Extra-Hepatic Comorbidity Burden Significantly Increases 90-day Mortality in Patients with Cirrhosis and High Model for Endstage Liver Disease

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Research article

Keywords: Cirrhosis, comorbidity, Charlson Comorbidity Index, liver transplantation, mortality

DOI: https://doi.org/10.21203/rs.3.rs-52868/v1

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Abstract

Background & aims

We examined how extra-hepatic comorbidity burden impacts mortality in patients with cirrhosis referred for liver transplantation (LT).

Methods

Adults with cirrhosis evaluated for their first LT in 2012 were followed through their clinical course with last follow up in 2019. Extra-hepatic comorbidity burden was measured using the Charlson Comorbidity Index (CCI). The endpoints were 90-day transplant free survival (Cox-Proportional Hazard regression), and overall mortality (competing risk analysis).

Results

The study included 340 patients, mean age 56 ± 11, 63% male and MELD-Na 17.2 ± 6.6. The CCI was 0 (no comorbidities) in 44%, 1–2 in 44% and >2 (highest decile) in 12%, with no differences based on gender but higher CCI in patients with fatty and cryptogenic liver disease. Thirty-three (10%) of 332 patients not receiving LT within 90 days died. Beyond MELD-Na, the CCI was independently associated with 90-day mortality (hazard ratio (HR), 1.32 (95% confidence interval (CI) 1.02–1.72). Ninety-day mortality was specifically increased with higher CCI category and MELD ≥ 18 (12% (CCI = 0), 22% (CCI = 1–2) and 33% (CCI > 2), (p = 0.002)) but not MELD-Na ≤ 17. At last follow-up, 69 patients were alive, 100 underwent LT and 171 died without LT. CCI was associated with increased overall mortality in the competing risk analysis (Sub-HR 1.24, 95%CI 1.1–1.4).

Conclusions

Extra-hepatic comorbidity burden significantly impacts short-term mortality in patients with cirrhosis and high MELD-Na. This has implications in determining urgency of LT and mortality models in cirrhosis and LT waitlisting, especially with an ageing population with increasing prevalence of fatty liver disease.

What You Need To Know

Background

- Extra-hepatic comorbidity burden, representing the aggregate weight of selected chronic medical conditions, is known to impact 1 year survival in general medical populations and post liver transplant outcomes, but little is known of the impact on pre-transplant outcomes.
Findings

- In this study we followed 340 patients with cirrhosis through their course of liver transplantation evaluation.
- Extra-hepatic comorbidity burden, as measured by the Charlson Comorbidity Index, negatively impacted short-term survival, particularly in patients with severe liver disease (MELD-Na ≥ 18), as well as long-term survival in all patients.

Implications for patient care

The assessment of extra-hepatic comorbidity burden may improve predictive models of short and long-term mortality in patients with advanced cirrhosis.

Introduction

Cirrhosis is a serious consequence of chronic liver diseases, and represents a substantial burden of morbidity, mortality and health-care expenditure. It carries a poor prognosis in the setting of decompensation or development of hepatocellular carcinoma, with liver transplantation (LT) being the only definitive and lifesaving therapy. In this context, extra-hepatic comorbidities may carry multiple hazards to patients with cirrhosis in need of LT. They carry direct risk of mortality related to the impact of comorbidity \(^1\), \(^2\), as well as risk of precluding candidacy for lifesaving LT \(^3\), and even risk of post LT mortality \(^4\).

The Charlson Comorbidity Index (CCI) is a well described and validated instrument determined by the presence, and in some cases severity, of 16 comorbid conditions, including liver disease \(^5\). The CCI predicts 1-year mortality in general populations and in patients with organ specific disease such as acute and chronic heart disease \(^5\)–\(^8\). Both liver disease severity, reflected in MELD, and HCC are known to impact mortality and LT considerations in patients with cirrhosis. Beyond MELD, CCI predicts mortality in patients with suspected drug-induced liver injury \(^9\). However, the impact of extra-hepatic comorbidity burden on short-term and overall mortality in patients with advanced cirrhosis referred for LT has not been well-studied or quantified. The assessment of overall comorbidity burden, rather than individual comorbid conditions considered by transplant centers, may provide an aggregate measure of risk posed by the burden of extra-hepatic conditions.

In this study we measured the extra-hepatic medical comorbidity burden in a cohort of consecutive patients referred for LT using CCI (excluding the contributions of liver disease and HCC). The aims of the study were to determine the impact of extra-hepatic comorbidity burden on 90-day mortality and overall mortality in the study cohort.

