MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2019; 25: 4521-4526
DOI: 10.12659/MSM.914669

Received: 2018.12.17
Accepted: 2019.02.26
Published: 2019.06.18

Renaissance of Modified Charlson Comorbidity Index in Prediction of Short- and Long-Term Survival After Liver Transplantation?

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Manuscript Preparation E
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Source of support: Michał Grąt was supported by the foundation for Polish Science (FNP) with a START stipend (START 032.2018)

Background: Orthotopic liver transplantation (OLT) is the standard of care for end-stage liver disease. The Charlson Comorbidity Index (CCI) was originally created to assess the survival rate of patients with chronic diseases, although it was modified and adopted in OLT recipients as CCI-OLT.

Material/Methods: In total of 248 consecutive liver transplant recipients with viral cirrhosis in 98 (39.5%) patients were included. CCI-OLT was calculated assigning a weight of 3 to chronic obstructive pulmonary disease; weight of 2 to coronary artery disease, connective tissue disease, and renal insufficiency; and a weight of 1 to diabetes mellitus.

Results: CCI-OLT was significantly correlated with recipient age ($p<0.001$; $R=0.333$) and was a significant risk factor for early post-transplant mortality ($p=0.004$). The presence of diabetes mellitus significantly increased the odds of early mortality ($p=0.010$). The optimal cut-off for CCI-OLT in prediction of mortality during the first 90 days after transplantation was ≥1, with an AUROC of 0.780 (95% CI: 0.670–0.891; $p<0.001$). Increasing CCI-OLT was a significant risk factor for worse 5-year post-transplant survival ($p=0.001$), along with coronary artery disease ($p=0.008$) and diabetes mellitus ($p=0.021$). The optimal cut-off for prediction of 5-year mortality for CCI-OLT was ≥1, with the AUROC of 0.638 (95% CI: 0.544–0.733; $p=0.004$).

Conclusions: CCI-OLT is a useful tool for measuring the effect of pretransplant comorbidities and to stratify the effect of risk on both short- and long-term outcomes after OLT. Recipient age and diabetes strongly affected short-term survival after OLT, and metabolic and vascular complications were the leading causes of death at 5 years after OLT.

MeSH Keywords: Comorbidity • Coronary Artery Disease • Diabetes Mellitus • Liver Transplantation

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/914669

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Background

Orthotopic liver transplantation (OLT) is a life-saving procedure for patients with end-stage liver disease (ESLD). In the last 2 decades, significant improvements in preoperative work-up, surgical technique, and intraoperative care of liver transplant recipients have resulted in decreased perioperative complications and increased patient survival. However, outcome after surgery is determined by donor, transplant, and recipient risk factors, and higher Model for End-Stage Liver Disease score (MELD) of the recipient is an independent risk factor of poor result of OLT [1]. The survival benefit for transplant patients with higher MELD is indisputable if they survive the first year after OLT [2], but they also have the highest 90-day waitlist mortality rate [3]. On the other hand, patients undergoing OLT nowadays have more severe ESLD, are older, and have more comorbidities. In addition, cardiovascular complications are the leading cause of long-term mortality in liver transplant patients [4]. Thus, in the present transplant organ shortage, it is rational to prioritize the patients to avoid short-term futility, defined as post-transplant 90-day mortality, as well as long-term survival below 50% at 5 years after OLT.

The Charlson Comorbidity Index (CCI) was originally created to assess the survival rate of patients with chronic diseases. This index has been used in various forms in multiple patients populations, including stem cell [5] and renal transplantation [6]. The CCI was modified and adopted in liver transplantation as the Charlson Comorbidity Index – Orthotopic Liver Transplantation (CCI-OLT) and represents the association between comorbidities present prior to transplantation and survival after OLT [7,8].

Although the OLT outcomes are attributable to recipients, donors, and operative procedural characteristics, the shortage of donor livers increases the need to maximize the life-saving capacity of procured livers. Allocation of deceased-donor livers to chronic liver failure patients might be improved by prioritizing patients by transplant survival benefit [2].

Aim of the study

To evaluate the role of CCI-OLT in a single liver transplant center in respect to short and long-term mortality of the recipients.

