Heliyon 10 (2024) e25739

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Establishment of a prognostic model for hospitalized cirrhotic patients with infection based on lumbar muscle mass

Qian Zhang, Siyi Lei, Qing Zhang, Yanchun Li, Jinhui Xu, Xiaofeng Wang, Shanbi Sun, Xinhua Luo *, Hong Peng **

Department of Infectious Diseases, Guizhou Provincial People's Hospital, Guiyang, 550002, Guizhou, China

ARTICLE INFO

Keywords:
Liver cirrhosis
Predictive model
Sarcopenia
Infection
Mortality
Skeletal muscle index

ABSTRACT

Background: Sarcopenia frequently complicates cirrhosis and leads to substantial mortality. Infection is a complication of cirrhosis that results in high mortality. Both sarcopenia and infection are accompanied by systemic inflammation and adversely affect the prognosis of cirrhosis. This article was designed to decipher the association of sarcopenia with infection occurrence, and to ascertain the risk factors for the 90-day death rate in hospitalized cirrhotic patients with infection.

Methods: A total of 808 cirrhotic patients (373 with infection and 435 without) who had undergone abdominal CT from 2017 to 2021 were recruited for this retrospective single-center research. The skeletal muscle index was assessed at the level of the third lumbar vertebra (L3 SMI). The optimal cutoff value of the CAIL3 model (CTP score, AKI, INR, and L3 SMI) for the prediction of the 90-day death rate was authenticated with receiver operating characteristic (ROC) analysis.

Results: L3 SMI was considered to be the independent risk factor for infection in cirrhotic patients and 90-day death rate in these patients with infection (HR 2.840 95% CI 2.076–3.886, $p < 0.001$ for infection and HR 2.097 95% CI 1.142–3.850, $p = 0.017$ for 90-day death rate, respectively). CAIL3 had an area under the ROC curve of 0.840, and a cutoff value of 0.21 for predicting the poor outcome (sensitivity 77.22% and specificity 76.53%, respectively).

Conclusion: L3 SMI is an essential factor associated with infection and 90-day death rate in cirrhotic patients. CAIL3 may be a novel model for the prediction of the 90-day death risk in cirrhotic patients with infections.

1. Introduction

Sarcopenia is a syndrome that is prevalent in adults with liver cirrhosis, which is featured a progressive loss of age-related skeletal muscle mass and strength. There is compelling evidence suggesting that sarcopenia has a deep impact on the prognosis of cirrhotic patients [1–4]. The screening for sarcopenia is based on the clinical practice guidelines of the European Association for the Study of the Liver (EASL) [5] together with the American Association for the Study of Liver Diseases (AASLD) [6] because early distinguishing is a key aspect of caring for these patients.

* Corresponding author. Department of Infectious Diseases, Guizhou Provincial People's Hospital, Guiyang, 550002, Guizhou, China.
** Corresponding author. Department of Infectious Diseases, Guizhou Provincial People's Hospital, Guiyang, 550002, Guizhou, China.
E-mail addresses: luoxinhua1972@126.com (X. Luo), penghonggz@126.com (H. Peng).

https://doi.org/10.1016/j.heliyon.2024.e25739
Received 23 May 2023; Received in revised form 9 January 2024; Accepted 1 February 2024
Available online 8 February 2024

Infection is the most common complication in patients with liver cirrhosis occurring in 25–35% of inpatients, about four times as many as in patients without liver cirrhosis [7–9]. Also, the infection has a relation to poor outcomes in cirrhotic patients [10]. It is one of the most frequent inducements of acute-on-chronic liver failure that is featured with organ failures, with high short-term mortality of 57% in 30 days [11–14]. Overall, infection quadruples the mortality, accounting for 30–50% of the death rate among all cirrhotic patients.

Low muscle mass is also associated with a higher susceptibility to infection and is a predictor of in-hospital death in cirrhotic patients [15]. Meanwhile, malnutrition is a major reason for lower resistance to infection, which in turn induces deterioration of nutritional status. Both sarcopenia and infection are accompanied by systemic inflammation and adversely affect the prognosis of cirrhosis. There may be a synergistic effect between the two entities in predicting the mortality risk of cirrhosis [16]. Nevertheless, the worse outcome that protein malnutrition may lead to in cirrhotic patients with bacterial infection has been less elucidated. Hence, we aimed to decipher the affinity between sarcopenia and infection occurrence and to identify the risk factors for the 90-day death rate in hospitalized cirrhotic patients with infection. Our results may help physicians stratify the mortality risk of patients by using a useful prognostic scoring system for appropriate management.

2. Materials and methods

2.1. Participants

From January 1st, 2017, and December 31st, 2021, 1055 cirrhotic patients were retrospectively screened at the Department of Infectious Disease, Guizhou Provincial People's Hospital. Finally, 808 patients were enrolled and 247 patients were excluded for reasons. Among these enrolled patients, 373 patients who had diagnosed with infection before or within 48 h after admission were divided into the infection group, and the remaining uninfected patients were divided into the noninfection group. In the infection group, 282 patients were sub-grouped into the sarcopenia group, and the remaining patients, the nonsarcopenia group. In the non-infection group, 204 patients were sub-grouped into the sarcopenia group, and the remaining patients, the nonsarcopenia group (Fig. S1). All patients received standard medical therapy, including energy supplementation, intravenous infusion of plasma and albumin, and prevention and treatment of complications post-admission. Empirical antibiotic treatment was developed following the standard recommendations, and the attending physicians made changes based on clinical evolution and antibiotic susceptibility tests. The research was carried out in accordance with the principles outlined in the Declaration of Helsinki. The protocol received approval from the institutional review board of our hospital (Guizhou Provincial People's Hospital, 2023-009). Consent from individuals was not required for this retrospective analysis.

