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Factors associated with early hospital readmission for acute decompensation of cirrhosis - prospective cohort study

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ABSTRACT

Introduction: The first months after the hospitalization of cirrhotic patients are considered at high risk for new complications. Knowing the factors associated with early readmission in these individuals may contribute to the development of preventive strategies that avoid the risks and costs related to a new hospitalization. **Objective:** To investigate the factors associated with the early readmission of hospitalized patients due to acute decompensation of cirrhosis. **Methods:** Data from the first hospitalization of each patient was considered during the study period and were followed up to the 90th day by telephone contact. A prospective cohort study in Southern Brazil. **Results:** Between 2011 and 2016, 280 patients were included in the study. The mean age was 55.68±11.21 years, and 71.8% were males with a mean MELD of 15.65±5.64 and 41.4% Child-Pugh C. Early readmission occurred in 91 cases (32.5%). In the logistic regression analysis, CLIF-SOFA variables (odds ratio [OR] 1.137, 95% confidence interval [CI] 1.003–1.289, p=0.045) and several complications present in the initial hospitalization (OR 1.503, 95% CI 1.074–2.105, p=0.018) independent of early readmission. Early readmission rates were 16.8% in patients with CLIF-SOFA <8 and less than 2 complications at admission and 49.2% in those with CLIF-SOFA ≥8 and 2 or more complications at the initial hospitalization. **Conclusion:** Simple parameters such as CLIF-SOFA and the number of complications of cirrhosis present at hospital admission are predictors of early readmission and can be used as tools to individualize the follow-up of cirrhotic patients after hospital discharge.

Keywords: liver cirrhosis; opportunistic infections; ascites; hepatic encephalopathy; liver function tests; patient readmission.

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INTRODUCTION

Liver cirrhosis is a progressive condition characterized by the extensive replacement of normal liver tissue with fibrous scar tissue. This fibrosis disrupts the normal structure and function of the liver, impairing its ability to perform essential tasks such as detoxification, metabolism, and synthesis of proteins[1]. The prevalence of cirrhosis varies

across different regions and is influenced by factors such as the prevalence of underlying liver diseases (such as viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, etc.)[2]. In the last Global Burden of Diseases, Injuries, and Risk Factors Study, there were an estimated 112 million cases of compensated cirrhosis and 10.6 million cases of decompensated cirrhosis worldwide[3]. Cirrhosis is becoming an increasingly significant contributor to morbidity and mortality. Globally, it ranks as the 14th most prevalent cause of death among adults, and in central Europe, it stands as the 4th leading cause of death, accounting for approximately one million fatalities annually worldwide[4].

The natural history of cirrhosis is a complex and dynamic process. Individuals with cirrhosis may remain asymptomatic for an extended period, but as the disease advances, clinical decompensation may occur, primarily due to portal hypertension and impaired hepatic function[5]. Decompensated cirrhosis is characterized by the emergence of specific complications such as ascites, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, and bacterial infections. Compensated cirrhosis usually has a good prognosis, with a lower risk of hospitalization[6]. On the other hand, patients with decompensated cirrhosis typically experience high mortality and frequent hospitalizations[7].

Hospital readmissions are instances where a patient is readmitted to an acute care facility within a defined period, typically up to 90 days after discharge[8]. This metric serves as a critical gauge for evaluating the quality of healthcare provided during the initial hospitalization, as individuals experiencing readmissions within this temporal window are associated with elevated risks of short- and long-term mortality[9]. In addition, early hospital readmissions are related to substantial financial burdens on healthcare institutions[10]. Liver cirrhosis is associated with particularly high hospital readmission rates[11]. A study from a large healthcare system in the United States showed that, compared to congestive heart failure or chronic obstructive pulmonary disease, chronic liver diseases had higher rates of hospitalization, longer hospital stays, and more readmissions[12]. Furthermore, early readmissions in patients with liver cirrhosis were associated with an increased risk of death[13]. Identifying predictive factors for hospital readmission in patients with liver cirrhosis may allow the adoption of strategies to mitigate the impacts of rehospitalization and improve the quality of care.