Material and Methods

The study population comprised 248 consecutive patients with end-stage liver disease (156 males and 92 females) after liver transplantation. The group included all adults ≥18 year with the median age 54 y. The major etiologies of ESLD were: viral in 98 patients (39.5%), alcoholic liver disease in 49 (19.8%), and autoimmune diseases in 84 (PSC 35–14.0%, AIH 27–10.8%, PBC 24–9.6%). The exclusion criteria were acute liver failure and liver re-transplantation.

CCI-OLT

A total of 5 comorbidities comprising the CCI-OLT were analyzed, including coronary artery disease (CAD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), connective tissue disease (CTD), and renal insufficiency. The CCI-OLT was calculated by assigning a weight of 3 to COPD; a weight of 2 to CAD, CTD and renal insufficiency; and a weight of 1 to diabetes mellitus.

Study design

The CCI-OLT was constructed to illustrate the associations between comorbidities present prior to transplantation and decreased survival after liver transplantation, and was considered the primary factor of interest. Patient survival was the primary outcome measure assessed in 3 time-frames. First, CCI-OLT and other covariates were assessed as risk factors for worse 5-year survival in general. Second, its associations with the risk of early (90-day) mortality were evaluated. Finally, assessment of risk factors for late mortality was performed in a subgroup of patients surviving at least 90 days after liver transplantation.

Statistical analysis

Continuous and categorical variables are presented as medians with interquartile ranges and numbers with percentages. Kaplan-Meier method was used to calculate survival, with log-rank test used for intergroup comparisons. Logistic regression models were applied to evaluate risk factors for early mortality. Cox proportional hazards regression models were applied to evaluate risk factors for both 5-year and late mortality. Spearman correlation coefficient was used to determine associations between quantitative variables. Fisher's exact test was used to compare early mortality rates between subgroups. Cut-offs were derived from analyses of the receiver operating characteristics curves. Hazard ratios (HRs), odds ratios (ORs), and areas under the ROC curves (AUROCs) are presented with 95% confidence intervals (95% CIs). Two-tailed $p<0.05$ was considered significant. STATISTICA v. 13.1 (Dell, Inc., Tulsa, USA) was used to compute statistical analyses.

Results

Baseline characteristics of the study cohort are shown in Table 1. Overall, the one-, three-, and five-year survival rates were 88.7%, 79.9%, and 75.2%, respectively (Figure 1), with

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Table 1. Baseline characteristics of patients included in the study.

Characteristics	n (%) or median (IQR)	
Gender: Male	156	(62.9)
Age	54	(38–60)
CCI-OLT	0	(0–1)
DM	48	(19.4)
CAD	21	(8.5)
Viral cirrhosis	98	(39.5)
Alcoholic disease	49	(19.8)
Autoimmune diseases	84	(33.9)

CAD – coronary artery disease; CCI-OLT – Charlson Comorbidity Index – Orthotopic Liver Transplantation; DM – diabetes mellitus.

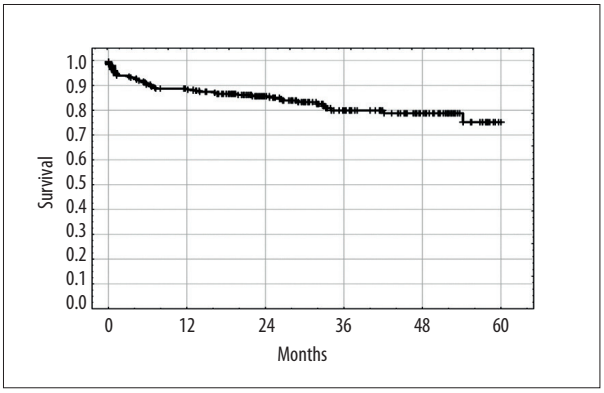

Figure 1. One-, three-, and five-year survival rates with 90-day mortality rate.

a 90-day mortality rate of 6.0% (15 of 248). CCI-OLT was significantly correlated with recipient age (p<0.001; R=0.333).