Patients And Methods

Patients
This study was approved by the Indiana University institutional review board, and was performed and reported per standardized reporting guidelines for qualitative research \(^{10}\). All patients with cirrhosis evaluated for LT at our center in 2012 were assessed. Patients were followed from the time of initial assessment through their pre and post-LT course until last follow-up in 2019. The selection of the study period was designed to allow for a relatively long post-LT follow-up (anticipated 5 years or more).

Patients with prior LT, absence of cirrhosis, or referred for multi-organ transplant were excluded. Demographic and clinical data were collected, including age, gender, body mass index (BMI), race, and etiology of liver disease. The severity of liver disease was measured using the MELD sodium equation (MELD-Na) \(^{11}\). Patients were followed until last contact for survivors or until death.

**Comorbidity Burden**

Extra-hepatic comorbidity burden was measured using the CCI (contributions of liver disease and HCC to the malignancy component were excluded). For example, a patient with no extra-hepatic comorbidities but with cirrhosis and HCC would have a CCI of 0. The CCI was chosen as an easily calculated and widely recognized comorbidity score that is validated in multiple populations including patients with chronic and acute liver disease \(^{5,9,12}\).

The CCI was analyzed primarily as a continuous variable in all risk-models. In addition, to examine the impact of low and high comorbidity burden we described outcomes within CCI categories using the following two thresholds; (i) patients with CCI=0, a physiological reference group with the lowest extra-hepatic comorbidity burden, and (ii) the highest decile of CCI (>2 in this cohort) to reflect the impact of the highest comorbidity burden. Patients with CCI=1-2 represented an intermediate comorbidity burden group.

**Study endpoints**

The cohort was followed through the LT evaluation process with long-term follow up. The primary outcomes was 90-day (short-term) mortality without LT from the time of initial evaluation, which was examined in patients not undergoing LT within 90-days. The secondary outcome was overall mortality (longer-term) with LT as a competing risk, which was examined in all patients.

**Additional analyses**

As a means of sensitivity testing for the association of comorbidity burden with mortality, we repeated all analyses while measuring comorbidities with an alternate score to CCI. The extra-hepatic comorbidity burden was measured and analyzed using the Cirrhosis Comorbidity score (CIRCOM), which has been validated in patients with cirrhosis \(^2\). Both CCI and CIRCOM are validated in patients with liver disease but they measure comorbidity burden somewhat differently. While CCI is a simple additive score, CIRCOM is designed as a conditional model based on priority scores and variable inclusion of specific groups of conditions. The individual comorbid conditions and their relative weights in CCI and CIRCOM are also not
uniformly shared nor equally weighted (Supplemental Table 1). We examined the associations of the two scoring systems and their component conditions with short and long-term mortality in this cohort.

**Statistical methods**

The analyses for factors associated with the study endpoints were performed using univariable and multivariable Cox proportional hazards regression for 90-day mortality, and univariable and multivariable competing risk regression for overall mortality, with LT as competing risk. The analyses were adjusted for age, gender, BMI, race, etiology of liver disease, MELD-Na and HCC. All analyses were two-sided with significance set at a p-value<0.05, and were performed using SPSS 26 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) or Stata SE 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

**Results**

Among the 387 patients evaluated for LT 47 were excluded, including 30 patients who were referred for multi-organ transplant, 7 with prior LT and 10 without underlying cirrhosis. The remaining 340 patients met the inclusion criteria. Baseline demographic and clinic characteristics are summarized in Table 1. The mean CCI was 1±1.2 and the median CCI was 1 (Interquartile range (IQR) 0, 1), with a score distribution of 0 in 44%, 1 to 2 in 44%, and >2 in 12% of patients. There were no differences in mean CCI in females and males, although females had a trend for higher frequency of connective tissue disease (6.2% vs. 2.3%, (p=0.06)). Mean CCI and patient age differed significantly according to etiology of cirrhosis (fatty liver (1.3±1.1 and 61±8), cryptogenic (0.9±1.4 and 62±8), viral (1.1±1.3 and 57±8), alcohol with viral (1.1±1.4 and 54±7), alcohol (0.6±0.8 and 53±10) and autoimmune (0.5±1.1 and 51±15) disease (p=0.003 and <0.001), respectively). While CCI did not correlate with patient age per se (Pearson coefficient 0.08, (p=0.15)), mean age increased with higher CCI category (55±10 with CCI=0, 56±9 with CCI=1-2 and 59±7 with CCI>2) (p=0.025).

