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Development and Validation of a Comorbidity Scoring System for Patients With Cirrhosis

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this CME activity, successful learners will be able to define comorbid diseases in patients with liver cirrhosis and compute their CirCom score.

See editorial on page 19.

BACKGROUND & AIMS: At least 40% of patients with cirrhosis have comorbidities that increase mortality. We developed a cirrhosis-specific comorbidity scoring system (CirCom) to help determine how these comorbidities affect mortality and compared it with the generic Charlson Comorbidity Index. **METHODS:** We used data from nationwide health care registries to identify Danish citizens diagnosed with cirrhosis in 1999−2008 (n = 12,976). They were followed through 2010 and characterized by 34 comorbidities. We used Cox regression to assign severity weights to comorbidities with an adjusted mortality hazard ratio (HR) ≥1.20. Each patient's CirCom score was based on, at most, 2 of these comorbidities. Performance was measured with Harrell's C statistic and the Net Reclassification Index (NRI) and results were compared with those obtained using the Charlson Index (based on 17 comorbidities). Findings were validated in 2 separate cohorts of patients with alcohol-related cirrhosis or chronic hepatitis C. **RESULTS:** The CirCom score included chronic obstructive pulmonary disease, acute myocardial infarction, peripheral arterial disease, epilepsy, substance abuse, heart failure, nonmetastatic cancer, metastatic cancer, and chronic kidney disease; 24.2% of patients had 1 or more of these, and mortality correlated with the CirCom score. Patients' CirCom score correlated with their Charlson Comorbidity Index (Kendall's $\tau = 0.57$; $P < .0001$). Compared with the Charlson Index, the CirCom score increased Harrell's C statistic by 0.6% (95% confidence interval: 0.3%−0.8%). The NRI for the CirCom score was 5.2% (95% confidence interval: 3.7%−6.9%), and the NRI for the Charlson Index was 3.6% (95% confidence interval: 2.3%−5.0%). Similar results were obtained from the validation cohorts. **CONCLUSIONS:** We developed a scoring system to predict mortality among patients with cirrhosis based on 9 comorbidities. This system had higher C statistic and NRI values than the Charlson Comorbidity Index, and is easier to use. It could therefore be a preferred method to predict death or survival of patients and for use in epidemiologic studies.

Keywords: End-Stage Liver Disease; Prognostic Factors; Outcome; Prediction Model.

At least 40% of patients diagnosed with cirrhosis also have other diseases, and these other diseases—comorbidities—increase patient mortality.[1,2] It is therefore important that clinicians and researchers are able to assess a cirrhosis patient's burden of comorbidity, but it is not clear how this is best done. To be operational, the comorbidity burden should be expressed as a number rather than a list of diagnoses; this is analogous to a patient's cirrhosis severity being expressed as a Child-Pugh or Model for End-Stage Liver Disease (MELD) score.[3] Such scores can be used for statistical analyses and streamline research communication.

The Charlson Comorbidity Index was developed in 1984 as a generic tool to grade comorbidity.[4] Including 17 diseases weighted according to their influence on short-term mortality, it has been shown to be associated with mortality in many diverse patient cohorts.[1,5−7] However, it can be cumbersome to determine the presence or absence of as many as 17 diseases, and there are several reasons why the Charlson Index might be suboptimal for use among patients with cirrhosis. First, it was not designed to score comorbidities for any specific disease, but some comorbid diseases might be more (or less) hazardous to cirrhosis patients than to other patients. Second, only 559 patients were included in Charlson's development cohort, so rare conditions might not have been selected for inclusion due to lack of power. Substance abuse and schizophrenia are examples of conditions that are much more common among cirrhosis patients than in a general hospital setting. Third, many chronic diseases have a better prognosis now than in 1984,[8] so both the weighting of Charlson conditions and the selection of conditions for inclusion in the index might be out of date. Fourth, the Charlson Comorbidity Index was designed to predict mortality 1 year into the future, so the mortality

Abbreviations used in this paper: **CI, confidence interval; HR, hazard ratio; MELD, Model for End-Stage Liver Disease; NRI, Net Reclassification Index.**

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associated with slowly progressing diseases might have been underestimated.

Given this background, we aimed to construct a comorbidity score, CirCom, for patients with cirrhosis of any etiology; to validate in separate cohorts its association with mortality and ability to discriminate between patients with a high or low mortality; and to compare its performance with the performance of the Charlson Comorbidity Index.

Methods

Study Cohorts

This study was based on 3 population-based cohorts: The nationwide Danish Patient Registry cohort (development cohort), the Aarhus alcoholic cirrhosis cohort, and a nationwide cohort of patients with chronic hepatitis C viral infection (validation cohorts). The study was approved by the Danish Data Protection Agency. According to Danish law, studies that require no patient contact do not need ethical approval or patient consent.