CCI-OLT was a significant risk factor for early post-transplant mortality (p=0.004; Table 2). Of its components, only the presence of diabetes mellitus significantly increased the odds of early mortality (p=0.010). The optimal cut-off for CCI-OLT in prediction of mortality over the first 90 days after transplantation was ≥1, with AUROC of 0.780 (95% CI: 0.670–0.891; p<0.001; Figure 2). Early mortality in patients with CCI-OLT of 0 points and ≥1 point was 1.3% (2 of 160) and 14.8% (13 of 88), respectively (p<0.001). Patients with diabetes mellitus exhibited an early mortality rate of 14.6% (7 of 48) as compared to 4.0% (8 of 200) in the remaining patients (p=0. 012).

Increasing CCI-OLT was a significant risk factor for worse 5-year post-transplant survival (p=0.001), along with coronary artery disease (p=0.008) and diabetes mellitus (p=0.021; Table 3). The optimal cut-off for prediction of 5-year mortality for CCI-OLT was ≥1, with an AUROC of 0.638 (95% CI: 0.544–0.733;

Table 2. Risk factors for early post-transplant mortality.

Factor	OR	95%CI	p
CCI-OLT	1.52	1.14–2.02	0.004
Age	1.05	0.99–1.10	0.106
CAD	2.99	0.77–11.56	0.113
DM	4.01	1.41–11.93	0.010

CAD – coronary artery disease; CCI-OLT – Charlson Comorbidity Index – Orthotopic Liver Transplantation; DM – diabetes mellitus.

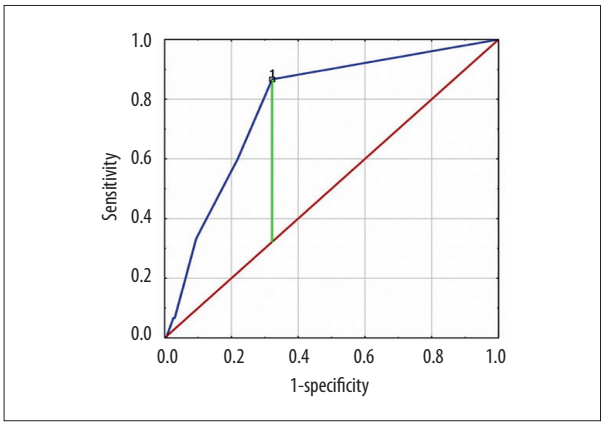

Figure 2. The optimal cut-off for CCI-OLT in prediction of mortality during the first 90 days after transplantation.

Table 3. Risk factors for 5-year mortality after liver transplantation.

Factor	HR	95%CI	p
CCI-OLT	1.27	1.10–1.46	0.001
Age	1.00	0.99–1.00	0.331
CAD	2.81	1.31–6.06	0.008
DM	2.10	1.12–3.96	0.021

CAD – coronary artery disease; CCI-OLT – Charlson Comorbidity Index – Orthotopic Liver Transplantation; DM – diabetes mellitus.

p=0.004; Figure 3). Survival at 5 years after transplantation for patients with CCI-OLT of 0 points and ≥1 point was 78.9% and 69.4%, respectively (p=0.001, Figure 4). After exclusion of patients who died in the early post-transplant period, CCI-OLT was not significantly associated with late mortality (p=0.112), but the presence of coronary artery disease was (p=0.036; Table 4).

Discussion

We presented our experience with CCI-OLT and its components as a predictor of early and late mortality after LT. CCI-OLT

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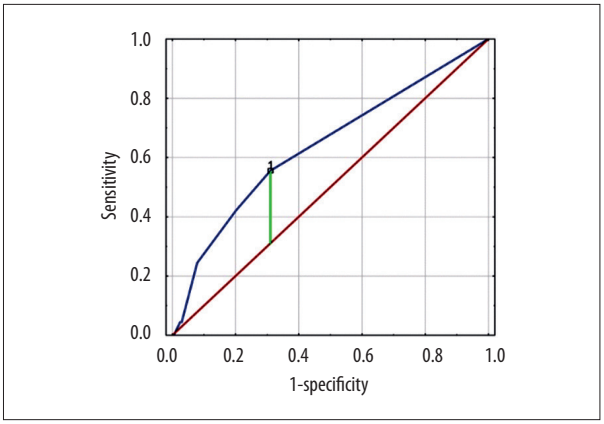

Figure 3. The optimal cut-off for prediction of 5-year mortality for CCI-OLT.