2.2. Inclusion and exclusion criteria

Cirrhosis was diagnosed based on clinical, biochemical, and imaging features. Ultimately, 808 patients met these diagnostic criteria. We excluded 247 patients for not meeting the inclusion criteria for various reasons: 76 had missing follow-up data, 71 had hepatocellular carcinoma, 32 had other extrahepatic malignancies, 23 had chronic kidney disease, 18 had severe cardiopulmonary disease, 15 had chronic obstructive pulmonary disease, and 12 were pregnant.

2.3. Diagnosis of infection

The diagnosis of infection was based upon clinical features, laboratory tests, as well as imaging findings, with its criteria showing below: (a) spontaneous bacterial peritonitis (SBP): the number of polymorphonuclear (PMN) cells in ascites were $\geq 250/mm^3$, and no source of infection was found; (b) pneumonia: chest X-ray/computed tomography (CT) showing new infiltrative lesions and/or presenting with clinical symptoms such as cough, expectoration, and fever; (c) urinary tract infection: urinary sediment abnormality (more than 10 leukocytes/field) and positive urinary culture, or if negative urinary culture, the number of leukocytes in each field could not be counted; (d) bacteremia: positive blood culture; and (e) cholecystitis: right upper quadrant pain with imaging signs.

2.4. Data acquisition

With a retrospective review of medical records, patient's demographic data and laboratory parameters were extracted. The laboratory indices included blood biochemistry, routine blood tests, routine urine tests, coagulation function, etc. The assessment of the liver reserve function was performed by measuring the indocyanine green retention rate at 15 min (R15) by using the indocyanine green (ICG) clearance test. The calculation of the Child-Turcotte-Pugh (CTP) scores, End-stage Liver Disease (MELD) scores, MELD-Na scores and CLIF Consortium Acute Decompensation Score (CLIF-C ADs) was based on the baseline values of the related parameters (measured at admission). The measurement of the skeletal muscle index at the level of the third lumbar (L3 SMI) was realized given our previous study method [17]. We collected the abdominal CT scan parameters either before admission or within one week after admission, along with the clinical parameters from the first blood test post-admission. Following the guidelines of the Japan Society of Hepatology, sarcopenia was defined as an L3 SMI less than 38 cm^2/m^2 for female patients and less than 42 cm^2/m^2 for male patients [18].

2.5. Statistics

SPSS 25.0 statistical analysis software (version 25.0, Chicago, USA) together with R statistical analysis software (version 3.6.0, Vienna, Austria) was implemented for data processing, and p-value less than 0.05 (two-sided) was indicated statistically significant. Continuous variables, expressed as the mean ± standard for data with a normal distribution or median for data with a nonnormal distribution, were processed with the Student's t-test or the Mann-Whitney *U* test. Categorical data, shown as numbers (percentages), were processed with the chi-square test. The independent predictors of infection or 90-day death rate were authenticated by univariate and multivariate logistic regression analyses, or Cox proportional hazard model in cirrhotic patients, followed by nomogram construction, and evaluation of Calibration curves and the C-index. Using receiver operating characteristic curve (ROC) analysis, the area under the ROC curves (AUC) was compared using Delong test. Cumulative rates of 90-day death rate were plotted using a Kaplan-Meier curve, which was compared with the log-rank test.

3. Results

3.1. Characteristics of the patients in the infection and noninfection cohorts

Infection occurred in 46.2% (373/808) of the patients in the entire cohort. The observations of Table 1 reflected the infected patients exhibited a higher frequency of hepatic encephalopathy (HE), acute kidney injury (AKT), and sarcopenia; higher CTP scores, R15, total bilirubin and international normalized ratio (INR); and lower body mass index (BMI), L3 SMI, serum albumin and sodium than the non-infected patients. Besides, the serum levels of inflammatory cytokines, including neutrophil count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein, and interleukin-6 (IL-6) in the infected patients were higher than those non-infected

Table 1
Baseline characteristics of the study participants.