**The impact of comorbidity burden on 90-day survival**

Among the 340 patients evaluated 33 died within 90 days without LT, while 8 underwent LT within 90-days and were excluded from this specific analysis. Causes of death included multiorgan failure (7), infection (4), gastrointestinal bleed (4), cardiac (3), stroke (1) and undetermined (14). The CCI was independently associated with increased 90-day mortality on multivariable Cox regression analysis (Table 2), as was MELD-Na. The factors not associated with 90-day mortality included age, gender, BMI, race, etiology of liver disease and HCC. The results were similar when excluding 7 patients with moderate to severe renal disease (contributing to CCI) which also contributed to higher MELD-Na. Extra-hepatic comorbidity burden as measured by CIRCOM was associated with an almost identical 90-day mortality risk (adjusted HR 1.34, 95%CI 1.02- 1.77).

On closer examination, the impact of CCI on 90-day mortality was largely related to increasing risk in patients with MELD-Na above the median value of 17. In patients with MELD-Na≥18, 90-day mortality
was 12% with CCI=0, 22% with CCI=1-2 and 33% with CCI>2, (p=0.03)). Whereas in patients with MELD-Na≤17, 90-day mortality was 1% with CCI=0, 1% with CCI=1-2 and 4% with CCI>2, (p=0.5)). Patients with MELD-Na≥18 also had increasing 90-day mortality with higher categories of CIRCOM (11% with CIRCOM=0, 18% with CIRCOM=1-2 and 39% with CIRCM>2 (highest decile for CIRCOM), (p=0.002)).

The Impact of comorbidity burden on overall survival

The median overall follow-up to time of death, LT or last follow-up was 332 days (IQR 161, 919). During this time 186 patient died with a median time to death of 303 days (IQR 126, 822). The median follow-up in 54 patients alive without LT was 6 years (IQR 0.6, 6.5), and in 100 patients who underwent LT was 5.7 years (IQR 4, 7.3). Post-LT patient and graft survival rates were both 90% at 1 year and 81% at 5 years. Patients who died without LT had higher comorbidity burden than those who survived or underwent LT (Table 3). Compared to surviving patients, they were also more commonly male with viral liver disease, higher MELD-Na and HCC.

The CCI was associated with increased overall mortality on multivariable competing risk regression analysis (Table 4). The risk-adjusted cumulative incidence of mortality increased with each CCI point (Figure 1). Extra-hepatic comorbidity burden as measured by CIRCOM was also associated with overall mortality (adjusted Sub-HR 1.3, 95%CI 1.2 – 1.5). The CCI was associated with overall mortality irrespective of baseline MELD-Na (adjusted sub-HR 1.3 (95%CI 1.1 – 1.6) with MELD-Na≤17, and adjusted sub-HR 1.2 (95%CI 1.1 – 1.4) with MELD-Na≥18).

Individual comorbidities versus comorbidity burden and mortality

We examined the association of individual components of the CCI and CIRCOM with 90-day and overall mortality using univariable models due to small numbers of patients with each condition (Table 5). Only renal disease defined by a creatinine≥1.5mg/dL ( included in CIRCOM and contributes to MELD-Na) was associated with 90-day mortality. The conditions common to CCI and CIRCOM that were associated with overall mortality included congestive heart failure, renal disease and metastatic malignancy. The conditions included in CCI, but not CIRCOM, that were associated with overall mortality included chronic obstructive pulmonary disease, diabetes mellitus with complications, cerebrovascular disease, connective tissue disease and acquired immune deficiency syndrome. At least one of these conditions was observed in 27.1% of patients. The condition included in CIRCOM, but not CCI, that was associated with overall mortality was substance abuse (excluding alcohol) observed in 19.6% of patients.

Discussion

The main novel finding in this study was that extra-hepatic comorbidity burden adversely impacted 90-day mortality among patients with cirrhosis evaluated for LT. This interplay between CCI and MELD-Na for short-term mortality was largely attributed to increased risk in patients with MELD-Na≥18. Interestingly, the inflection threshold for improving survival benefit for LT in cirrhosis was recently demonstrated at a MELD-Na range of 18-20. In other words, extra-hepatic comorbidity burden appears
to amplify short-term mortality in patients with cirrhosis who benefit the most from LT, and may be an important consideration for LT urgency in these patients.