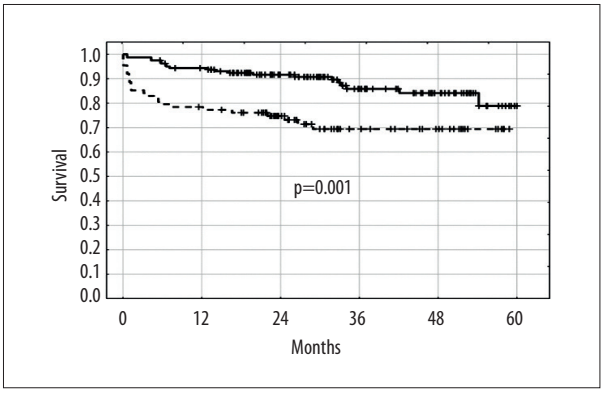

Figure 4. Survival at 5 years after transplantation for patients with CCI-OLT of 0 points and ≥1 point.

Table 4. Risk factors for mortality between 90 days and 5 years after transplant.

Factor	HR	95%CI	p
CCI-OLT	1.19	0.96–1.46	0.112
Age	1.00	0.99–1.00	0.705
CAD	2.81	1.07–7.37	0.036
DM	1.49	0.64–3.47	0.358

CAD – coronary artery disease; CCI-OLT – Charlson Comorbidity Index – Orthotopic Liver Transplantation; DM – diabetes mellitus.

performed well, although AUROCs for predicting early (to 90 days) and late mortality for CCI-OLT ≥1 point were lower than 0.8, but the components of index had higher predictive value. Diabetes mellitus was the risk factor for early mortality (in the first 90 days) and coronary artery disease was the risk factor for late mortality following OLT. CCI-OLT was correlated significantly with the age of liver transplant recipients. Patients with higher CCI-OLT had worse 5-year survival after OLT as compared to patients with lower CCI-OLT and to the whole studied group. Thus, the results of this study confirmed the need to minimize risk factors of cardiovascular events. Liver transplant recipients are at risk of metabolic syndrome and its components, increasing the risk of death with a functioning liver graft. These results also to point to the increasing problem of atherosclerosis in liver transplant patients, and they are in line with previously published observations.

CCI is a simple tool for the evaluation of comorbidity, showing that increased preoperative patient comorbidity increases the risk of graft loss and patient death after liver transplantation [9]. The Charlson Comorbidity Index is an extensively studied scale for predicting mortality, and it is a valid and reliable method to measure the effect of comorbidities for clinical purposes [10]. The CCI is an important tool for improving risk stratification and thus has potential applications for patient management [9]. Unlike long-term survival, CCI-OLT did not seem to predict early (30-day) mortality after OLT in a single-center liver transplant report [8]. However, the results of the present study confirmed its utility as a short-term (90-day) stratifying tool. Previous studies found that the CCI and individual comorbidities, including coronary artery disease, diabetes mellitus, chronic obstructive pulmonary disease, connective tissue disorders, and renal insufficiency, were associated with decreased survival after OLT [7]. A study by Petrowsky et al. found that the highest and age-adjusted CCI was highly predictive of liver transplant futility [11], suggesting that cardiac and other comorbidities were the most important predictors of futile OLT in the most severely ill individuals [11]. Petrowsky et al. also reported that cardiac and metabolic complications, as well as age, were associated with inferior long-term graft and patient survival, with the strongest effect of metabolic syndrome [11], which was also found in the present study.

Over the years, survival after OLT has increased but metabolic complications have become more common, which is contributed to by patient morbidity and mortality, with arterial hypertension and dyslipidemia present in many diabetic patients after OLT [12]. Short-term patient survival after OLT mainly depends on recipient risk factors, including age, MELD, sodium, ventilatory support, and the presence of diabetes mellitus before OLT [13]. Additionally, diabetes mellitus was, among others, a risk factor for intracardiac and pulmonary thromboembolism leading to liver recipient death within 24 h after OLT in multivariable regression analysis [14]. Meta-analysis of the results of OLT in 15 768 diabetic recipients and 60 176 nondiabetic OLT patients clearly showed that preexisting diabetes increased the risk of death after surgery by 40%, as well as increasing graft loss, with a hazard ratio (HR) of 1.28 [15]. Of note, patients with sustained post-transplant diabetes had significantly increased risk of major cardiovascular events after OLT, with HR 1.95, and cumulative risk of 13% and 27% at 5 and 10 years after OLT, respectively [16]. Ramos-Prol et al.