The present study aimed to identify the factors associated with the early readmission of patients with liver cirrhosis hospitalized due to acute decompensation.

METHODS

Sample characteristics

Between January 2011 and October 2016, a prospective cohort study consecutively included individuals admitted to the emergency department of a Brazilian tertiary hospital due to acute decompensation of liver cirrhosis and who were discharged from the hospital. The patients in the following situations were excluded: admission for elective procedures, admissions unrelated to complications of liver cirrhosis, hepatocellular carcinoma outside the Milan criteria, dubious diagnosis of liver cirrhosis, and incomplete examination. All patients were initially admitted to the emergency unit. The decision to transfer the patient to the ward or the intensive care unit was made at the discretion of the attending physician, according to the severity of the acute decompensation. The diagnosis of cirrhosis was histologically established (when available). In the absence of histology, the presence of clinically significant portal hypertension was required (by endoscopy, imaging or ascites with serum-ascites albumin gradient ≥1.1) and combined with one or more clinical parameters (splenomegaly, telangiectasia, palmar erythema, gynecomastia, presence of collateral circulation) and laboratory results (hypoalbuminemia, extended prothrombin time, increased bilirubin and thrombocytopenia). All patients were evaluated by a senior hepatologist during hospitalization to ensure a correct diagnosis.

Readmissions were analyzed. Acute hepatic decompensation was defined as the development of hepatic encephalopathy, massive ascites, upper gastrointestinal bleeding from varices, bacterial infection, or any combination of those. The number of complications from the initial admission was the simple sum of the following complications, if present at the first admission: Ascites, upper gastrointestinal bleeding secondary to portal hypertension, encephalopathy, and bacterial infections.

All patients hospitalized for acute hepatic decompensation were evaluated within 24 hours of admission and subsequently at each admission, up to the 90th day after the first admission, by one of the investigators involved in the study. The following clinical variables were collected: Age, sex, cause of cirrhosis, diabetes, social drinking, current ascites, digestive bleeding, bacterial infections, encephalopathy, and number of complications (as defined above). All individuals were hospitalized under the care of the hepatology service, which defined the best therapeutic strategy and discharge criteria.

All subjects underwent laboratory evaluation on admission, and the following tests were performed for this study: Creatinine, sodium, international normalized ratio (INR), total bilirubin, albumin, and C-reactive protein (CRP).

Active alcoholism was defined as the global average consumption of 21 drinks or more drinks per week for men, and 14 drinks or more drinks per week for women, during the four weeks before admission (a standard drink is equivalent to 12 g of absolute alcohol)[14]. Patients were monitored during hospitalization and eventual readmissions up to 90 days after the index hospitalization. Telephone contact was made to verify cases of readmissions to other institutions.

Individuals with suspected bacterial infection on admission to hospital underwent clinical investigation to confirm this diagnosis and to identify the main primary source of infection. The diagnosis of infection was performed according to the Center for Disease Control criteria[15]. Diagnostic paracentesis was performed in all patients with ascites at the time of admission. Spontaneous bacterial peritonitis (SBP) was diagnosed when the ascitic fluid neutrophil count was ≥250 neutrophils/mm^3 in the absence of an intra-abdominal source of infection, regardless of negative culture[16]. All patients with SBP received weight-adjusted, intravenous ceftriaxone and albumin on the first and third day after diagnosis. Other antibiotic choices could be made in cases that characterize healthcare-associated infections.

Hepatic encephalopathy was graded according to the West-Haven[17] criteria and, if present, a precipitating factor was investigated and lactulose was started, with doses adjusted as needed. All patients with acute variceal bleeding received intravenous octreotide, an antibiotic (oral norfloxacin or intravenous ceftriaxone), and underwent urgent endoscopic therapy after stabilization. The severity of liver disease was estimated using the Child-Pugh[18] classification and the Model for End-Stage Liver Disease (MELD)[19] was calculated based on laboratory tests performed at admission. Acute-on-chronic liver failure (ACLF) and the Chronic Liver Failure - Sequential Organ Failure Assessment (CLIF-SOFA) were defined as proposed by the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF)[20].

