BMJ Open Recompensation factors for patients with decompensated cirrhosis: a multicentre retrospective case-control study

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ABSTRACT

Objectives We aimed to evaluate recompensation factors among patients with decompensated cirrhosis.

Design A multicentre retrospective case-control study was conducted. Data were collected from and compared between groups of patients with recompensated and acute decompensated cirrhosis. Univariable and multivariable logistic regressions were used to select indicators associated with recompensation among patients with decompensated cirrhosis with different complications. A decision tree with 10-fold cross-validation was used to develop the model to identify patients with recompensation. We followed the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline for development and reporting of the new model.

Setting The study was conducted in six tertiary public hospitals in Chongqing, China.

Participants This study included 3953 patients with decompensated cirrhosis.

Results In the total sample of included patients, there were 553 patients with recompensation and 3400 patients with acute decompensation, including 1158 patients with gastrointestinal bleeding, 1715 patients with a bacterial infection, 104 patients with hepatic encephalopathy and 423 patients with ascites. The most relevant indicator of recompensation selected by the decision tree model was albumin, with a threshold of 40 g/L. Total protein, haemoglobin, basophil percentage, alanine aminotransferase, neutrophil-to-lymphocyte ratio and diabetes were also selected to subsequently distinguish patients. The terminal nodes with a probability of recompensation was 0.89. The overall accuracy rate of the model was 0.92 (0.91–0.93), and it exhibited high specificity (86.9%) and sensitivity (92.6%).

Conclusions The occurrence of recompensated cirrhosis could be identified by albumin, total protein, haemoglobin, basophil percentage, alanine aminotransferase, neutrophil-to-lymphocyte ratio and diabetes. These simple variables may help clinicians develop a treatment plan to encourage patients with decompensated cirrhosis to recompensate.

INTRODUCTION

Patients with decompensated cirrhosis have a poor prognosis, and are more likely to

Strengths and limitations of this study

- The data contain more than 3000 patients with decompensated liver cirrhosis from six centres, making it the largest data sample for analysing recompensation indicators.
- The indicators included in the model are available in the information systems of hospitals at all levels, which makes our indicators easier to apply in clinical and even community hospitals.
- The knowledge of recompensated indicators may be useful for supporting different prevention strategies, so as to reduce the occurrence of acute decompensation.
- The cut-off values of the model in other regions need further external validation.

undergo hospital readmissions, liver transplantation, death or hepatocellular carcinoma.¹ In patients with acute decompensated cirrhosis without acute-on-chronic liver failure (ACLF), the 28-day mortality rate was 4.6%, which increased to 12.6% at 3 months, 18.3% at 6 months, and 27.6% at 1 year. In addition, acute decompensated cirrhosis occurs in up to 15% of cirrhotic patients each year.²

Fortunately, due to aetiology control, effective treatment or prevention, some patients with decompensated cirrhosis may no longer have decompensation-related complications, for a long period of time, which is considered to be 'recompensation'.^{3 4} Some studies have shown that patients with decompensated cirrhosis have improved transplant-free survival rates, Child-Turcotte-Pugh and model for end-stage liver disease scores after receiving antiviral treatment.^{5–10} For patients with alcoholic decompensated cirrhosis listed for liver transplantation, the model for end-stage liver disease score less than 20 and serum albumin greater than or equal

to 32 g/L at enrollment were independent predictors of recompensation/withdrawal from the transplant list.¹¹

Despite that, controversies remain regarding the evaluation time, evaluation indicators, and influencing factors of recompensation. Currently, research data on the recompensation markers of decompensated cirrhosis is scant. Better identification and understanding of recompensation in patients with decompensated liver cirrhosis is very important for the design of preventive interventions that reduce the overall burden. Hence, the purpose of this study was to describe the clinical characteristics of patients with recompensation and to determine the clinical variables relevant to recompensation.

PATIENTS AND METHODS

Patient and public involvement statement

This was a retrospective study. Therefore, the patients and the public were not directly involved in the design and conception of this study.

