Comorbidity Index as a Selection Tool for Living Donor Liver Transplantation in Elderly Patients

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ABSTRACT

Background. Previously published data have shown that age alone is not a contraindication for living donor liver transplantation (LDLT). However, careful evaluation is needed to identify the patients who are unlikely to benefit from LDLT. We hypothesized that the Charlson Comorbidity Index (CCI) could be used as one of the criteria for risk stratification in elderly patients undergoing LDLT.

Patients and Methods. There were 951 patients who underwent LDLT between October 2004 and February 2018. All recipients who were older than 60 years of age at the time of transplantation were identified. The comorbidity score was retrospectively assessed for each elderly patient according to the Charlson Comorbidity Index. Univariate and multivariate Cox regression analyses were performed to identify independent predictive factors for survival in elderly patients after LDLT.

Results. There were 96 patients (10.1%) in the age of $>$ 60 years. All patients received the right lobe of their donor. Out of these patients, 18 (18.7%) died in the median time of 4 months. The remaining 78 patients (81.2%) are alive, with a median survival of 33 months. The CCI of these patients was significantly lower compared to the other 18 patients (2 versus 4). None of the patients with a CCI above 4 survived longer than 12 months. The results of the multivariate Cox regression analyses have shown that pulmonary disease, renal disease, and CCI are independent negative predictive factors for survival.

Conclusion. The results of our study show clearly that the CCI has a significant influence on survival after LDLT in elderly patients and can be used as one of the selection criteria for LDLT in elderly patients.

INTRODUCTION

LIVER transplantation (LT) is an effective treatment option for a wide spectrum of liver diseases, where similar outcomes have been reported either with deceased donor or living donor grafts [1]. Patient selection for LT is a risk-benefit analysis in which the inherent risks of major surgery and lifelong immunosuppression must be weighed against potential improvement in survival and a better health-related quality of life. In deceased donor liver transplantation, the organs are allocated according to the model for end-stage liver disease (MELD) score, which determines the survival benefit of LT by assessing the reduction of the risk for death from end-stage liver disease [2]. To justify the donor risk for LDLT, not only the disease severity but also the likelihood of post-transplant survival should be taken into consideration during the decision-making process. Particularly in the elderly population, evaluation of the physiological status and identification of the pretransplant comorbidities that would have a negative

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impact on post-transplant outcomes is essential for risk stratification. The report of the A2ALL Consortium has previously demonstrated that each 10-year increase in recipient age was associated with a 41% higher risk of graft failure and recipient age was a significant independent risk factor for graft failure after LDLT [3]. Although, diabetes, renal insufficiency, and coronary artery disease have been demonstrated in previous studies to be risk factors for decreased post-transplantation survival, the use of comorbidity scores for prognostic assessment have not been widely adopted in the area of LT [4–7]. One of the most commonly used comorbidity models in medicine is the Charlson Comorbidity Index (CCI), which is based on comorbid conditions with varying assigned weights, resulting in a composite score [6]. In this study, we hypothesized that the CCI could be used for risk stratification in elderly patients undergoing LDLT.

MATERIAL AND METHODS

Between October 2004 and February 2018, a total of 951 patients underwent adult-to-adult right lobe LDLT at our center. Of these patients, we retrospectively analyzed the data of all recipients who were older than 60 years of age at the time of transplantation. Patient characteristics, including the demographic data; pre-, intra- and postoperative data; and the survival data were retrospectively reviewed. All patients underwent an extensive pretransplant assessment and were discussed in the weekly multidisciplinary patient selection conference. The pretransplant work-up for the elderly liver transplant candidates did not differ from that of younger patients. All patients underwent echocardiography, and a cardiac risk evaluation was performed using the Lee index [8]. Nuclear myocardial perfusion testing was used selectively in high-risk patients. Screening colonoscopy was performed routinely. Performance status was evaluated using the WHO performance score (Table 1). The comorbidity score was calculated for each patient according to the CCI (Table 2) [6]. For the assessment of sarcopenia, the cross-sectional skeletal muscle area (cm^2) was measured manually in each patient at the caudal end of the third lumbar vertebra using the preoperative 2 mm slice abdominal computed tomography (CT) and was analyzed with the sliceOmatic 4.3 software (TomoVision, Magog, Canada). The donor selection criteria and evaluation process have been described elsewhere [9]. The minimum evaluation requirements included age over 18, absence of any history of medical condition that would significantly increase the perioperative risks, blood group compatibility with the recipient, and relatedness to the recipient within the fourth degree of consanguinity. All unrelated donors and those beyond the fourth degree of consanguinity were evaluated by the central Ethical Commission of Ministry of Health. All living donors are required to sign an informed consent, which included the items recommended by the ethics statement of the Vancouver Forum [10]. All patients received a right lobe graft, with or without anterior sector venous drainage. The technical details of both donor and recipient operations have been described elsewhere [11]. Patients were routinely followed at the intensive care unit for the first 36 to 48 postoperative hours and were taken to the surgical ward thereafter. A tight glycemic control was maintained with target blood glucose levels of 120-150 mg/dL. The standard immunosuppressive regimen included the combination of corticosteroids in conjunction with a calcineurin inhibitor and mycophenolate mofetil. Initial triple immunosuppression was weaned onto monotherapy with calcineurin inhibitors after the sixth post-transplant month. The routine follow-up of the patients consisted of blood tests weekly until the third post-transplant month, bi-weekly until the sixth postoperative month, and monthly until the first year. A routine physical examination was performed every 3 months during the first post-transplant year and annually thereafter. The study was conducted following the Declaration of Helsinki 2000 criteria as well as Declaration of Istanbul 2008 criteria.