The association of CCI and 90-day mortality persisted even when excluding patients with moderate to severe renal disease that may confound the association due to contribution of creatinine to MELD-Na. Beyond renal dysfunction, which is already reflected in higher MELD-Na, no component conditions of CCI or CIRCOM were associated with 90-day mortality. Therefore, the overall burden of extrahepatic comorbidities, as measured by CCI or CIRCOM, rather than specific conditions were the drivers of risk for 90-day mortality. This underscores the potential utility of an aggregate comorbidity burden score, beyond individual conditions, in risk assessment for patients with advanced liver disease.

Liver transplantation was an important factor in the consideration of overall mortality, with expected high rates of patient survival at 5 years post LT. This necessitated the assessment of overall mortality with competing-risk regression as described by Fine and Gray\(^1\). Since few patients underwent LT within 90-days of initial evaluation the short-term mortality risk with CCI could not be attributed to the impact of CCI on transplant eligibility. However, comorbidities may represent barriers for LT candidacy, and not surprisingly comorbidity burden was higher in patient who died compared with those undergoing LT or surviving without LT. This data suggests that comorbidity may carry dual risks for patients with cirrhosis. An increased short-term risk in those with more advanced disease, and longer-term risk of both mortality and potential barriers to life-saving LT as their liver disease deteriorates\(^11-12\%\).

The examination of the impact of individual comorbid conditions also demonstrated that no scoring system captured all conditions that appeared to impact overall mortality in the cohort. The CCI does not measure substance abuse which is included in CIRCOM, and CIRCOM does not measure 5 conditions included in CCI (chronic obstructive pulmonary disease, diabetes mellitus with complications, cerebrovascular disease, connective tissue disease and acquired immune deficiency syndrome). These differences would have impacted comorbidity burden measurement in 19.4% and 27.1% of patients, respectively. Both scores still performed well as measures of extra-hepatic comorbidity burden with very similar adjusted hazard and sub-hazard ratios. It is not within the scope nor the intent of this study to suggest modifications of comorbidity scoring systems, but we acknowledge the interesting differences between these scores that could impact 1 in 4 to 5 patients with advanced cirrhosis.

The CCI was developed as a continuous scale or variable and the categorical descriptive analysis warrants discussion. A CCI=0 reflects a physiologically important reference group with no or very low comorbidity burden. A CCI >2 highlighted the risks associated with the highest decile of extra-hepatic comorbidity burden, e.g. in patients with higher MELD-Na. Notably, other studies have demonstrated increased mortality in patients with cardiac disease and in patients without cirrhosis presenting with acute liver injury, using the same threshold \(^9,15,16\). However, the ideal thresholds if any for estimating CCI related risk in the context of pre-LT outcomes may be refined with additional studies.
A higher comorbidity burden was observed in patients with fatty and cryptogenic liver disease. The latter is commonly attributed to undiagnosed fatty liver disease, which is known to be associated with extra-hepatic comorbidities and increasingly driving the need for LT in the United States. While we observed age differences according to disease etiology, extra-hepatic comorbidity burden did not correlate with age per se, suggesting that the observed associations were mainly related to differences in disease associations rather than older age alone. Gender-based disparities in LT eligibility have been described with increased pre-LT and waitlist mortality in women. Additionally, gender-based differences in medical comorbidities have been described in hospitalized patients with higher rates of diabetes and connective tissue disease but without evident differences in hospital mortality. In our cohort, there were no gender-based differences in CCI, although women had a trend for more frequent connective tissue disease. Higher 90-day mortality was observed in men, but that association was fully attenuated in the risk-adjusted analysis.

The strengths of this study include the comprehensive characterization of comorbid conditions and the long-term follow up of patients with cirrhosis consecutively evaluated for LT. The assessment of extra-hepatic comorbidity burden using two validated systems (CCI and CIRCOM) and convergence of the observed associations also support the clinical premise of the study. The limitations of the study include the retrospective design, limited racial diversity, the absence of comprehensive information on socioeconomic status. Finally, the use of CCI and CIRCOM in this study was demonstrative of the impact of comorbidity burden on mortality and was not a judgement of superiority of a specific score over other available instruments.

In summary, this study demonstrates and quantifies the risk associated with extra-hepatic comorbidity burden with increased short and long-term mortality in patients with advanced cirrhosis. These data are timely, given an ageing population and increasing burden of fatty liver disease on transplant and other healthcare resources. Assessment of comorbidity burden may identify a subset of patients with the highest mortality risk and increased LT urgency. If validated, standardized measurement of extra-hepatic comorbidity burden may also be an important modifier of mortality risk models and mortality-related healthcare metrics in cirrhosis. Further studies are needed to confirm these findings, and to determine the ideal comorbidity scoring system and thresholds in patients with advanced cirrhosis.