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reported a trend for higher mortality in liver graft recipients with diabetes, showing to the need for more rigorous pretransplant evaluation and closer monitoring after OLT in order to reduce associated complications in diabetics [17]. Additionally, transplanted patients with hepatitis B-related hepatocellular carcinoma and diabetes mellitus had decreased survival and poor OLT outcomes at 1, 3, and 5 years after the procedure [18]. Moreover, preexisting DM with renal manifestations was associated with a significantly higher mortality rate within 90 days after OLT, in comparison with the non-DM cohort in a study with 558 liver transplant patients with diabetes [19]. Stratified analyses also demonstrated that the DM cohort had higher mortality risk in patients with liver cancer, as well as in patients without hypertension, ischemic heart disease, and COPD. DM was also associated with a significantly elevated 90-day, but not 30-day, risk of post-OLT stroke. Thus, special attention should be paid to post-OLT monitoring and care in DM patients in order to minimize the potential complications of stroke [19]. The opposite results are rare. However, Kwon et al. published retrospective data from 814 liver graft recipients without overt cardiovascular disease, with no impact of diabetes mellitus with or without arterial hypertension on graft survival or all-cause mortality in OLT recipients [20].

Liver transplantation is categorized as a surgery with high cardiovascular risk [21] and cardiac complications such as heart failure, myocardial infarction, and arrhythmias, and is a major cause of transplant-related morbidity and mortality [22]. The results of the present study are in line with the previously described reports. Pretransplant coronary artery disease was the risk factor for cardiovascular events after OLT in a single-center German cohort of 352 recipients at a median follow up of 4.0 years [23] and in the experience of our group with short-term cardiovascular morbidity after OLT in 105 consecutive liver transplant recipients [24]. Of note, cardiac risk and age-adjusted comorbidities were associated with the highest risk for futile outcome in a study Petrowsky et al. with 1522 liver recipients, including 169 patients with MELD >40 points. Cardiac risk was defined as a history of any cardiovascular disease and/or elevated serum pretransplant troponin level, and was highly predictive of mortality and graft loss within 1 year after OLT [11]. More precisely, Yong et al. found that none of the traditional clinical predictors of cardiovascular events (age, gender, diabetes, creatinine, ejection fraction, and MELD score) were predictive of higher mortality among transplant recipients, but multivessel coronary artery disease was, regardless of the severity of coronary stenosis [25]. In a study by D'Avola et al. with more than 1800 individuals, cardiovascular events were responsible for 12% of recipient deaths at 5 years after OLT, emphasizing the importance of preexisting risk factors such as age, pre-OLT history of cardiovascular disease, diabetes, metabolic syndrome implicated post-OLT cardiac morbidity and mortality, but also pointing to the role of new onset of obesity and dyslipidemia as cofactors of late cardiovascular complications [4]. The importance of this issue is confirmed by the results of a Spanish study, showing the incidence of post-transplant metabolic syndrome at 5 years after OLT in 38.2% of grafted patients, with major roles of obesity and diabetes, both before and within the first year after OLT [26]. Moreover, in the observational period of 10 years, diabetes was associated with a higher risk of liver graft rejection and lower graft survival time, and cardiovascular events were also more likely in the group of recipients with diabetes in the Spanish study by Ramos-Prol et al. [17].

Conclusions

We found that CCI-OLT was correlated with the age of liver transplant recipients. Recipients with higher CCI-OLT had worse 5-year survival than patients with lower CCI-OLT, due to increased early mortality. Diabetes mellitus was the risk factor for early mortality and coronary artery disease for late mortality following OLT in this single-center experience. CCI-OLT seems to a useful stratification tool to measure the effect of pretransplant comorbidities on mortality after liver transplantation. Efforts should be made to optimize risk patterns of vascular and metabolic comorbidities in liver transplant candidates to avoid liver transplant patient mortality with functioning graft, especially in aged recipients.

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