Characteristic	Total (N = 808)	Infection (N = 373)	Noninfection (N = 435)	*p* value
Age, y	52.0 (45.0–62.0)	52.0 (44.0–64.0)	52.0 (47.0–60.0)	0.278
< 45 y	192 (23.8)	88 (23.6)	104 (23.9)	0.916
45-65 y	468 (57.9)	207 (55.5)	261 (60.0)	0.196
> 65 y	148 (18.3)	78 (20.9)	70 (16.1)	0.077
Male, n (%)	595 (73.6)	266 (71.3)	329 (75.6)	0.165
CTP score	9.0 (8.0–11.0)	10.0 (8.0–11.0)	9.0 (7.0–10.0)	< 0.001
CTP A, n (%)	100 (12.4)	17 (4.6)	83 (19.1)	< 0.001
CTP B, n (%)	382 (47.3)	152 (40.8)	230 (52.9)	0.001
CTP C, n (%)	326 (40.3)	204 (54.7)	122 (28.0)	< 0.001
Etiology, n (%)				
HBV/HCV	403 (49.9)	177 (47.5)	226 (52.0)	0.202
Alcohol	233 (28.8)	116 (31.1)	117 (26.9)	0.198
Autoimmune liver disease	57 (7.1)	28 (7.5)	29 (6.7)	0.642
Others	115 (14.2)	52 (13.9)	63 (14.5)	0.826
Diabetes, n (%)	102 (12.6)	45 (12.1)	57 (13.1)	0.658
Complications, n (%)				
Variceal bleeding	164 (20.3)	68 (18.2)	96 (22.1)	0.176
Hepatic encephalopathy	188 (23.3)	103 (27.6)	85 (19.5)	0.007
Acute kidney injury	178 (22.0)	107 (28.7)	71 (16.3)	< 0.001
Previous decompensation events, n (%)	363 (44.9)	187 (50.1)	176 (40.5)	0.006
BMI, kg/m^2	22.9 (20.8–25.4)	22.6 (20.7–25.0)	23.4 (21.3–25.6)	< 0.001
L3 SMI, cm^2/m^2	38.5 (33.4–43.5)	37.0 (31.9–41.5)	40.6 (35.4–45.0)	< 0.001
Sarcopenia, n (%)	486 (60.1)	282 (75.6)	204 (46.9)	< 0.001
ICG R15, %	38.0 (22.7–51.7)	40.1 (23.1–53.1)	35.0 (20.7–50.7)	0.003
Laboratory data				
Platelet (× 10^9/L)	79.0 (50.0–123.0)	80.0 (50.0–125.0)	79.0 (50.0–122.0)	0.949
Neutrophil (× 10^9/L)	3.35 (2.03–5.43)	3.74 (2.26–5.96)	2.78 (1.82–4.39)	< 0.001
Lymphocyte (× 10^9/L)	0.85 (0.61–1.27)	0.83 (0.61–1.27)	0.91 (0.62–1.26)	0.114
NLR	3.80 (2.33–6.13)	4.63 (2.69–7.38)	3.02 (2.05–4.90)	< 0.001
PLR	92.21 (56.98–140.66)	97.34 (57.18–145.72)	85.15 (56.78–136.55)	0.094
Serum albumin, g/L	28.0 (24.6–31.6)	27.3 (23.6–30.3)	29.1 (25.4–33.4)	< 0.001
Alanine aminotransferase, U/L	34.0 (20.0–71.0)	34.5 (20.0–81.5)	33.0 (20.3–67.0)	0.543
Total bilirubin, μmol/L	50.9 (24.0–166.7)	61.4 (27.4–196.8)	42.5 (19.9–123.3)	< 0.001
C-reactive protein, mg/L	10.07 (3.49–24.49)	14.68 (6.43–36.24)	5.39 (1.89–12.55)	< 0.001
Interleukin-6, pg/mL	23.63 (11.73–48.65)	29.59 (15.18–67.48)	17.70 (7.79–32.60)	< 0.001
International normalized ratio	1.46 (1.20–1.68)	1.52 (1.23–1.75)	1.37 (1.14–1.64)	< 0.001
Sodium, mmol/L	137.0 (135.0–139.0)	136.0 (133.4–139.0)	138.0 (136.0–140.0)	< 0.001
Alpha-fetoprotein, mmol/L	4.49 (2.52–13.75)	4.2 (2.3–14.8)	4.7 (2.8–12.5)	0.653

Continuous variables are expressed as the median (IQR), were processed with the Mann-Whitney *U* test. Categorical data, shown as numbers (percentages), were processed with the chi-square test.
Abbreviations: CTP score, Child-Turcotte-Pugh score; HBV, hepatitis B virus; HCV, hepatitis C virus; L3 SMI, L3 skeletal muscle index; BMI, body mass index; ICG R15 indocyanine green retention rate at 15 min; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

patients without infection. Furthermore, it was demonstrated that infection and L3 SMI were independent predictors of the 90-day death rate in cirrhotic patients (Table S1).

3.2. Effects of sarcopenia on infected patients

We analyzed the impact of sarcopenia on infected patients. It was observed that patients infected with sarcopenia exhibited the highest short-term mortality rates compared to those in the non-infected and non-sarcopenia groups (Fig. S2). Within the infection cohort, the incidence rates were as follows: 59.8% for pneumonia (223 patients, including 146 with pneumonia only, 59 with both pneumonia and SBP, 13 with pneumonia and other site infections, and 5 with pneumonia, SBP, and other site infections), 41.8% for SBP (159 patients, including 92 with SBP only, 59 with SBP and pneumonia, 3 with SBP and other site infections, and 5 with SBP, pneumonia, and other site infections), and 20.4% for other site infections (76 patients, including 55 with other site infections only, 13 with other site infections and pneumonia, 3 with other site infections and SBP, and 5 with other site infections, SBP, and pneumonia). The 90-day cumulative survival rates were similar for SBP patients, pneumonia patients, and patients with other infections. Furthermore, we compared the 90-day cumulative incidence rate of mortality between patients with and without sarcopenia across different infection sites within each group. Notably, the mortality risk was significantly higher in SBP patients with sarcopenia than in those without (HR = 2.841, 95% CI 1.249–6.463) (Fig. S3).