Statistical analysis

Patients were divided into two groups, according to the presence or absence of early readmission (within 90 days). The groups were compared regarding clinical and laboratory variables.

Numerical variables with normal distribution were expressed as mean and standard deviation (SD) and compared using Student's *t*-test. Numerical variables with non-normal distribution were expressed as median and compared using the Mann-Whitney test. The normality of the variable distribution was determined by the Kolmogorov-Smirnov test. Qualitative variables were represented by frequency (%) and, for their analysis, the chi-square or Fisher's exact test was used, as appropriate. Logistic regression analysis was performed to identify variables independently associated with early readmission.

All tests used were performed using the statistical program Statistical Package for the Social Sciences, version 22.0 (IBM SPSS Statistics, Chicago, Illinois, United States). P values less than 0.05 were considered statistically significant.

The study protocol complies with the ethical precepts of the Declaration of Helsinki and was approved by the local research ethics committee under number 948.198.

RESULTS

Characteristics of the sample

Between January 2011 and October 2016, there were 616 admissions due to acute decompensation of liver cirrhosis. Repeated admissions totaled 163. One hundred and seventy-three patients were excluded: 159 for missing data and 14 for having been admitted electively. Therefore, 280 patients were eligible for the study.

Table 1 exhibits the characteristics of included patients. The mean age was 55.7±11.2 years and the majority were male (71.8%). The mean MELD was 15.7±5.6, and 36.7% of patients were classified as Child-Pugh C. ACLF was observed in 19.3%. Active alcohol consumption was reported by 60.8% of patients. The main etiologies of cirrhosis were alcohol (55.0%) and hepatitis C virus (35.7%). The 90-day mortality after the index hospitalization was 8.6%.

Variables associated with early hospital readmission

Ninety-one patients were early readmitted (32.5%). When compared to patients who were not readmitted within 90 days, patients with early readmission had a higher median number of complications (2.0 versus 1.0; p<0.001), a higher proportion of individuals with ascites (63.9% versus 44.1%; p=0.026%), higher median INR (1.47 versus 1.39; p=0.023), bilirubin (2.00 versus 1.55 mg/dL; p=0.032), and higher MELD means (16.8±5.7 versus 15.1±5.6; p=0.011) and CLIF-SOFA (6.7±2.3 versus 5.6±2.3; p=0.001).

A logistic regression analysis (forward conditional) was performed, including the following variables with p<0.050 in the bivariate analysis: current ascites, number of complications, INR, bilirubin, MELD, and CLIF-SOFA. CLIF-SOFA (odds ratio [OR] 1.137, 95% confidence interval [CI] 1.003–1.289, p=0.045) and number of complications at initial hospitalization (OR 1.503, 95% CI 1.704–2.105; p=0.018) were identified as independently associated with early readmission.

Early readmission rates according to the number of complications in the initial hospitalization (p<0.001) are shown in Figure 1. Readmission rates according to CLIF-SOFA and the number of complications at initial admission are shown in Figure 2.

DISCUSSION

Decompensated cirrhosis denotes the advanced and late stages of liver disease, characterized by a profound deterioration in liver function and the emergence of complications such as upper gastrointestinal bleeding from portal hypertension, ascites, spontaneous bacterial peritonitis, and other infections, and hepatorenal syndrome. Acute decompensation is the main cause of hospitalization in individuals with cirrhosis[6,21]. More recently, the concept of ACLF was introduced to identify cases of acute decompensation accompanied by hepatic and extrahepatic organ dysfunction[20].