Declarations

Ethics and approval and consent to participate and consent to publish

This study was approved by the Indiana University institutional review board, and as a minimal risk study, consent to participate and publish was waived.

Data and material availability

Per the Indiana University institutional review board, data is to be deidentified and stored on a secure server, but no permission to store on a publicly accessible server. Specific data points requests, excluding
any patient identifiers, directed to the corresponding author will be considered and honored.

Conflicts or competing interests

Dr. Chalasani holds consulting agreements from several pharmaceutical companies for activities related to NAFLD, DILI and liver disease in general. His institution receives research grants on his behalf from Intercept, Lilly, Cumberland, Galectin, and Exact Sciences. But none represent a conflict of interest for this paper. Scott Coppel, Karam M Mathur, Lauren Nephew, Kavish Patidar, Eric Orman, Archita Desai, Eduardo Vilar-Gomez, Burcin Ekser, Chandrashekhar Kubal, and Marwan Ghabril report no potential conflicts of interest.

Funding

This study was not funded.

Author Contributions

Scott Coppel: Study design, data collection and analysis, manuscript preparation, final approval
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Lauren Nephew: Study design, data collection and analysis, manuscript preparation, final approval
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Acknowledgements

None

Abbreviations

BMI, body mass index
CCI, Charlson Comorbidity Index
CIRCOM, Cirrhosis Comorbidity score
CI, confidence interval
HCC, hepatocellular carcinoma
HR, hazard ratio
LT, liver transplantation
MELD, model for endstage liver disease
MELD-Na, model for endstage liver disease with sodium modification

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Tables

Table 1. Baseline demographic and clinical characteristics of the 340 patients evaluated for liver transplantation for complications of cirrhosis. Data are shown as mean ± standard deviation or percentage unless otherwise specified.
| Demographic and clinical characteristics | Patients assessed |
|----------------------------------------|-------------------|
| **N=340**                              |                   |
| Age                                    | 56±11             |
| Gender (male) (%)                       | 63                |
| **Race (%)**                           |                   |
| White                                  | 90                |
| Black                                  | 5                 |
| Hispanic                               | 3                 |
| Asian                                  | 1                 |
| Other                                  | 1                 |
| Body mass index                        | 30±7              |
| **Etiology of liver disease (%)**      |                   |
| Alcohol                                | 19                |
| Alcohol and viral                      | 16                |
| Viral                                  | 32                |
| Autoimmune                             | 21                |
| Fatty liver                            | 2                 |
| Cryptogenic                            | 2                 |
| MELD-Na                                | 17.2±6.6          |
| Hepatocellular carcinoma (%)           | 23                |
| CCI (mean)                             | 1±1.2             |
| (median (IQR))                         | 1 (0,1)           |
| **CCI category (%)**                   |                   |
| CCI = 0                                | 44                |
| CCI = 1-2                              | 44                |
| CCI > 2                                | 12                |
| CIRCOM (mean)                          | 0.8±1.2           |
| (median (IQR))                         | 0 (0,1)           |
Abbreviations: CCI, Charlson Comorbidity Index (excluding liver disease and liver cancer); IQR, interquartile range; LT, liver transplantation; MELD-Na, Model for End-stage Liver Disease with sodium modification.

Table 2. The analysis of factors associated with 90-day mortality without liver transplant (LT) by Cox regression in 332 patients with cirrhosis referred for LT, 33 of whom died within 90 days of initial evaluation. Eight of 340 patients assessed underwent LT within 90-days from initial assessment and were excluded from this analysis.

