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Modified Charlson comorbidity index as a survival prediction tool for older patients after liver transplantation

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Purpose: An increasing number of older patients now undergo liver transplantation (LT). Although the overall outcomes in older patients are not different from those of younger patients, there is no tool to predict LT prognosis in older patients. We hypothesized that a modified Charlson comorbidity index (mCCI) and 5-factor modified frailty index (mFI-5) can predict outcomes in older patients after LT.
Methods: This retrospective study included 155 patients (aged >65 years) who underwent LT at Seoul National University Hospital. The recipients were subcategorized into 2 groups based on the mCCI score and mFI-5: the low (0–1) and high (2–5) mCCI groups, and low (≤0.4) and high (>0.4) mFI-5 groups. The independent effect of each variable on post-LT survival was determined using the mCCI subgroup, age at transplantation, sex, Child-Turcotte-Pugh score, model for end-stage liver disease (MELD) score, and mFI-5 subgroup.
Results: The high-mCCI group (41 patients) showed significantly lower 1- and 3-month and 1-, 3-, and 5-year survival than the low-mCCI group. Using the Cox regression model, the mCCI, sex, and MELD score remained significant. The mFI-5 was not a significant factor to predict patients' survival.
Conclusion: The mCCI and MELD scores could be used to predict post-LT survival in older patients.
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Key Words: Acute liver failure, End stage liver disease, Hepatocellular carcinoma, Immunosuppression, Patient care

INTRODUCTION

Liver transplantation (LT) is an effective treatment for severe liver diseases, such as end-stage liver disease, hepatocellular carcinoma (HCC), and fulminant hepatic failure [1]. Post-LT outcomes have improved with advances in surgical techniques, immunosuppression, and patient care, and the eligibility criteria for possible recipients are gradually expanding [2]. Thus, the number of LTs performed in older patients is increasing.

Differences in LT outcomes exist depending on the recipients' ages. Numerous studies have shown that LT can be performed safely in older patients only if the patients are carefully selected [3,4]. However, no survival-predicting tool exists for older patients that are potential candidates for LT. Furthermore, there are few comorbidity indices that predict postoperative outcomes based on preoperative factors.

The Charlson comorbidity index (CCI) is a model that predicts patients' morbidity and mortality based on 9 types of comorbidities [5]. Volk et al. [6] recalibrated the CCI for use in LT patients and named it the modified CCI (mCCI). Although

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the mCCI is proposed to be useful in predicting morbidity and mortality, its effectiveness in older patients has not yet been studied. Furthermore, since the pattern and etiology of liver diseases differ between Western and Asian societies, the mCCI requires validation in Asian populations.

The 5-factor modified frailty index (mFI-5), which is based on 5 clinical factors, is another model that predicts patients' morbidity and mortality [7]. Although the mFI-5 is a model of the 11-factor modified frailty index revised for clinical use, it has not been validated in older patients who undergo LT.

This study aimed to assess whether the mCCI and mFI-5 could be used to predict post-LT mortality and morbidity in older patients.

METHODS

A total of 1,136 patients underwent LT at Seoul National University Hospital between August 2011 and May 2019. Of these, this study included 155 patients who were over 65 years old, a demographic classified as elderly according to the OECD (Organisation for Economic Co-operation and Development) definition. The time period was selected to achieve a follow-up time of at least 1 year. Patients whose medical records were insufficient were excluded from the study.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki 2013 as reflected in prior approval by the appropriate Institutional Review Committee (2011-134-1174), and individual consent for this retrospective analysis was waived. No organs from executed prisoners were used.

The mCCI and mFI-5 scores were calculated according to a previously described method [6-9]. The mCCI score, which includes coronary disease, chronic obstructive pulmonary disease, diabetes mellitus (DM), connective tissue disease, and renal insufficiency, was calculated. The mFI-5 includes functional status, DM, chronic obstructive pulmonary disease, congestive heart failure, and hypertension. Comorbidities other than renal insufficiency were defined based on the diagnosis made by the medical specialist. Renal insufficiency was defined as a serum creatinine level of >1.5 in the most recent preoperative test [6]. The functional status was defined as abnormal if the portosystemic encephalopathy grade was ≥2. For the mCCI, the patients were divided into 2 groups: the low-mCCI group (0–1) and the high-mCCI group (2–5). In the case of mFI-5, patients were subcategorized into 2 groups: the low mFI-5 group (0–0.4) and the high mFI-5 group (>0.4). Regarding each index, the score with the most remarkable difference in survival was set as the cutoff score.