3.3. Factors associated with infection

In the univariate analysis, the existence of sarcopenia, HE, AKI, CTP score ≥7, serum sodium <135 mmol/L, INR ≥1.5, R15 > 30%, and serum albumin ≤25 g/L were regarded as risk factors for infection. In the multivariate analysis, among these factors, CTP score (OR 3.084, 95% CI 1.749–5.438; P < 0.001), serum sodium (OR 1.643, 95% CI 1.142–2.363; P = 0.007), serum albumin (OR 1.542, 95% CI 1.089–2.184; P = 0.015), and sarcopenia (OR 2.840, 95% CI 2.076–3.886; P < 0.001) were recognized as independent predictors for infection (Table 2).

3.4. Factors associated with the 90-day death rate of cirrhotic patients with infection

A total of 105 (13.0%) deaths occurred within 90 days in our cohort: 63 (7.8%) in patients with infection and sarcopenia, 16 (2.0%) in patients with infection but without sarcopenia, 18 (2.2%) in patients without infection but with sarcopenia, and 8 (1.0%) in patients without either infection or sarcopenia. We then analyzed the short-term death risk in cirrhotic patients with infection. The Cox proportional hazard model revealed a CTP score ≥10, INR ≥1.5, sodium <135 mmol/L, R15 > 30%, NLR >5.3, L3 SMI <38.0 cm^2/m^2, and the presence of HE or AKI to be associated with the 90-day death rate of the cirrhotic patients with infection. Nevertheless, the multivariate analysis recognized only CTP score ≥10, INR ≥1.5, L3 SMI <38.0 cm^2/m^2, and the presence of AKI as independent predictors of infection (Table 3).

Table 2
Factors associated with infection.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*P* value
Age, y						
< 45	Reference					
45–65	1.317	0.857–2.024	0.209			
> 65	1.405	0.970–2.035	0.072			
Male	1.249	0.913–1.708	0.165			
CTP score ≥7	4.938	2.871–8.492	< 0.001	3.084	1.749–5.438	< 0.001
BMI ≤18.5	0.705	0.414–1.200	0.198			
Diabetes	1.099	0.724–1.669	0.658			
Sodium < 135 mmol/L	2.356	1.675–3.317	< 0.001	1.643	1.142–2.363	0.007
International normalized ratio ≥1.5	2.395	1.802–3.183	< 0.001			
Platelet < 125 × 10^9/L	1.105	0.795–1.537	0.553			
ICG R15 > 30%	1.498	1.102–2.035	0.010			
Albumin ≤25 g/L	2.217	1.601–3.070	< 0.001	1.542	1.089–2.184	0.015
Alpha-fetoprotein > 7 mmol/L	1.032	0.769–1.384	0.835			
Sarcopenia	3.509	2.594–4.747	< 0.001	2.840	2.076–3.886	< 0.001
Variceal bleeding	1.270	0.898–1.797	0.177			
Hepatic encephalopathy	1.571	1.131–2.181	0.007			
Acute kidney injury	2.062	1.469–2.895	<0.001			

The independent predictors of infection were authenticated by univariate and multivariate logistic regression analyses. In the univariate analysis, the index of P < 0.05 was further included in the multivariate analysis.
Abbreviations: OR, odds ratio; CI, confidence interval; CTP score, Child-Turcotte-Pugh score; BMI, body mass index; ICG R15 indocyanine green retention rate at 15 min.

Table 3
Univariate and multivariate Cox proportional hazard models to predict 90-day death rate in cirrhotic patients with infection.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*P* value
Age, y						
< 45	Reference					
45–65	1.551	0.863–2.787	0.142			
> 65	1.751	0.896–3.420	0.101			
Male	1.067	0.661–1.724	0.791			
CTP score ≥10	6.701	3.451–13.012	< 0.001	3.123	1.464–6.661	0.003
BMI ≤18.5	1.360	0.680–2.724	0.385			
Sodium < 135 mmol/L	1.976	1.267–3.081	0.003			
International normalized ratio ≥1.5	6.489	3.342–12.600	< 0.001	3.008	1.408–6.424	0.004
Platelet < 125 × 10^9/L	1.512	0.849–2.694	0.160			
ICG R15 > 30%	2.887	1.405–5.931	0.004			
NLR > 5.3	2.144	1.368–3.361	0.001			
Alpha-fetoprotein > 7 mmol/L	1.267	0.801–2.004	0.312			
L3 SMI < 38.0 cm^2/m^2	1.857	1.143–3.017	0.012	2.097	1.142–3.850	0.017
Variceal bleeding	1.537	0.917–2.575	0.103			
Hepatic encephalopathy	2.667	1.714–4.151	< 0.001			
Acute kidney injury	2.503	1.608–3.895	<0.001	2.368	1.350–4.151	0.003

The independent predictors of 90-day death rate were authenticated by univariate and multivariate Cox proportional hazard model in cirrhotic patients. In the univariate analysis, the index of $P < 0.05$ was further included in the multivariate analysis.
Abbreviations: HR, hazard ratio; CI, confidence interval; CTP score, Child-Turcotte-Pugh score; ICG R15 indocyanine green retention rate at 15 min; NLR, neutrophil-to-lymphocyte ratio; L3 SMI, L3 skeletal muscle index.

3.5. A predictive model of 90-day death rate in cirrhotic patients with infection

In the Cox proportional hazard model analysis, the probability of the 90-day death rate was predicted by establishing a nomogram incorporating four predictors, and the corresponding score was obtained by projecting the status of each predictor to the upper point scale (0–100) using a straight line, followed by calculating the total score by adding the total scores of the four predictive factors. The probability of the 90-day death rate could be acquired by projecting the total score line directly to the bottom of the probability scale line. We named it CAIL3 (C represents the CTP score, A represents AKI, I represents INR, and L3 represents L3 SMI) (Fig. 1a). Subsequently, we drew a calibration curve to assess our model following the actual incidence and the prediction rate, and the curve disclosed a similar prediction function in contrast to the ideal model. Besides, the C-index was calculated to be 0.801, demonstrating a high degree of accuracy and differentiation (Fig. 1b).