Table 1. World Health Organization Performance Score

Grade	Explanation of activity
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

STATISTICAL ANALYSIS

The values are reported either as median and interquartile range or as mean and standard deviation. Continuous variables were compared using the Mann-Whitney U test. Comparisons of proportions were performed using Fisher's exact test. The Kaplan-Meier method was used for survival

Table 2. Charlson Comorbidity Index

Score	Condition
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease
	Diabetes without end-organ damage
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage
	Tumor without metastases
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor disease
	AIDS

For each decade > 40 years of age, score of 1 is added to the score above.
Liver disease is excluded since all of our patients have moderate or severe liver disease.

Table 3. Results and Comparison of the Results

	All Patients	Survived Patients	Death Patients	*P* Value
n	96	78	18	
Age (years)	63 (60-69)	63 (60-66)	65 (63-66)	.09
BMI	28 (24-30)	28 (24-29)	29 (25-33)	.08
MELD-score	15 (11-18)	14 (11-17)	17 (9-20)	.12
CVD (patients)	31 (32.6%)	28 (35.9%)	3 (16.6%)	.16
Pulmonal disease (patients)	18 (18.9%)	14 (17.9%)	4 (22.2%)	.74
Renal disease (patients)	15 (15.8%)	11 (14.1%)	4 (22.2%)	.47
Diabetes mellitus (patients)	29 (30.5%)	24 (30.7%)	5 (27.8%)	1.0
Several comorbidities (patients)	10 (10.5%)	5 (6.4%)	5 (28.8%)	.01*
GRWR	1.1 (1.1-1.3)	1.2 (1.0-1.3)	1.0 (0.9-1.4)	.56
CCI	2.0 (2.0-3.0)	2.0 (2-3)	4.0 (2-6)	< .0001*
Total ischemic time (minutes)	85 (62-100)	98 (77-146)	123 (90-199)	.04*
Duration of surgery (minutes)	460 (410-535)	460 (405-525)	470 (415-590)	.11
Major complications (patients)	26 (27.4%)	20 (25.6%)	6 (33.3)	.56
Hospital stay (days)	17 (14-22)	16 (14-20)	17 (12-32)	.03*

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CVD, cardiovascular disease; GRWR, graft to recipient weight ratio; MELD, Model for End-Stage Liver Disease.
*$P < .05$ = significant.

calculation, and comparison between groups were performed using the log-rank test. Univariate and multivariate regression analysis was performed to identify independent prognostic factors for survival. A $P < .05$ was considered as significant.