Table 1: Characteristics of patients included in the study and bivariate analysis of factors associated with early readmission

	Total (n=280)	Early readmission absent (n=189)	Early readmission present (n=91)	p
Age (years), average ± SD	55.7 ± 11.2	55.4 ± 11.0	56.3 ± 11.7	0.502
Male sex	71.8%	71.2%	72%	0.898
Aetiology of cirrhosis*				
Alcohol	55%	55.5%	47.2%	0.352
HCV	35.7%	36.0%	36.1%	0.991
HBV	5.4%	5.8%	4.4%	0.634
Cryptogenic	7.5%	7.4%	7.7%	0.783
Diabetes mellitus	27.0%	25.6%	38.9%	0.097
Current alcohol consumption	29.8%	31.8%	16.7%	0.065
Current ascites	47.1%	44.1%	63.9%	0.026
Digestive bleeding	41.4%	42.4%	36.1%	0.478
Bacterial infections	38.9%	37.3%	52.8%	0.076
Encephalopathy	47.9%	45.8%	58.3%	0.159
Number of complications, median	2.00	1.00	2.00	**< 0.001**
Creatinine (mg/dL), median	1.00	1.00	1.10	0.506
Sodium (mEq /L), average ± SD	135.6 ± 5.3	135.7 ± 5.2	135.6 ± 5.6	0.921
INR, median	1.40	1.39	1.47	**0.023**
Total bilirubin (mg/dL), median	1.70	1.55	2.00	**0.032**
Albumin (g/dL), average ± SD	2.6 ± 1.9	2.5 ± 0.6	2.5 ± 0.6	0.872
CRP (mg/L), median	11.85	9.8	13.2	0.279
MELD, average ± SD	15.7 ± 5.6	15.1 ± 5.6	16.8 ± 5.7	**0.011**
CLIF-SOFA, average ± SD	5.9 ± 2.3	5.6 ± 2.3	6.7 ± 2.3	**0.001**
ACLF	19.3%	18.2%	30.6%	0.084
Child-Pugh classification				
Child-A	9.4%	11.2%	5.5%	0.123
Child-B	54.0%	55.1%	55.6%	0.590
Child-C	36.7%	36.3%	36.1%	0.980

SD = standard deviation; HCV = hepatitis C virus; HBV = hepatitis B virus; INR = international normalized ratio; CPR = C-reactive protein; MELD = Model for End-Stage Liver Disease; CLIF-SOFA = Chronic Liver Failure- Sequential Organ Failure Assessment; ACLF = acute-on-chronic liver failure.
#More than one etiologic factor may be present

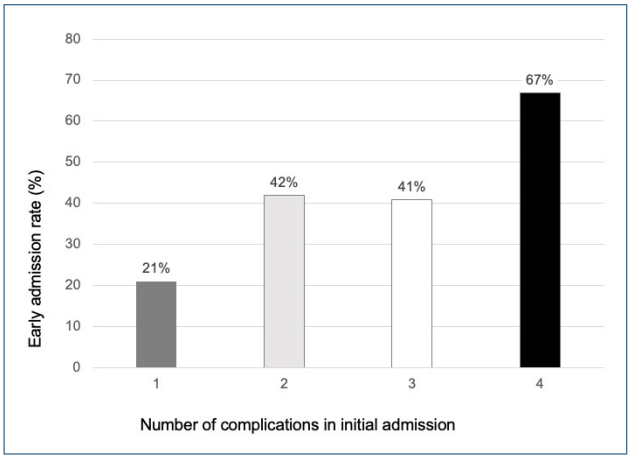

Figure 1: Early admission rates according to the number of complications in initial admission (p<0.001).

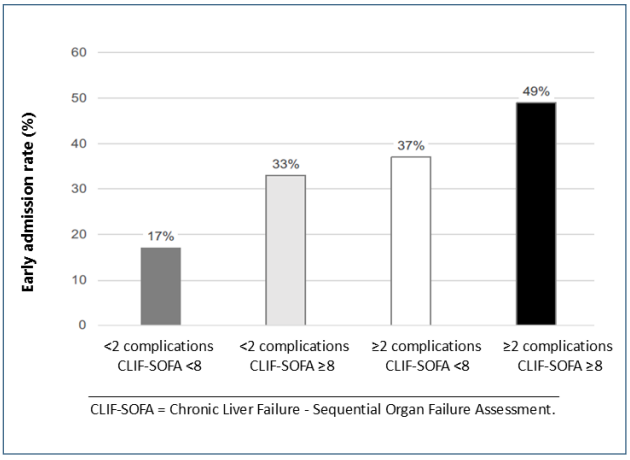

Figure 2: Readmission rates according to CLIF-SOFA and the number of complications in the initial hospitalization (p<0.001).

