000 (1994–2005)
Follow-up time (yr)		4.3 (0.1–12.3)
MELD*		16 (6–47)
CTP*		10 (5–14)
Male gender	395 (63)	
Death	219 (35)	
Retransplantation	34 (5)	
Hepatocellular carcinoma	82 (13)	
Etiology of liver disease		
Alpha-1-antitrypsin	12 (2)	
Autoimmune hepatitis	24 (4)	
Cryptogenic	79 (13)	
Alcohol	97 (16)	
Hepatitis B	36 (6)	
Hepatitis C	244 (39)	
Hemochromatosis	7 (1)	
Nonalcoholic steatohepatitis	9 (1)	
Primary biliary cirrhosis	48 (8)	
Primary sclerosing cholangitis	53 (8)	
Other	15 (2)	
Comorbidities		
Congestive heart failure	3 (0.5)	
Coronary disease	18 (3)	
Diabetes mellitus	141 (23)	
Stroke	3 (0.5)	
Peripheral arterial disease	2 (0.3)	
COPD	7 (1)	
Connective tissue disease	11 (2)	
Renal insufficiency	101 (16)	
Malignancy†	20 (3)	

Abbreviation: CTP, Child-Turcotte-Pugh score, where >6 is Child B and >9 is Child C.
*Data available for n = 492.
†Excludes hepatocellular carcinoma.

RESULTS

Of the 710 patients receiving transplants during the study period, 624 met the eligibility criteria for the study. Demographic and comorbidity data were available for all patients, and complete laboratory data for calculation of the MELD score was available for 492 (79%) patients. A total of 224 deaths occurred during a median follow-up time of 4.3 (range, 0.1-12.3) yr. Table 1 shows the characteristics of the study population. A total of 40% of patients had at least 1 comorbid condition prior to transplantation, with diabetes and renal insufficiency being the most common. The mean CCI score among the transplantation patients was 0.9 (standard deviation 1.3), compared with a mean CCI score of 1.2 (standard deviation 1.3) in patients who died on the waiting list, and 1.8 (standard deviation 1.5) in patients who were evaluated but not listed for trans-

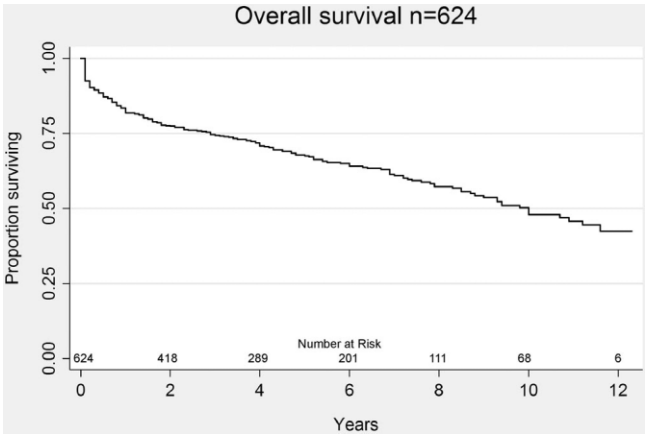

Figure 1. Kaplan-Meier graph of posttransplantation survival in the entire cohort.

plantation ($P < 0.001$). There was no correlation between the year of transplantation and the number of comorbidities. The survival curve for the entire cohort is displayed in Figure 1. The 1-, 3-, and 5-yr survival rates were 83%, 75%, and 68%, respectively.

Unadjusted Cox regression analysis of the CCI revealed a significant association with decreased posttransplantation survival ($P < 0.001$). None of the other pre-OLT variables such as age, gender, Child-Turcotte-Pugh, MELD, or presence of hepatocellular carcinoma showed significant association with decreased posttransplantation survival, though viral etiology of liver disease neared significance, with $P = 0.053$. Analysis by graft survival (death or retransplantation) revealed similar results (data not shown). After adjusting for age and viral etiology, the CCI remained significant with an HR for death after transplantation of 1.21 (95% confidence interval, 1.10-1.32, $P < 0.001$) per unit increase.

The independent contribution of each individual component of the CCI was then explored to determine which components provided the maximum risk of death. Multivariate analysis of the individual comorbidities revealed that coronary disease (HR 2.33), diabetes (HR 1.38), COPD (HR 2.67), connective tissue disease (HR 2.32), and renal insufficiency (HR 1.61) were all significant predictors of posttransplantation mortality, after adjusting for age and viral etiology (Table 2). These results were used to derive the CCI-OLT using a simplified weighting by rounding the HRs to the nearest integer as follows: coronary disease (2), diabetes (1), COPD (3), connective tissue disease (2), and renal insufficiency (2).