| Factor                               | Univariable analysis |          | Multivariable analysis |          |
|--------------------------------------|----------------------|----------|------------------------|----------|
|                                      | Hazard ratio         | (95% confidence interval) | Hazard ratio         | (95% confidence interval) |
| CCI                                  | 1.2                  | (0.97 – 1.5) | 1.33                  | (1.02 – 1.73) |
| MELD-Na                              | 1.22                 | (1.16 – 1.29) | 1.26                  | (1.18 – 1.33) |
| Age                                  | 1.01                 | (0.98 – 1.06) | 1.02                  | (0.96 – 1.07) |
| Male gender (%)                      | 2.4                  | (1.03 – 5.4) | 1.2                   | (0.5 – 3) |
| Body mass index                      | 1.01                 | (0.96 – 1.07) | 1.02                  | (0.96 – 1.09) |
| Race (%)                             |                      |          |                        |          |
| Black                                | 2.2                  | (0.7 – 7.1) | 2.9                   | (0.8 – 11) |
| Hispanic                             | 1.9                  | (0.5 – 7.9) | 0.4                   | (0.1 – 1.7) |
| Asian                                | NA*                  |          | NA*                   |          |
| Etiology liver disease (%)           |                      |          |                        |          |
| (Reference alcohol)                  |                      |          |                        |          |
| Alcohol and viral                    | 2.4                  | (0.7 – 8) | 2.8                   | (0.8 – 9.8) |
| Viral                                | 1.9                  | (0.6 – 6) | 2.3                   | (0.7 – 7.8) |
| Autoimmune                           | NA*                  |          | NA*                   |          |
| Fatty liver                          | 1.6                  | (0.5 – 5.5) | 3.3                  | (0.8 – 14.3) |
| Cryptogenic                          | 2.1                  | (0.2 – 18.8) | 2.6                  | (0.2 – 31) |
| Hepatocellular carcinoma (%)         | 1.4                  | (0.7 – 2.9) | 2                    | (0.8 – 5) |

Abbreviations: CCI, Charlson Comorbidity Index (excluding liver disease and liver cancer); MELD-Na, Model for End-stage Liver Disease with sodium modification; NA, not applicable.
Footnotes: * no patients in the analysis or with the endpoint to analyze

**Table 3.** Baseline demographic and clinical characteristics of the patients evaluated for liver transplantation (LT) for complications of cirrhosis among patients who; (i) were alive at last follow up without LT, (ii) died without LT or (iii) underwent LT. Data are shown as mean ± standard deviation or percentage.
| Demographic and clinical characteristics | Survived without LT n=54 | Died without LT n=186 | Underwent LT n=100* | P-value |
|-----------------------------------------|--------------------------|------------------------|----------------------|---------|
| Age                                     | 54±10                    | 57±9                   | 56±10                | 0.14    |
| Gender (male) (%)                       | 43                       | 64                     | 71                   | 0.002   |
| Race (%)                                |                          |                        |                      | 0.4     |
| White                                   | 87                       | 91                     | 91                   |         |
| Black                                   | 4                        | 4                      | 6                    |         |
| Hispanic                                | 6                        | 4                      | 1                    |         |
| Asian                                   | None                     | 1                      | 1                    |         |
| Other                                   | 3                        | None                   | 1                    |         |
| Body mass index                         | 28±6                     | 30±7                   | 30±6                 | 0.4     |
| Etiology of liver disease (%)           |                          |                        |                      | 0.001   |
| Alcohol                                 | 29                       | 34                     | 30                   |         |
| Alcohol and viral                       | 12                       | 21                     | 10                   |         |
| Viral                                   | 29                       | 18                     | 13                   |         |
| Autoimmune                              | 9                        | 2                      | 17                   |         |
| Fatty liver                             | 19                       | 20                     | 24                   |         |
| Cryptogenic                             | 2                        | 2                      | 3                    |         |
| MELD                                    | 13.9±4.4                 | 17.7±7.1               | 18.1±5.9             | <0.001  |
| Hepatocellular carcinoma (%)            | 7                        | 27                     | 25                   | 0.01    |
| CCI (mean)                              | 0.6±0.9                  | 1.1±1.3                | 0.6±0.8              | <0.001  |
| (median (IQR))                          | 0 (IQR 0,1)              | 1 (IQR 0,2)            | 0 (IQR 0,1)          |         |
| CCI Category (%)                        | 59                       | 34                     | 56                   |         |
| CCI = 0                                 |                          |                        |                      |         |
| CCI = 1-2                               | 33                       | 50                     | 38                   | 0.001   |
| CCI > 2                                 | 8                        | 16                     | 6                    |         |
| CIRCOM                                  | 0.6±0.8                  | 1.1±1.3                | 0.4±0.9              | <0.001  |
|                                         | 0 (IQR 0,1)              | 1 (IQR 0,2)            | 0 (IQR 0,1)          |         |
Abbreviations CCI, cirrhosis-modified Charlson Comorbidity Index (excluding liver disease and liver cancer); IQR, interquartile range; MELD-Na, Model for End-stage Liver Disease with sodium modification.