Unadjusted and multivariate-adjusted analyses were performed to identify the independent effect of each pretransplantation factor on post-LT survival using the Cox proportional hazards regression model. In addition to mCCI and mFI-5, age, sex, Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD) score, etiology of liver disease, and HCC were included as confounders. Subsequent statistical analyses for each mCCI and mFI-5 were performed separately. The Kaplan-Meier method was then performed to estimate the patients' early mortality (1-month and 3-month) and late mortality (1-year, 3-year, and 5-year survival). Severe postoperative complications (Clavien-Dindo classification of ≥IIIa) between the subgroups of mCCI and mFI-5 were compared using the chi-square test [10].

RESULTS

Among the 1,136 patients who underwent LT during the study period, 160 recipients were >65 years of age, but 5 patients were excluded because of insufficient medical records.

Table 1. Characteristics of the patients that underwent liver transplantation in Seoul National University Hospital

Characteristic	Data
No. of patients	155
Age at transplant (yr)	69.2 (65–82)
Follow-up (yr)	3.6 (0.1–9.1)
CTP[a]	
A	42 (27.1)
B	46 (29.7)
C	67 (43.2)
MELD	18 (6–42)
Sex	
Male	92 (59.4)
Female	63 (40.6)
Transplantation type	
Living donor	104 (67.1)
Deceased donor	51 (32.9)
Death	41 (26.5)
Hepatocellular carcinoma	99 (63.9)
Etiology of liver disease	
HBV-related LC	60 (38.7)
HCV-related LC	35 (22.6)
Alcoholic LC	26 (16.8)
Biliary cirrhosis	5 (3.2)
NBNC LC	22 (14.2)
Others	7 (4.5)
Comorbidity	
Coronary disease	2 (1.3)
Diabetes mellitus	45 (29.0)
COPD	2 (1.3)
Connective tissue disease	1 (0.6)
Renal insufficiency	38 (24.5)
Congestive heart failure	0 (0)
Hypertension	46 (29.7)

Values are presented as number only, median (range), or number (%).
CTP, Child-Turcotte-Pugh score, MELD, model for end-stage liver disease; LC, liver cirrhosis; NBNC LC, non-B, non-C hepatocellular carcinoma LC; COPD, chronic obstructive pulmonary disease.
[a]Where >6 is Child B and >9 is Child C.

The CTP score, MELD score, and comorbidities of all 155 patients were analyzed. The overall patient characteristics are described in Table 1. The median age at LT was 69 years (range, 65–82 years) and the median follow-up duration was 3.6 years (range, 0.1–9.1 years). One patient died immediately after LT. Sixty percent of the patients had at least 1 comorbidity during the pretransplantation state. Hypertension was the most common comorbidity. One person suffered from connective tissue disease and congestive heart failure. The mean mCCI and mFI-5 scores were 0.83 and 0.15, respectively. A total of 41 patients died until December 2020, and the 1-, 3-, and 5-year survival rates were 81%, 77%, and 74%, respectively.

Table 2 displays the results of the Cox proportional hazards analysis for 5-year survival after LT. The unadjusted Cox regression analysis showed that the mCCI, MELD score, and sex were significantly associated with post-LT mortality. Other variables, including mFI-5, did not show a significant association with post-LT mortality. After adjusting the MELD score and sex, the mCCI was still a significant factor with a hazard ratio for post-LT mortality of 2.409 (95% confidence interval, 1.08–5.36). Table 3 presents the distribution of the mCCI and mFI-5.