RESULTS

In a cohort of 951 LDLT patients, 96 patients (10.1%) were > 60 years of age at the time of LT. The upper age limit in this elderly group was 75 years, and one-third of elderly patients had age > 65 (n = 32). The most common etiology of liver cirrhosis was hepatitis B (27.8%), which was followed by nonalcoholic steatohepatitis (24.7%), hepatitis C (16.5%), and ethanol (12.4%). Hepatocellular carcinoma (HCC) was present in 35 patients (36.5%). The median lab MELD score was 15.0 (11.0-18.0) (Table 3). All elderly patients had performance scores ≤ 3, with a median pretransplant WHO score of 2 (1-2). The measured median skeletal muscle area, using a preoperative CT scan, was 98 cm^2 (95-125) in male (n = 69) and 68 cm^2 (61-87) in female (n = 26) patients. The median comorbidity score of all patients was 3.0 (2.0-3.0) (Table 3). The median blood transfusion was 3.0 (2.0-7.0) units. The anastomosis of the bile duct was duct to duct in 91 patients (95%), and hepaticojejunostomy with Roux-J reconstruction was performed in 5 patients (5%). The total graft ischemic time was 85 minutes (62-100). The median graft to recipient weight ratio was 1.1 (1.1-1.3). The median time of surgery was 460 minutes (410-535). Major perioperative complications were seen in 17 patients (17.7%): 8 developed biliary complications, 4 patients had graft failure, and 5 patients had sepsis. The biliary complications were treated by interventional procedures in 5 patients, and 3 patients underwent reoperation with conversion hepaticojejunostomy and Roux-J reconstruction. The median hospital stay was 17.0 days (14.0-22.7). Out of 96 patients, there were 18 patients (18.7%) who died in a median time of 4 months (1.0-12.0) postoperation. Perioperative death, defined as 90-day mortality, was seen in 16 patients (16.6%) due to major postoperative complications such as graft failure, biliary complications, pneumonia followed by sepsis, and cardiac arrest. Two patients died due to recurrent HCC disease 26 and 16 months after LT. The remaining 78 patients (82.0%) are still alive with a median survival of 33.0 months (16.0-52.0). The 1- and 3-year survival rates were 86.0% and 77.4%, respectively. The rate of early allograft dysfunction, defined as aspartate transaminase > 2000 IU during the first post-transplant week and postoperative day 7 bilirubin of > 10 mg/dL and INR of > 1.6, was seen in 15 patients (15.6%) [12]. The comparison between the 18 patients who died and the remaining 78 patients has shown that there is no significant difference in operative characteristics expect for significantly longer graft ischemic time (98.0 vs 123.0 minutes, $P = .04$) and hospital stay (16.0 vs 17.0 days, $P = .03$). The comorbidity score of these patients was significantly higher (2.0 vs 4.0, $P < .0001$). There were no other significant differences between the groups (Table 3). The results of the univariate analyses have shown that pulmonary disease, renal disease, total ischemic time, and CCI are independent negative predictive factors for survival (Table 4). The results of the multivariate Cox regression analyses have shown that pulmonary disease, renal disease, and CCI are independent negative predictive factors for survival (Table 5). There was no statistically defined cutoff regarding the comorbidity score. However, there was no patient with a comorbidity score above 4 who survived in the long term (Fig 1).

Table 4. Univariate Analyses

Variable	Beta	HR (95% CI for HR)	*P* Value
Sex	-0.093	0.91 (0.32-2.6)	.86
Age	0.1	1.1 (0.98-1-2)	.099
BMI	0.082	1.1 (1-1.2)	.048*
Cardiovascular disease	-0.73	0.48 (0.064-3.6)	.48
Pulmonary disease	2	7.1 (2-25)	.0021*
Renal disease	1.7	5.5 (1.6-19)	.0076*
Diabetes mellitus	-0.24	0.78 (0.28-2.2)	.64
Hypertension	0.51	1.7 (0.48-5.8)	.42
Lab MELD score	0.07	1.1 (0.99-1.2)	.098
Graft volume	-0.00014	1 (1-1)	.92
GRWR	-0.78	0.46 (0.05-3.8)	.47
Total ischemic time	0.0074	1.7 (1.2-2.3)	.049*
Duration of surgery	0.0038	1 (1-1)	.1
RBC	0.093	1.1 (1-1.1)	< .0001*
Biliary complications	-0.36	0.7 (0.26-1.9)	.47
Hospital stay	0.025	1 (1-1)	.031*
CCI	3.3	28 (9.8-79)	< .0001*

Abbreviations: CCI, Charlson Comorbidity Index; GRWR, graft to recipient weight ratio; MELD, Model for End-Stage Liver Disease; RBC, red blood cells.
*$P < .05$ = significant, n = 96.