Furthermore, the AUCs of CAIL3 and the other traditional models in predicting the 90-day death rate of cirrhotic patients with infection were analyzed (Fig. 2). The sensitivity and specificity for the CTP score were 87.34 and 54.08%, 70.90 and 74.80% for MELD score, 69.60 and 78.60% for the MELD-NA score, and 86.1% and 38.1% for the CLIF-C ADs respectively. When CTP score, AKI, INR, and L3 SMI were combined (CAIL3), the AUC for the prediction of the mortality was 0.840, and the AUC for CAIL3 was statistically different from all other individual measures (Delong test $p < 0.05$), implying a higher discriminative performance than other traditional models, and the cutoff value, sensitivity, as well as specificity, were 0.21, 77.22%, and 76.53%, respectively.

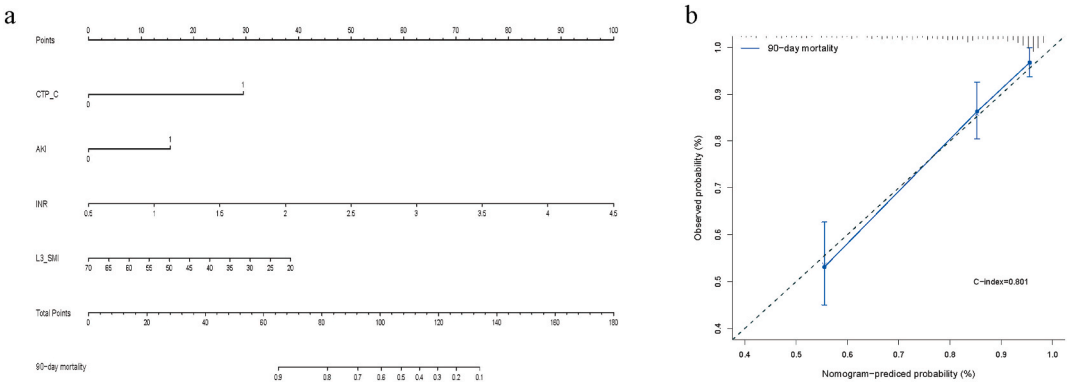

Fig. 1. The nomogram was implemented for predicting the probability of the 90-day death rate in cirrhotic patients complicated with infection (a). Calibration curves were used for predicting the probability of the 90-day death rate (b).

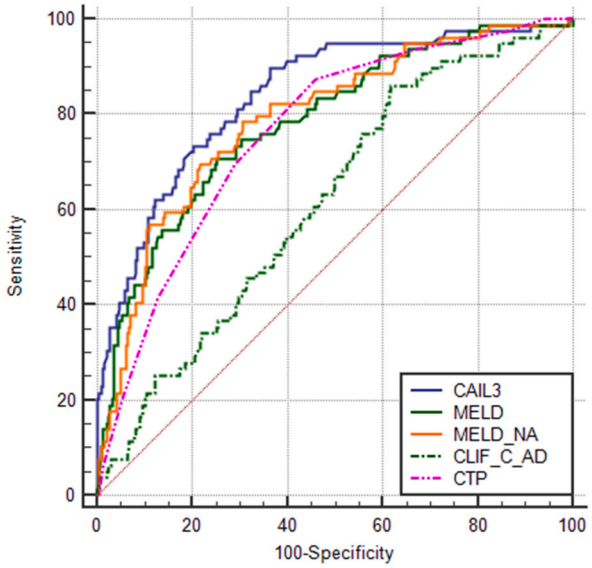

Fig. 2. Receiver operating characteristic (ROC) curves and the areas under the ROC curves (AUC) used to estimate the predictive efficiency for the 90-day mortality rate in cirrhotic patients with infection. These predictions were based on the Child-Turcotte-Pugh (CTP) score, End-stage Liver Disease (MELD) scores, MELD-Na scores, CLIF Consortium Acute Decompensation Score (CLIF-C ADs), and the combination of CTP score, acute kidney injury, international normalized ratio (INR) and L3 SMI (CAIL3).

3.6. Prediction of 90-day death rate in two risk groups

Lastly, the patients were assigned into the high-risk and the low-risk groups following the preselected cutoff points for the comparison of the 90-day death rate. In our study, the patients with CTP C, MELD score ≥20, and MELD-NA score ≥25 were regarded to be at high risk, and 204, 304, and 193 cirrhotic patients with infection met these criteria. Besides, the cutoff values of CLIF-C ADs and CAIL3 were 18 and 0.21, respectively. In total, the ROC analysis screened 236 and 98 high-risk patients. In the low- and high-risk groups, the comparisons of the 90-day cumulative survival rates were implemented using different models. The survival for patients with CAIL3 ≥ 0.21 was 50.3%, while those with CTP C, MELD score ≥20, MELD-NA score ≥25, and CLIF-C ADs ≥18 were 66.2, 74.9, 66.2 and 74.1%, respectively. Similarly, the median survival was 66.2 days based on CAIL3 (95% CI (55.9–68.5)), 71.8 days based on CTP C (95% CI (67.9–75.7)), 76.6 days based on MELD score ≥20 (95% CI (73.6–79.5)), 71.6 days based on MELD-NA score ≥25 (95% CI (67.5–75.6)), and 75.9 days based on CLIF-C ADs ≥18 (95% CI (72.5–79.2)). A difference was witnessed in the survival curves in the groups (Fig. 3).