ACLF represents ACLF represents a late point in the natural history of chronic liver disease, characterized by rapid clinical worsening and poor prognosis. Piano et al. described the presence of ACLF in the first hospitalization, as a strong predictor of readmission within 30 days (OR=2.48; p=0.008)[22]. Subsequently, the CLIF consortium developed the CLIF-SOFA score to assess disease severity and prognosis in the presence of ACLF, which was validated by our group as a strong predictor of short-term mortality in cirrhotic patients admitted for acute decompensation[23]. In the current investigation, we elucidate the relevance of assessing

CLIF-SOFA during the initial admission for decompensated cirrhosis, establishing a correlation between higher CLIF-SOFA values and an increased likelihood of early readmission.

In the context of liver cirrhosis, there have been studies investigating factors associated with early readmission. Finding these factors is imperative, as hospital readmissions can be detrimental to patients and impose substantial costs on the health system[6]. It is important to point out that readmission rates may be underestimated in the studies, as they usually assess a population of a reference academic center, and the patients could have been readmitted to another hospital not included in the analysis[24]. In the United States of America, around 20% to 37% of patients with cirrhosis experience readmission within one month of hospital discharge[22,25-30] and 53% within 90 days[11], indicating notably high rates. In the present study, the readmission rate was 32.5% in 90 days, which is lower than reported in the North American Consortium for the Study of End-Stage Liver Disease (NACSELD)[11]. This discrepancy can be explained by specific characteristics of the institutions participating in the NACSELD study[31], as well as admission criteria and cohort peculiarities. Regarding the time frame for evaluating readmissions, when assessing 30 days, the aim is to associate it with the immediately preceding hospitalization; however, this approach has the drawback of potentially underestimating the true readmission rate. In the evaluation of extended periods, such as the 90-day readmission in this study, external factors beyond the prior hospitalization may come into play, but this method might more accurately reflect the actual readmission rate.

In this study, it was identified that the number of cirrhosis complications present in the first hospitalization can predict readmission. Volk et al.[25] had identified a similar finding, and other authors have described the relationship between cirrhosis complications and individual readmissions, such as the presence of hepatic encephalopathy[11,29], ascites[29], and variceal bleeding[29]. The relationship between CLIF-SOFA and the number of complications of cirrhosis and its implication in readmission has not been demonstrated yet. Individuals with two or more complications of cirrhosis and CLIF-SOFA greater than or equal to 8 have about a 50% chance of being readmitted within 90 days. Other risk factors for hospital readmission of patients were previously described, in addition to those found in this study, and it should be noted that the concepts of ACLF and CLIF-SOFA had not yet been defined at the time of the publication of some of the studies mentioned and, therefore, they were not evaluated. Many predictors of readmission reflect the severity of the liver disease or comorbidities such as MELD score[11,25-27], Charlson index[27], Elixhauser score[29,30], serum sodium[25], prophylactic antibiotic use[11], paracentesis[29,30], and be on the transplant list[25]. Other factors were reported, including age[29,30], male sex[26,27], health insurance[29,30], non-alcoholic etiology of cirrhosis[29,30], hospital infections[11], and specific comorbidities such as diabetes[11,26], hepatocellular carcinoma[29,30], hemodialysis[29], the number of medications in use[25], the use of proton pump inhibitors[11], and hospital discharge against medical advice[29].

Among the study limitations, we can mention the fact that it included patients from a single reference center for hepatology, which could limit the generalizability of the results. However, a single center allows for the standardization of laboratory test results and a more restricted and homogeneous team involved in data collection and management of complications, and this study consists of a cohort with prospective follow-up.

Conclusion

In conclusion, straightforward parameters like CLIF-SOFA and the number of cirrhosis complications at hospital admission serve as predictors for early readmission. These can be utilized as tools to personalize the post-hospital discharge follow-up for cirrhotic patients, enabling the planning of interventions that may prevent readmission, enhance prognostic precision, and facilitate appropriate management, thereby minimizing the cost of treating these individuals.

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