Fig. 1 shows the significant difference in overall survival

Table 2. Multivariate analyses for predicting patients' overall survival

Variable	HR (95% CI)	P-value
Age at transplant (yr)	1.00 (0.91–1.11)	0.945
CTP[a]		
A		0.126
B	1.12 (0.41–3.04)	0.830
C	0.36 (0.1–1.32)	0.124
MELD	1.11 (1.04–1.18)	0.001*
Female sex	0.45 (0.20–0.98)	0.044*
Hepatocellular carcinoma	1.93 (0.87–4.27)	0.107
Etiology of liver disease		
HBV-related LC		0.678
HCV-related LC	1.78 (0.73–4.36)	0.205
Alcoholic LC	1.98 (0.60–6.53)	0.265
Biliary cirrhosis	0	0.978
NBNC LC	2.33 (0.77–7.05)	0.135
Others	2.36 (0.60–9.37)	0.222
Modified CCI score	2.41 (1.08–5.36)	0.031*
5-Factor modified frailty index	1.04 (0.35–3.05)	0.945

HR, hazard ratio; CI, confidence interval; CTP, Child-Turcotte-Pugh score, MELD, model for end-stage liver disease; LC, liver cirrhosis; NBNC LC, non-B, non-C hepatocellular carcinoma LC; CCI, Charlson comorbidity index.
[a]Where >6 is Child B and >9 is Child C.
*P < 0.05, statistically significant.

Table 3. Distribution of mCCI score and mFI-5

Variable	No. of patients (%)
mCCI score	
0	84 (54.2)
1	30 (19.4)
2	26 (16.8)
3	13 (8.4)
4	1 (0.6)
5	1 (0.6)
mFI-5	
0.0	63 (40.6)
0.2	70 (45.2)
0.4	18 (11.6)
0.6	4 (2.6)
0.8	0 (0)
1.0	0 (0)

mCCI, modified Charlson comorbidity index; mFI-5, 5-factor modified frailty index.

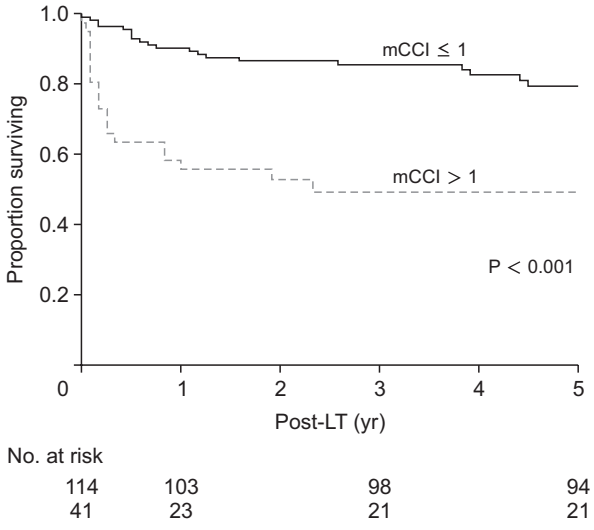

Fig. 1. Kaplan-Meier graph of overall survival in patients with modified Charlson comorbidity index (mCCI) ≤1 and >1.

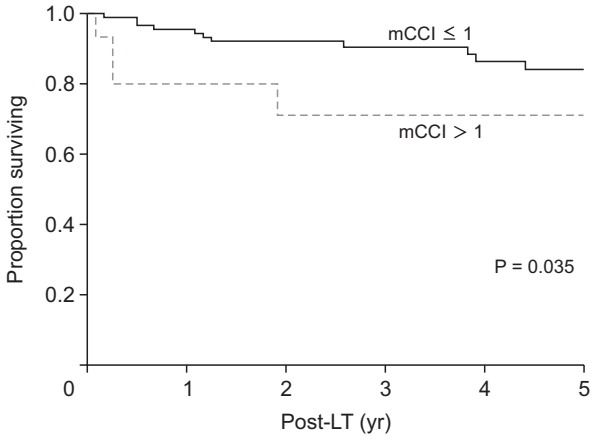

Fig. 2. Kaplan-Meier graph of survival in patients with modified Charlson comorbidity index (mCCI) ≤1 and >1 who underwent living donor liver transplantation.

rates according to the subgroup for mCCI ($P < 0.001$). The high-mCCI group showed a significantly lower survival rate in early mortality (1-month, $P < 0.001$ and 3-month, $P < 0.001$) and later mortality (1-year, $P < 0.001$; 3-year, $P < 0.001$; and 5-year, $P < 0.001$). The subgroups of high- and low-mCCI showed significant differences in the living donor LT (LDLT) ($P = 0.035$, Fig. 2), deceased donor LT (DDLT) ($P = 0.05$, Fig. 3), and cancer-free survival ($P < 0.001$, Fig. 4) patient groups.