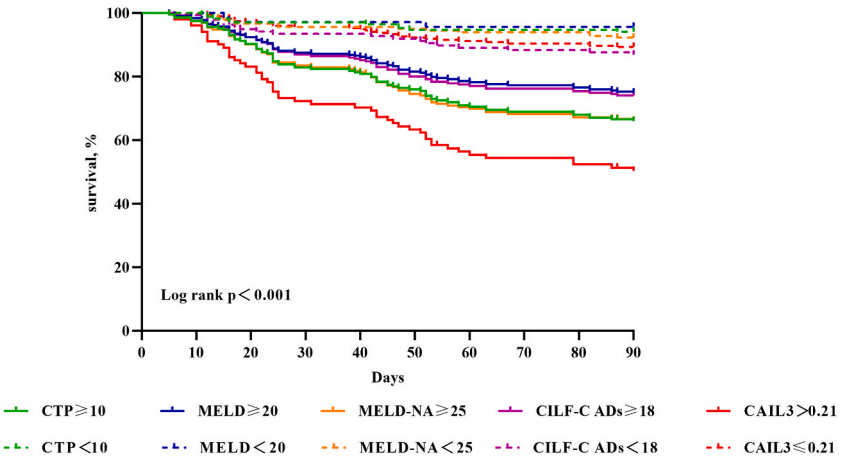

Fig. 3. Kaplan-Meier curve was utilized for depicting the 90-day death rate in cirrhotic patients with complicated infection, and these curves were compared with the log-rank test.

4. Discussion

Infections in patients with liver cirrhosis can have devastating consequences. As the mortality rate of hospitalized patients with cirrhosis decreases [19], it is crucial to predict the prognosis among patients with infection. Therefore, clinicians need a simple and correct prognostic model for the assessment of disease severity, thereby optimizing treatment strategies and improving patient survival. Our analyses of this cirrhotic cohort revealed three major findings. First, we found that the reduction in L3 SMI correlated to an increased risk of infection and mortality in cirrhotic patients, especially those with infection. Second, in the infection group, we demonstrated that L3 SMI (HR 2.097), AKI (HR 2.368), INR $\geq$1.5 (HR 3.008), as well as Child-Pugh class C (HR 3.123) were independent predictors of the 90-day death rate. Third, we developed, for the first time, a predictive model CAIL3 for short-term death rate risk in cirrhotic patients with infection.

In this cohort, AKI, INR, and CTP score were screened as important indicators of the prognostic model under the Cox proportional hazard regression model because these indicators have a close relationship with the clinical outcome of patients. The literature has illustrated that AKI is largely responsible for adverse consequences in cirrhotic patients [20–22]. In addition, the liver is crucial for synthesizing many coagulation factors. INR, one of the commonly used indicators of liver injury, is indicative of the mortality of liver diseases. Emerging evidence has revealed that INR can predict the rapid deterioration and short-term high mortality of hospitalized patients with cirrhosis or advanced liver fibrosis [23]. As the most prevalent scoring model to evaluate hepatic functional reserve in patients with cirrhosis, the CTP score has been widely recognized by clinicians. Patients with CTP C have lower 90-day survival rates when compared with those patients with CTP A and B [24]. All of these are important indices for evaluating the outcome of liver cirrhosis, but there is still no independent system for evaluating the outcome of liver cirrhosis complicated with infection.

Moreover, patients with liver disease often overlook their nutritional status. Malnutrition, or even low muscle mass, has been revealed to exert significant effects on the prognosis of cirrhotic patients. Low muscle mass is predictive of a lower survival rate [2] and a higher complication rate [25], such as HE, attacks, and ascites. A low muscle index can enhance the risk of infection in patients, regardless of the presence of underlying liver diseases [15,26]. Montano-Loza et al. also supported that sarcopenia is related to 5-fold elevated risk of mortality in cirrhotic patients [27]. Consistently, our study unveiled that a low muscle index was a risk predictor for infection and even short-term death rate in cirrhotic patients. One research disclosed that sarcopenia may increase the risk of infection by decreasing immunity [28]. However, the specific mechanism by which low muscle mass causes infection and mortality is still unclear. Proinflammatory cytokines can trigger muscle atrophy [29]. The occurrence and development of infection are accompanied by the excessive release of inflammatory factors. Therefore, we speculated that muscle catabolism was enhanced in cirrhotic patients complicated with infection. Furthermore, the maintenance of the immune response of the body requires energy consumption to respond to infection because inflammatory mediators may contribute to a catabolic state, which is mainly featured with an increased demand for arginine in the muscle. The consumption of this kind of amino acid may damage the reaction of T cells and lead to a negative nitrogen balance [26]. Briefly, we believe that the existence of a causal relationship between malnutrition and infection, as well as malnutrition, is a vital factor affecting the natural course of cirrhosis.

In this study, the infections occurred mainly in the lung and abdominal cavities, while there is a lower proportion of bloodstream infection. In patients with liver cirrhosis, the risk factors for bloodstream infection mainly include central venous catheters, intestinal barrier damage, intensive care unit accommodation, as well as mechanical ventilation. Patients in this cohort were all from the general ward and did not require mechanical ventilation and intensive care unit accommodation, which might be the main reason for the relatively lower prevalence of bloodstream infection. Furthermore, no difference was witnessed in the short-term mortality between the patients with SBP and pneumonia, which was in accord with the findings of another prior article [30].