DISCUSSION

This study presents a significant association between the pretransplant comorbidities and post-transplant survival in elderly patients. The CCI is an independent risk factor for perioperative mortality, as well as long-term survival in elderly patients undergoing LDLT. The study population included a group of recipients over the age of 60 who underwent LDLT with relatively low MELD scores. Consistent with the previously published reports, the survival data of our cohort shows that the perioperative survival as well as the long-term survival in elderly patients is not significantly impaired in elderly patients [13]. However, these patients need to be selected carefully. Although the experience of the transplant team significantly contributes to the results, the outcome of LDLT is mostly dependent on the characteristics of the patient at the time of surgery. In liver transplantation, more accurate patient selection can be achieved by mathematical models, which can help to make a specific risk/benefit analysis and justify the risk incurred by the donor. Since the original publication in 1987 [14], the CCI has been validated for its ability to predict mortality in different patient populations. It has been modified for analyses of kidney transplant recipients [15], and it has been evaluated for orthotopic liver transplant recipients in 2 studies [6,16]. In our study, the CCI gains importance for elderly patients since the combination of higher age and comorbidity can impair the postoperative recovery, especially if surgical complications arise. The results of our study show that comorbidities have a significant impact on the survival rate in elderly patients and the CCI is an independent factor to predict survival. None of the patients with CCI above 4 survived long term. One shortcoming of our study is the retrospective nature with all its drawbacks. Another weak point is that the age of the patients is > 60 years, which does not meet the definition of elderly patients in some Western countries since it is very close to their average age of the patients. Western countries often define ≥ 70 years of age as an elderly patient. The number of the patients ≥ 70 years of age in our study population was too small to perform multivariate analyses and define statistically independent factors for survival. A further limitation is that we do not have any patients in our study group with very high MELD score nor patients in bad general condition, which is a selection bias. However, based on our experience with LDLT, we can say that the advantage of LDLT is the fact to perform the liver transplantation in an early stage of the disease, which leads to short-term survival rates of over 90% and long-term survival rates over 85%. Under these conditions, the question arises if the transplantation is really necessary since the patient has a low MELD score and is in good general condition. All of the patients have either HCC or at least 1 of the index complications, such as therapy resistant ascites, recurrent variceal bleeding, or severe encephalopathy. These complications lead to significant impediment of the daily life, hospitalization of the patient, and a shortening of life expectancy, and liver transplantation is the only treatment option. Kwon et al describe their results of 15 recipients over 70 years. It was shown that these patients had similar survival data compared to the younger group. The

Table 5. Multivariate Analyses

Variable	Beta	HR (95% CI for HR)	*P* Value
Pulmonary disease	1.86	6.41	.03*
Renal disease	1.90	6.69	.02*
Total ischemic time	0.01	1.01	.08
RBC	0.08	1.09	.02*
Hospital stay	0.02	1.02	.23
CCI	2.21	9.11	.00*

Abbreviations: CCI, Charlson Comorbidity Index; GRWR, graft to recipient weight ratio; MELD, Model for End-Stage Liver Disease; RBC, red blood cells.
*$P < .05$ = significant, n = 96.

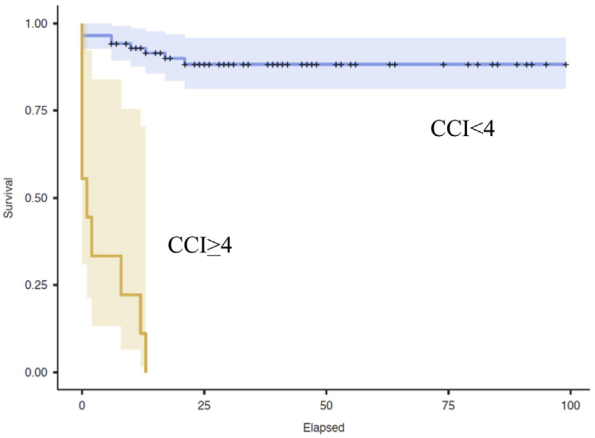

Fig 1. Survival comparison between patients with CCI ≥ 4 and < 4. CCI, Charlson Comorbidity Index.

American Society of Anesthesiologists (ASA) score and Eastern Cooperative Oncology Group (ECOG) was used as a selection tool. Patients with ASA $\geq$ IV and/ or ECOG $\geq$ IV were excluded. The median MELD score was 10. The main conclusion was that patients with an age over 70 should not be excluded from LDLT and careful selection of recipients and donors is necessary for successful results [17]. ASA and/or ECOG $\geq$ IV are also exclusion criteria for liver transplantation in younger patients or any other major operation with high risk. It is not a selection tool for elderly patients. The elderly patients have good results due to a low MELD score and most likely they were selected based on the experience of the transplant team without using any specific tool. Patients with an age over 70 and combination of multiple comorbidities, even if their ASA score is below IV, are most likely excluded based on the clinical experience of the transplant team without calculating of any scores. The goal of our study is to have scores that are not based on individual experience but can be easily assessed and have an impact on the expected survival. The experience is of course absolutely essential but difficult to measure and to standardize the decision-making process.

CONCLUSION

In elderly patients undergoing LDLT, comorbidity is prevalent and significantly affects survival after transplantation. The comorbidities must therefore be described and quantified. The CCI is easy to use and operational in liver transplant patients. It could be a preferred method for risk stratification and prediction of post-transplant mortality.

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