Danish Patient Registry cohort (development). The Danish Patient Registry cohort included all Danish citizens who received their first diagnosis of cirrhosis between January 1, 1999 and December 31, 2008, and was based on data from the National Patient Registry and the Central Psychiatric Registry. These 2 nationwide registries record data from nonpsychiatric and psychiatric hospitals, respectively: inpatient hospitalizations from 1977 and outpatient and emergency room visits from 1995. Data are individual-level and include demographic data, dates for hospital contacts, type of hospital contact (inpatient, outpatient, or emergency room), and discharge diagnosis codes. Laboratory data are not recorded. Diagnosis codes are given by the attending physician after all hospital contacts and have been coded according to the 10th edition of the *International Classification of Diseases* since 1994 and according to the 8th edition before that. We defined cirrhosis by a discharge diagnosis of alcoholic cirrhosis (K70.3) or unspecified cirrhosis (K74.6) from an inpatient hospitalization or outpatient visit. The Danish Patient Registry cohort was nationwide, except that we excluded those who were members of the 2 validation cohorts described next.

The validity of diagnosis codes for cirrhosis has been examined previously in a study of 198 patients with a hospital discharge diagnosis of cirrhosis.[9] After chart review, investigators found that 169 (85.4%) patients had biopsy-proven cirrhosis or a clinical cirrhosis diagnosis based on standard criteria (presence of cirrhosis complications, >5 vascular spiders, or 1−5 vascular spiders and coagulation factor II, VII, and X <0.70 [roughly equivalent to an international normalized ratio >1.2]). Another study took a random sample of 100 patients with a hospital discharge diagnosis of liver disease (including but not limited to cirrhosis) and found that all 100 did in fact have a liver disease according to their charts.[10] For the current study, we sampled 30 patients to validate cirrhosis diagnoses. We were able to retrieve 26 of these patients' charts and found that 25 (96% [95% confidence interval [CI]: 80−100]) did in fact have cirrhosis according to their medical chart and the discharge summary. The chart reviewer (PJ) was not blinded to the purpose of the review, and the attending physician's conclusion at discharge was accepted, no matter which diagnostic tests had been conducted.

Aarhus alcoholic cirrhosis cohort (validation). The Aarhus alcoholic cirrhosis cohort included 466 patients followed from diagnosis of alcoholic cirrhosis in 1993−2005.[11] All patients lived in the catchment area of Aarhus University Hospital when they received their first diagnosis of alcoholic cirrhosis. They were categorized as having compensated or decompensated cirrhosis, the latter defined by ascites, variceal bleeding, or hepatic encephalopathy at the time of cirrhosis diagnosis or any time before that. Information on these complications was extracted from the patients' charts, and we also extracted information on their MELD score and alcohol drinking status (drinking or abstaining) on the date that the cirrhosis diagnosis was established. This study included only 419 of the original 466 cohort members because we excluded those who did not have their MELD score recorded and those who were diagnosed with alcoholic cirrhosis in 1993, because the coding of comorbidity diagnoses according to the 10th edition of the International Classification of Diseases did not begin until 1994.

DANVIR chronic hepatitis C cohort (validation). The DANVIR chronic hepatitis C cohort included 4656 Danish citizens who tested positive for hepatitis C virus RNA between 1999 and 2005. They were identified through the DANVIR database of patients with viral hepatitis.[12,13] All were considered as having chronic hepatitis and followed from the first positive hepatitis C virus RNA test. Liver biopsy data were obtained from the Danish National Pathology Registry and Data Bank[14]; 745 had a liver biopsy at the time of inclusion, and 25% of those had cirrhosis.

Identification of Comorbid Diseases

Comorbidities for patients in all 3 cohorts were identified in the National Patient Registry and the Central Psychiatric Registry. All inpatient or outpatient diagnoses given in the 5 years before a patient was diagnosed with cirrhosis were used to identify 34 candidate comorbidities (Table 1). Diagnoses given after cirrhosis diagnosis were not considered because the CirCom score applies to the time of cirrhosis diagnosis and must be applicable to prospective studies. The Charlson Comorbidity Index was defined according to Quan et al using diagnoses from the same 5-year time period.[15]

We validated the diagnosis codes for the CirCom candidate diseases against chart data for the Aarhus alcoholic cirrhosis cohort. Of the total 303 comorbid diseases, data were available for 253, and 232 (92%; 95% CI: 88−95) were confirmed. The validity of the individual comorbidities ranged from 75% to 100%, except that none of the Aarhus cohort members had a diagnosis code for human immunodeficiency virus infection, bipolar disorder, or chronic inflammatory bowel disorder, so the validity of these diagnoses was not determined. Finally, we validated the absence of