The limitations of this study are as follows: (1) this retrospective single-center research limits the generalization of our outcomes, which should be evaluated in multicenter research. (2) It is unknown to us whether the dynamic changes in L3 SMI levels may have a greater clinical value in the prediction of the short-term death rate in cirrhotic patients complicated with infection. (3) The limited positive detection rate of humoral samples of infected patients, and no pathogens were found in most of the infected patients, limited further analysis of the infected group.

5. Conclusion

In conclusion, the current work underlines that the L3 SMI is an essential factor associated with infection and 90-day death rate in cirrhotic patients. Therefore, it is important to impede or correct malnutrition in cirrhotic patients. CAIL3 may be a novel model for the prediction of the 90-day death risk in cirrhotic patients with infection.

Funding

This work was supported by the Guiyang Bureau of Science and Technology (Grant numbers [ZKH [2022]4-1-2]).

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval statement

The present study was approved by the ethics committee of Guizhou Provincial People's Hospital and performed according to the ethical guidelines of the 1975 Declaration of Helsinki.

Consent for publication

The requirement for obtaining informed consent from patients was waived because of the retrospective nature of the study.

CRediT authorship contribution statement

Qian Zhang: Conceptualization. **Siyi Lei:** Data curation. **Qing Zhang:** Methodology. **Yanchun Li:** Software. **Jinhui Xu:** Software. **Xiaofeng Wang:** Writing – original draft. **Shanbi Sun:** Writing – review & editing. **Xinhua Luo:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Hong Peng:** Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to acknowledge the reviewers for their helpful comments on this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25739.

References

[1] S. Dasarathy, M. Merli, Sarcopenia from mechanism to diagnosis and treatment in liver disease, J Hepatol 65 (2016) 1232–1244, https://doi.org/10.1016/j.jhep.2016.07.040.
[2] A.J. Montano-Loza, J. Meza-Junco, C.M. Prado, J.R. Lieffers, V.E. Baracos, V.G. Bain, et al., Muscle wasting is associated with mortality in patients with cirrhosis, Clin Gastroenterol Hepatol 10 (2012) 166–173, https://doi.org/10.1016/j.cgh.2011.08.028, 173 e161.
[3] M. Ney, J.G. Abraldes, M. Ma, D. Belland, A. Harvey, S. Robbins, et al., Insufficient protein intake is associated with increased mortality in 630 patients with cirrhosis awaiting liver transplantation, Nutr Clin Pract 30 (2015) 530–536, https://doi.org/10.1177/0884533614567716.
[4] H.Y. Kim, J.W. Jang, Sarcopenia in the prognosis of cirrhosis: going beyond the MELD score, World J Gastroenterol 21 (2015) 7637–7647, https://doi.org/10.3748/wjg.v21.i25.7637.
[5] e.e.e. European, Association for the study of the liver. Electronic address, L. European association for the study of the, EASL clinical practice guidelines on nutrition in chronic liver disease, J Hepatol 70 (2019) 172–193, https://doi.org/10.1016/j.jhep.2018.06.024.
[6] J.C. Lai, P. Tandon, W. Bernal, E.B. Tapper, U. Ekong, S. Dasarathy, et al., Malnutrition, frailty, and sarcopenia in patients with cirrhosis: 2021 practice guidance by the American association for the study of liver diseases, Hepatology 74 (2021) 1611–1644, https://doi.org/10.1002/hep.32049.
[7] C. Bunchorntavakul, N. Chamroonkul, D. Chavalitdhamrong, Bacterial infections in cirrhosis: a critical review and practical guidance, World J Hepatol 8 (2016) 307–321, https://doi.org/10.4254/wjh.v8.i6.307.
[8] A.R. Bonnel, C. Bunchorntavakul, K.R. Reddy, Immune dysfunction and infections in patients with cirrhosis, Clin Gastroenterol Hepatol 9 (2011) 727–738, https://doi.org/10.1016/j.cgh.2011.02.031.
[9] J. Fernandez, V. Arroyo, Bacterial infections in cirrhosis: a growing problem with significant implications, Clin Liver Dis (Hoboken) 2 (2013) 102–105, https://doi.org/10.1002/cld.169.
[10] J.S. Bajaj, J.G. O'Leary, K.R. Reddy, F. Wong, S.W. Biggins, H. Patton, et al., Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures, Hepatology 60 (2014) 250–256, https://doi.org/10.1002/hep.27077.
[11] R. Martin Mateos, A. Albillos, Sepsis in patients with cirrhosis awaiting liver transplantation: new trends and management, Liver Transpl 25 (2019) 1700–1709, https://doi.org/10.1002/lt.25621.
[12] G. Cullaro, R. Sharma, J. Trebicka, A. Cardenas, E.C. Verna, Precipitants of acute-on-chronic liver failure: an opportunity for preventative measures to improve outcomes, Liver Transpl 26 (2020) 283–293, https://doi.org/10.1002/lt.25678.
[13] J.G. O'Leary, K.R. Reddy, G. Garcia-Tsao, S.W. Biggins, F. Wong, M.B. Fallon, et al., NACSELD acute-on-chronic liver failure (NACSELD-ACLF) score predicts 30-day survival in hospitalized patients with cirrhosis, Hepatology 67 (2018) 2367–2374, https://doi.org/10.1002/hep.29773.
[14] R. Moreau, R. Jalan, P. Gines, M. Pavesi, P. Angeli, J. Cordoba, et al., Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis, Gastroenterology 144 (2013) 1426–1437, https://doi.org/10.1053/j.gastro.2013.02.042, 1437 e1421-1429.
[15] M. Merli, C. Lucidi, V. Giannelli, M. Giusto, O. Riggio, M. Falcone, et al., Cirrhotic patients are at risk for health care-associated bacterial infections, Clin Gastroenterol Hepatol 8 (2010) 979–985, https://doi.org/10.1016/j.cgh.2010.06.024.
[16] C. Lucidi, B. Lattanzi, V. Di Gregorio, S. Incicco, D. D'Ambrosio, M. Venditti, et al., A low muscle mass increases mortality in compensated cirrhotic patients with sepsis, Liver Int 38 (2018) 851–857, https://doi.org/10.1111/liv.13691.
[17] H. Peng, Q. Zhang, L. Luo, S. Lei, T. Xiong, L. Long, et al., A prognostic model of acute-on-chronic liver failure based on sarcopenia, Hepatol Int 16 (2022) 964–972, https://doi.org/10.1007/s12072-022-10363-2.
[18] H. Nishikawa, M. Shiraki, A. Hiramatsu, K. Moriya, K. Hino, S. Nishiguchi, Japan Society of Hepatology guidelines for sarcopenia in liver disease (1st edition): recommendation from the working group for creation of sarcopenia assessment criteria, Hepatology research : the official, journal of the Japan Society of Hepatology 46 (2016) 951–963, https://doi.org/10.1111/hepr.12774.