Meanwhile, there was no significant difference in early and late mortality in the mFI-5 groups (1-month, $P = 0.138$; 3-month, $P = 0.373$; 1-year, $P = 0.104$; 3-year, $P = 0.181$; and 5-year, $P = 0.223$).

The incidence of overall postoperative complications and severe complications was not significantly different in the mCCI and mFI-5 subgroups (overall complications [$P = 0.099$] and severe complications [$P = 0.182$] in the mCCI subgroups, and overall complications [$P = 0.634$] and severe complications [$P = 0.611$] in the mFI-5 subgroups).

DISCUSSION

A study predicting post-LT outcomes in older patients using CCI was previously conducted [11]. However, CCI is not clinically practical because it includes 9 comorbidities. The mCCI is simpler and more useful than the mCCI, as it only includes 5 comorbidities known to affect post-LT outcomes. In addition, a previous study revealed that the mCCI had a superior prognostic power than CCI for patients who undergo LT. The present study is the first to validate the predictive potential and clinical utility of the mCCI in older recipients who undergo LT.

For the study design, we planned to include the donor factors in the preoperative selection tool. In LDLT, the donors were generally healthy individuals. Although 7 donors had either hypertension or DM, the comorbidities were all well-managed. In cases of DDLT, it is difficult to predict the preoperative factors before LT, which is usually performed in emergencies. Therefore, it was not appropriate to include the donor factors in the selection tool cases of DDLT. Thus, we concluded that it

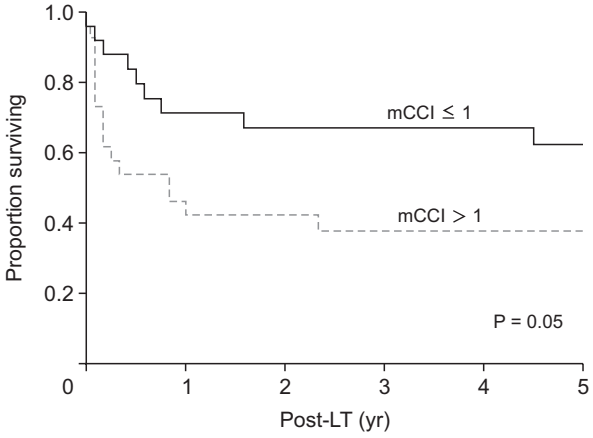

Fig. 3. Kaplan-Meier graph of survival for patients with modified Charlson comorbidity index (mCCI) ≤1 and >1 who underwent deceased donor liver transplantation.

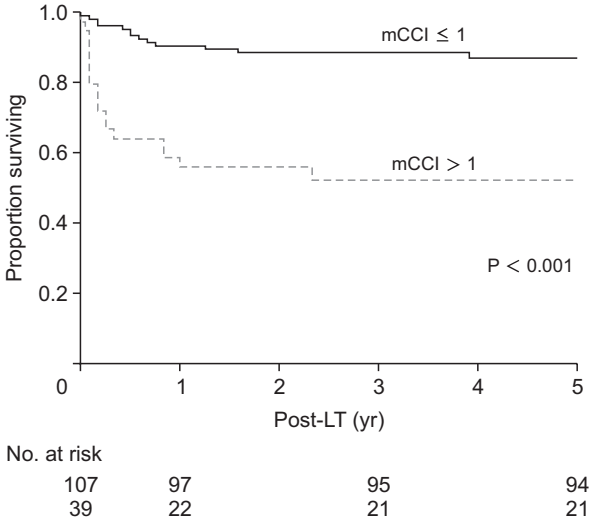

Fig. 4. Kaplan-Meier graph of survival for patients with modified Charlson comorbidity index (mCCI) ≤1 and >1, excluding those with hepatocellular carcinoma.