The distribution of the CCI-OLT scores is displayed in Table 3. The CCI-OLT had an HR for death after transplantation of 1.32 per unit increase (95% confidence interval, 1.15-1.52, $P < 0.001$), after adjusting for age and viral etiology of liver disease. Table 4 demonstrates a progressive increase in HR for death after LT among patients with CCI-OLT scores of 0, 1, and >1. Figure 2 shows a significant difference in survival according to the CCI-OLT score ($P < 0.001$). The CCI-OLT had a likelihood ratio chi-squared value of 24 for predicting survival after transplantation, compared to a likelihood ratio chi-squared value of 15 for the original CCI, indicating that the CCI-OLT has superior prognostic power. When combined with age and etiology of liver disease, the CCI-OLT had an AUROC of 0.63 for predicting 5-yr survival after transplantation.

TABLE 2. Results of the Multivariate Analysis of Individual Comorbidities

Comorbidities	HR (95% CI)	*P*
Congestive heart failure	2.08 (0.29–15.0)	0.5
Coronary disease	2.33 (1.27–4.26)	**0.006**
Diabetes mellitus	1.38 (1.01–1.89)	**0.04**
Stroke	0.67 (0.26–1.75)	0.4
Peripheral arterial disease	0.92 (0.13–6.76)	0.9
COPD	2.67 (1.09–6.54)	**0.03**
Connective tissue disease	2.32 (1.02–5.25)	**0.04**
Renal insufficiency	1.61 (1.16–2.25)	**0.005**
Malignancy	1.14 (0.56–2.33)	0.5

NOTE: Adjusted for viral etiology of liver disease and age at transplantation. Significant predictors of posttransplant mortality, after adjusting for age and viral etiology, are in bold.
Abbreviation: CI, confidence interval; HR, hazard ratio.

TABLE 3. Distribution of CCI-OLT Scores

CCI-OLT score	Number of patients (%)
0	390 (62)
1	100 (16)
2	91 (15)
3	40 (6)
4	2 (<1)
5	1 (<1)

TABLE 4. Risk of Posttransplantation Mortality by CCI-OLT Score

CCI-OLT score	n	HR (95% CI)	*P*
0	390	1	Reference
1	100	1.61 (1.12–2.31)	0.01
>1	134	2.19 (1.61–2.98)	<0.001

Abbreviation: CI, confidence interval.

DISCUSSION

This study represents the first comprehensive analysis of the association between comorbidities present prior to transplantation and survival after transplantation. Pretransplant comorbidities were surprisingly common in our transplant population despite extensive screening during the transplant evaluation process, with 40% of patients having at least 1 comorbid condition, as

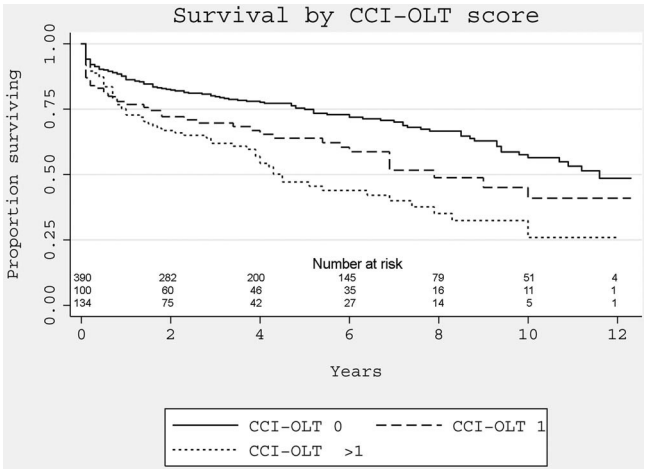

Figure 2. Kaplan-Meier graph of survival for patients with CCI-OLT scores of 0 (no comorbidities, n = 390), CCI-OLT scores of 1 (n = 100), and CCI-OLT scores >1 (n = 134) (*P* < 0.001 for log-rank and log-rank trend).

compared to 22% of kidney transplant patients.[15] As expected, patients who underwent LT had fewer comorbidities than those who were evaluated but not listed and those who died on the waiting list. In our cohort of 624 patients, pretransplantation coronary disease, COPD, connective tissue disease, diabetes, and renal insufficiency all independently contributed to decreased posttransplantation survival. Although diabetes[19] and renal insufficiency[11] have been demonstrated in previous studies to be risk factors for decreased posttransplantation survival, coronary disease, COPD, and connective tissue disease represent prognostic variables that have not been previously reported.