Footnotes: * includes one patient who underwent LT at another center.

**Table 4.** The factors associated with overall mortality in the competing-risk regression analysis with liver transplantation as the competing risk.

| Factor                        | Univariable analysis | Multivariable analysis |
|-------------------------------|----------------------|------------------------|
|                               | Sub-Hazard ratio     | (95% confidence interval) | Sub-Hazard ratio | (95% confidence interval) |
| CCI                           | 1.25                 | (1.14 – 1.38)          | 1.24             | (1.1 – 1.4)               |
| MELD-Na                       | 1.05                 | (1.02 – 1.08)          | 1.05             | (1.02 – 1.09)             |
| Age                           | 1.01                 | (0.99 – 1.02)          | 1.01             | (0.99 – 1.03)             |
| Male gender (%)               | 1.2                  | (0.9 – 1.6)            | 0.94             | (0.7 – 1.3)               |
| Body mass index               | 1.01                 | (0.98 – 1.03)          | 1.01             | (0.98 – 1.03)             |
| **Race** (reference white) (%)|                      |                        |                  |                          |
| Black                         | 0.9                  | (0.5 – 1.7)            | 0.8              | (0.4 – 1.7)               |
| Hispanic                      | 1.5                  | (0.7 – 3.3)            | 1.4              | (0.5 – 3.5)               |
| Asian                         | 1.3                  | (0.4 – 5)              | 3.1              | (1.6 – 5.7)               |
| **Etiology liver disease** (%) |                      |                        |                  |                          |
| Alcohol and viral             | 1.7                  | (1.02 – 2.7)           | 1.6              | (0.96 – 2.67)             |
| Viral                         | 1.2                  | (0.8 – 1.8)            | 1.1              | (0.7 – 1.8)               |
| Autoimmune                    | 0.2                  | (0.08 – 0.6)           | 0.2              | (0.09 – 0.7)              |
| Fatty liver                   | 1.1                  | (0.7 – 1.7)            | 0.9              | (0.6 – 1.6)               |
| Cryptogenic                   | 1.1                  | (0.5 – 2.7)            | 0.7              | (0.4 – 2.2)               |
| Hepatocellular carcinoma (%)  | 1.3                  | (0.9 – 1.7)            | 1.1              | (0.7 – 1.6)               |