Table 4. Accumulated mortality cases according to the mCCI subgroups in LDLT and DDLT

LT type	Subgroup	No. of patients	Mortality cases					
			1 mo	3 mo	1 yr	3 yr	5 yr	Overall
LDLT	Low-mCCI	89	0	1	4	8	11	11
	High-mCCI	15	1	3	3	4	4	4
	P-value		0.015	<0.001	0.016	0.02	0.035	0.035
DDLT	Low-mCCI	25	2	3	7	8	9	10
	High-mCCI	26	7	11	15	16	16	16
	P-value		0.087	0.019	0.034	0.032	0.05	0.075

mCCI, modified Charlson comorbidity index; LT, liver transplantation; LDLT, living donor LT; DDLT, deceased donor LT.

would be more clinically useful and practical to consider only the recipient factors.

There are several differences between LDLT and DDLT, such as cold ischemic time and recipient status. Therefore, subgroup analyses were performed after dividing the study population into the LDLT and DDLT groups. Figs. 2 and 3 show the Kaplan-Meier survival curve. In both groups, the high-mCCI group showed significantly lower early and late survival rates compared with those of the low-mCCI group (Table 4).

Overall, 41 patients died during the study period and there were 5 major causes of death: rejection, cerebral vascular accidents, *de novo* cancer, infection, and recurrence. Since the mCCI does not include malignancy, death due to recurrence of HCC might have had a low association with the mCCI score. Therefore, we additionally analyzed the survival data after excluding 9 patients who died owing to recurrence of HCC. As displayed in Fig. 4, the 1-, 3-, and 5-year survival rates were significantly lower in the high-mCCI group than in the low-mCCI group.

A Clavien-Dindo grade of ≥IIIa indicated a severe complication that required intervention [12]. Since the mCCI was not significantly associated with severe post-LT complications, it may not be a useful tool for predicting post-LT morbidity. Nevertheless, infection-related immediate mortality was significantly higher in the high-mCCI group than in the low-mCCI group. Older patients who undergo LT are vulnerable to infection due to compromised immunity, resulting from aging and lifelong immunosuppressant therapy. Furthermore, the presence of comorbidities may worsen the patients' healing reserve. We believe that older patients with a high-mCCI score who undergo LT may require more intensive care than those with a low-mCCI score, owing to the possibility of infections. A high-mCCI score may not have been significantly correlated with the postoperative complication rate because most complications after LT are directly related to the surgical outcome. The high mortality rate in older patients with a high-mCCI score is believed to be owing to the difficulty in overcoming these postoperative complications.

The mFI-5 is a useful predictor tool that is widely used in various operations, such as arthroplasty and brain tumor surgery [13,14]. However, there was no significant association between the mFI-5 score and post-LT morbidity and mortality. Thus, we believe that the mFI-5 is not applicable to older patients who undergo LT.

This study has several limitations. The first limitation is the retrospective nature of the study and its inherent information bias. Another limitation is the possibility of selection bias. Since the study was conducted on patients who underwent LT, their medical status might have been better than those who did not undergo LT. The former is more likely to have fewer comorbidities than the latter. Further, we did not compare our study groups with a group of younger patients. To identify the predictive potential of the mCCI in older patients, it is necessary to compare the post-LT outcomes in older patients with those in young patients with similar mCCI scores.

In conclusion, this study is the first to demonstrate the effectiveness of the mCCI in predicting post-LT mortality in older patients. The mCCI and MELD scores successfully predicted short-term and long-term mortality.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization, Methodology: YRC, JL, SKH, NJY, KWL, KSS
Formal Analysis: JC, EWC, YRC
Investigation: JC, SYH, SS, KH, ESH, JL
Writing – Original Draft: All authors
Writing – Review & Editing: All authors

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, YoungRok Choi, under the permission of tthe permission from the Institutional Review Board of Seoul National University Hospital (SNUH IRB). The data are not publicly available because of the restrictions and regulations of the SNUH IRB.

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