We present the first application of the CCI to the LT population. This index has been used in various forms in multiple patient populations, including stem cell and renal transplantation.[14,15] In this study we have modified this index to create the CCI-OLT, which can be easily calculated using 5 comorbidities and has better prognostic power when compared with the original CCI. When combined with age and etiology of liver disease, the CCI-OLT had an AUROC of 0.63 for predicting survival at 5 yr after LT. By comparison, the only other model predicting 5-yr survival using recipient characteristics (age, body mass index, creatinine, etiology of liver disease, United Network for Organ Sharing status, and race) also had an AUROC of 0.63.[9] Why is predicting posttransplantation survival so difficult? Operative and donor variables certainly play a role, but even models including these variables are unable to improve the AUROC beyond 0.7 at 1 yr.[7] One reason for the difficulty in predicting survival for the entire LT population is that the majority of patients lack identifiable prognostic indicators. For example, in our study 60% of the patients did not have pretransplantation comorbidities. There may also be unmeasured variations in graft quality or the quality of clinical care. Further research in this area is still needed. However, our study shows that comorbidities play an important role in determining posttransplantation survival, and this information will be useful when counseling patients with comorbidities about outcomes after transplantation.

This study is limited by the fact that it is a single-center, retrospective cohort study. While different versions of the CCI have been used in multiple prior studies, our modification requires validation in a separate cohort. Results of future studies may alter the weighting or identify additional comorbidities that are also significant predictors of posttransplantation survival. Studies including more patients with multiple comorbidities may also be able to discriminate posttransplant survival between patients with CCI scores >1. Another limit is that this study was designed to examine comorbidities for prognostic purposes only. We were unable to determine to what extent the various comorbidities are simply manifestations of advanced liver disease. For example, cirrhosis is diabetogenic and renal insufficiency may reflect hepatorenal syndrome rather than intrinsic kidney disease. Prospective studies with attention to the onset and duration of these comorbidities prior to transplantation may help to improve our understanding of their effects on survival, and potentially lead to strategies for risk mitigation.

In conclusion, we demonstrate the usefulness of a modified comorbidity index, the CCI-OLT, for predicting survival after LT. We found that the posttransplantation survival was diminished in patients with pretransplantation coronary disease, diabetes, COPD, connective tissue disease, and renal insufficiency. In the future, the addition of comorbidities to multivariable models may be useful in developing new allocation algorithms, which incorporate the likelihood of post-LT survival, as has been adopted for lung transplantation.

REFERENCES

1. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
2. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567-580.
3. Merion RM. When is a patient too well and when is a patient too sick for a liver transplant? Liver Transpl 2004;10:S69-S73.
4. Brown RS Jr, Lake JR. The survival impact of liver transplantation in the MELD era, and the future for organ allocation and distribution. Am J Transplant 2005;5:203-204.
5. Coke M, Edwards LB. Current status of thoracic organ transplantation and allocation in the United States. Clin Transpl 2004:17-26.
6. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005;5:307-313.
7. Jacob M, Lewsey JD, Sharpin C, Gimson A, Rela M, van der Meulen JH. Systematic review and validation of prognostic models in liver transplantation. Liver Transpl 2005;11:814-825.
8. Desai NM, Mange KC, Crawford MD, Abt PL, Frank AM, Markmann JW, et al. Predicting outcome after liver transplantation: utility of the model for end-stage liver disease

and a newly derived discrimination function. Transplantation 2004;77:99-106.

9. Thuluvath PJ, Yoo HY, Thompson RE. A model to predict survival at one month, one year, and five years after liver transplantation based on pretransplant clinical characteristics. Liver Transpl 2003;9:527-532.
10. Nair S, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. Hepatology 2002;35: 105-109.
11. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. Hepatology 2002;35:1179-1185.
12. Smith CM, Davies DB, McBride MA. Liver transplantation in the United States: a report from the Organ Procurement and Transplantation Network. Clin Transpl 2000:19-30.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
14. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, Storer B. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005;106:2912-2919.
15. Jassal SV, Schaubel DE, Fenton SS. Baseline comorbidity in kidney transplant recipients: a comparison of comorbidity indices. Am J Kidney Dis 2005;46:136-142.
16. Ghobrial RM, Gornbein J, Steadman R, Danino N, Markmann JF, Holt C, et al. Pretransplant model to predict posttransplant survival in liver transplant patients. Ann Surg 2002;236:315-322; discussion 322-313.
17. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. Liver Transpl 2004;10:886-897.
18. Marrero JA, Fontana RJ, Barrat A, Askari F, Conjeevaram HS, Su GL, Lok AS. Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. Hepatology 2005;41:707-716.
19. Shields PL, Tang H, Neuberger JM, Gunson BK, McMaster P, Pirenne J. Poor outcome in patients with diabetes mellitus undergoing liver transplantation. Transplantation 1999;68:530-535.