[19] F. Kanwal, A. Tansel, J.R. Kramer, H. Feng, S.M. Asch, H.B. El-Serag, Trends in 30-day and 1-year mortality among patients hospitalized with cirrhosis from 2004 to 2013, Am J Gastroenterol 112 (2017) 1287–1297, https://doi.org/10.1038/ajg.2017.175.
[20] D.A. Simonetto, P. Gines, P.S. Kamath, Hepatorenal syndrome: pathophysiology, diagnosis, and management, BMJ 370 (2020) m2687, https://doi.org/10.1136/bmj.m2687.
[21] A.S. Allegretti, G. Ortiz, J. Wenger, J.J. Deferio, J. Wibecan, S. Kalim, et al., Prognosis of acute kidney injury and hepatorenal syndrome in patients with cirrhosis: a prospective cohort study, Int J Nephrol 2015 (2015) 108139, https://doi.org/10.1155/2015/108139.
[22] J. Xiong, L. Pu, H. Xiong, P. Xiang, M. Zhang, J. Liu, et al., Evaluation of the criteria of hepatorenal syndrome type of acute kidney injury in patients with cirrhosis admitted to ICU, Scand J Gastroenterol 53 (2018) 1590–1596, https://doi.org/10.1080/00365521.2018.1545423.
[23] Y. Wang, F. Dong, S. Sun, X. Wang, X. Zheng, Y. Huang, et al., Increased INR values predict accelerating deterioration and high short-term mortality among patients hospitalized with cirrhosis or advanced fibrosis, Front Med (Lausanne) 8 (2021) 762291, https://doi.org/10.3389/fmed.2021.762291.
[24] G. Acharya, R.M. Kaushik, R. Gupta, R. Kaushik, Child-turcotte-pugh score, MELD score and MELD-Na score as predictors of short-term mortality among patients with end-stage liver disease in northern India, Inflamm Intest Dis 5 (2020) 1–10, https://doi.org/10.1159/000503921.
[25] E.J. Huisman, E.J. Trip, P.D. Siersema, B. van Hoek, K.J. van Erpecum, Protein energy malnutrition predicts complications in liver cirrhosis, Eur J Gastroenterol Hepatol 23 (2011) 982–989, https://doi.org/10.1097/MEG.0b013e32834aa4bb.
[26] U.E. Schaible, S.H. Kaufmann, Malnutrition and infection: complex mechanisms and global impacts, PLoS Med 4 (2007) e115, https://doi.org/10.1371/journal.pmed.0040115.
[27] A.J. Montano-Loza, Clinical relevance of sarcopenia in patients with cirrhosis, World journal of gastroenterology 20 (2014) 8061–8071, https://doi.org/10.3748/wjg.v20.i25.8061.
[28] G. Cosqueric, A. Sebag, C. Ducolombier, C. Thomas, F. Piette, S. Weill-Engerer, Sarcopenia is predictive of nosocomial infection in care of the elderly, Br J Nutr 96 (2006) 895–901, https://doi.org/10.1017/bjn20061943.
[29] H.Q. Han, X. Zhou, W.E. Mitch, A.L. Goldberg, Myostatin/activin pathway antagonism: molecular basis and therapeutic potential, The international journal of biochemistry & cell biology 45 (2013) 2333–2347, https://doi.org/10.1016/j.biocel.2013.05.019.
[30] P. Atteberry, B. Biederman, A. Jesudian, C. Lucero, R.S. Brown Jr., E. Verna, et al., Mortality, sepsis, and organ failure in hospitalized patients with cirrhosis vary by type of infection, J Gastroenterol Hepatol 36 (2021) 3363–3370, https://doi.org/10.1111/jgh.15633.