Abbreviations: CCI, Charlson Comorbidity Index (excluding liver disease and liver cancer); MELD-Na, Model for End-stage Liver Disease with sodium modification; NA, not applicable.
Table 5. The association of individual components of the Charlson Comorbidity Index (excluding liver disease and liver cancer) and CIRCOM with 90-day and overall mortality in the unadjusted analyses.
| Comorbid conditions | Analysis of 90-day mortality | Analysis of overall mortality |
|---------------------|-------------------------------|------------------------------|
|                     | n=332                         | n=340                        |
| **Patients**        | **Hazard ratio**              | **95% confidence interval**  | **Patients**        | **Sub-Hazard ratio** | **95% confidence interval** |
| with condition (%)  |                               |                              | with condition (%)  |                             |                              |
| **Myocardial**      | 1.8                           | NA*                          | 1.8                | 1.3                        | (0.8 – 2.2)                  |
| **infarction**      |                               |                               |                    |                             |                              |
| **Coronary artery** | 18.4                          | 0.4                          | (0.1 – 1.4)        | 18.5                        | 1.1                          | (0.8 – 1.5)                  |
| **disease (no**     |                               |                               |                    |                             |                              |
| **infarction)**     |                               |                               |                    |                             |                              |
| **Congestive heart**| 4.2                           | 0.8                          | (0.1 – 5.6)        | 4.4                         | 2                            | (1.4 – 2.9)                  |
| **failure**         |                               |                               |                    |                             |                              |                              |
| **Peripheral**      | 3.3                           | NA*                          | 3.2                | 1.1                        | (0.6 – 2.2)                  |
| **vascular**        |                               |                               |                    |                             |                              |                              |
| **disease**         |                               |                               |                    |                             |                              |                              |
| **Cerebrovascular** | 2.7                           | 1.2                          | (0.16 – 8.8)       | 2.7                         | 2                            | (1.1 – 3.4)                  |
| **disease**         |                               |                               |                    |                             |                              |                              |
| **Dementia**        | 0.9                           | 4 (                          | 0.5 – 29)          | 1.2                         | 2                            | (0.5 – 7.6)                  |
|                     |                               |                               |                    |                             |                              |                              |
| **Chronic**         | 15.1                          | 1.5                          | (0.6 – 3.4)        | 13.5                        | 1.6                          | (1.1 -2.2)                  |
| **obstructive**     |                               |                               |                    |                             |                              |                              |
| **pulmonary**       |                               |                               |                    |                             |                              |                              |
| **disease**         |                               |                               |                    |                             |                              |                              |
| **Connective**      | 3.6                           | 3.1                          | (0.9 – 10)         | 3.8                         | 1.9                          | (1.1 – 3.4)                  |
| **tissue**          |                               |                               |                    |                             |                              |                              |
| **disease**         |                               |                               |                    |                             |                              |                              |
| **Peptic**          | 6                             | 1.7                          | (0.5 – 5.5)        | 5.3                         | 1.5                          | (0.8 – 2.6)                  |
| **ulcer**           |                               |                               |                    |                             |                              |                              |
| **disease**         |                               |                               |                    |                             |                              |                              |
| **Diabetes**        | 23.8                          | 0.6                          | (0.2 – 1.4)        | 24.4                        | 0.95                         | (0.7 – 1.3)                  |
| **without**         |                               |                               |                    |                             |                              |                              |
| **complications**   |                               |                               |                    |                             |                              |                              |
| **Diabetes**        | 8.1                           | 0.7                          | (0.2 – 3)          | 7.9                         | 1.6                          | (1.1 – 2.4)                  |
| **with**            |                               |                               |                    |                             |                              |                              |
| **complications**   |                               |                               |                    |                             |                              |                              |
| **Hemiplegia**      | 0.6                           | NA*                          | 0.6                | 0.9                        | (0.1 – 6.1)                  |
|                     |                               |                               |                    |                             |                              |                              |
| **Renal**           | 2.1                           | 1.5                          | (0.2 – 11)         | 1.8                         | 5.1                          | (0.9 – 30)                   |
| **disease (creatinine** |                               |                               |                    |                             |                              |                              |
| **>3 mg/dL)**       |                               |                               |                    |                             |                              |                              |
| **Renal**           | 15.4                          | 4.2                          | (2.1 – 8.5)        | 15.9                        | 2.4                          | (1.6 – 3.5)                  |
| **disease (creatinine** |                               |                               |                    |                             |                              |                              |
| **≥ 1.5 mg/dL)**    |                               |                               |                    |                             |                              |                              |
| **Leukemia**        | None                          | NA                           | None               | NA                         |                              |                              |
|                     |                               |                               |                    |                             |                              |                              |
| **Lymphoma**        | None                          | NA                           | None               | NA                         |                              |                              |
|                     |                               |                               |                    |                             |                              |                              |
| **Non-metastatic**  | 2.3                           | 2.4                          | (0.6 – 2.1)        | 2.1                         | 1.8                          | (0.6 – 5)                    |
|                              |          |          |        |         |
|------------------------------|----------|----------|--------|---------|
| solid tumor † ¥             | 10.1     |          |        |         |
| Metastatic solid tumor † ¥  | 0.3      | NA*      | 0.3    | 6.8     | (5.1 – 9.1) |
| AIDS †                      | 0.3      | NA*      | 0.3    | 4.1     | (3.3 – 5.2) |
| Epilepsy ¥                  | 3.3      | NA*      | 3.5    | 1.1     | (0.6 – 2.3) |
| Substance abuse other than   | 19.9     | 1.3      | 19.4   | 1.5     | (1.1 – 2)   |
| alcoholism ¥                |          |          |        |         |

Abbreviations: AIDS, acquired immune deficiency syndrome; CCI, Charlson Comorbidity Index (excluding liver disease and liver cancer); HR, CI, confidence interval; hazard ratio; LT, liver transplant; NA, not applicable.

* No patients in the analysis met this endpoint

† Scored in the CCI

¥ Scored in the CIRCOM

**Figures**
Overall mortality in the competing risk model (liver transplant as the competing risk) stratified by comorbidity burden using the Charlson Comorbidity Index (CCI) (excluding liver disease and liver cancer). The analysis was adjusted for age, gender, race, model for endstage liver disease with sodium modification, body mass index, liver disease etiology and presence of hepatocellular carcinoma. The subhazard ratio for each 1 point increment in CCI was 1.24 (95% confidence interval 1.1 – 1.4).

Supplementary Files

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- CCIandpreLT73120Supp.docx