Patients and definitions

This was a multicentre retrospective case-control study. Consecutive follow-up patients with decompensated cirrhosis came from six hospitals: the Second Affiliated Hospital of Chongqing Medical University, Yongchuan Hospital of Chongqing Medical University, the Third Affiliated Hospital of Chongqing Medical University, University-Town Hospital of Chongqing Medical University, the People's Hospital of Tongliang District and the Southeast Hospital of Chongqing. Clinical data of patients treated between January 2014 and October 2019 were collected using electronic medical record systems.

The inclusion criteria were as follows: (1) diagnosis of decompensated liver cirrhosis based on clinical, biochemical, ultrasonographic and/or endoscopic findings and (2) age ≥ 18 years old. The exclusion criteria were as follows: (1) patients with liver cancer or other active malignancy; (2) ACLF, the diagnosis of which was based on the criteria from the consensus recommendation of the Asian Pacific Association for the Study of the Liver¹²; (3) congestive heart failure, chronic kidney disease or other significant chronic extrahepatic disease; (4) selective admission, such as reasons for hospitalisation that were either to perform liver biopsy, endoscopy with potential band ligation or an evaluation for liver transplantation or (5) more than 20% of the data missing for the patients or indicators.

Acute decompensated cirrhosis was defined as the rapid development of one or more major complications of liver disease, such as ascites, encephalopathy, gastrointestinal haemorrhage and bacterial infection, requiring hospitalisation.^{13–17} Recompensated cirrhosis was defined as clinically stable outpatients with either controlled ascites or previously treated decompensation events who were in a stable clinical state for at least 1 year.³

Ascites was recorded as the primary reason for admission if this was the sole criterion for admission and infection was absent.

Hepatic encephalopathy as characterised by altered mental status or neuropsychiatric abnormalities in the presence of liver cirrhosis after exclusion of other causes.¹⁸

Gastrointestinal bleeding was defined as the development of an upper and/or lower gastrointestinal haemorrhage of any aetiology.¹⁵

Bacterial infection was defined in cases of spontaneous bacterial peritonitis, pneumonia, cellulitis, biliary tract infection, urinary system infection and spontaneous bacteraemia.¹⁷ None of the included patients developed acute decompensated cirrhosis due to bacterial infection alone.

In the presence of more than one contributory factor, the main cause of admission was defined as follows: (1) in patients admitted with gastrointestinal bleeding in the presence of ascites, bacterial infection or hepatic encephalopathy, gastrointestinal bleeding was considered the main cause because it frequently causes bacterial infection or hepatic encephalopathy; (2) in the absence of bleeding at admission, bacterial infection was the main cause of hospitalisation and (3) in patients with hepatic encephalopathy and ascites, the main cause was the former.¹⁹ The principal cause of hospitalisation was subsequently assessed independently by two subspecialist physicians.

Treatment

Standard medical therapies were used for all patients after diagnosis, such as antiviral therapy and symptomatic and supportive therapies.

Data collection

Demographic, clinical and routine laboratory data were recorded during the first contact visit to the hospital. Demographic characteristics included age and sex. The aetiological characteristics, including hepatitis B virus (HBV)/hepatitis C virus (HCV) infection, autoimmunity and alcohol consumption, were assessed from the medical history. Clinical data included complications related to liver cirrhosis and comorbidities (such as hypertension and diabetes). Laboratory analyses included red cell counts, white cell counts, platelet counts, haemoglobin, basophil percentage, eosinophil percentage, total protein, albumin, direct bilirubin, indirect bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyl aminotransferase (γ -GT), alkaline phosphatase (ALP), neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio. Data from patients with recompensated cirrhosis were recorded during the first contact visit. For patients with acute decompensated cirrhosis, data were obtained within 24 hours of the initial diagnosis.

Statistical analysis

All statistical analyses were conducted using R software (V.4.0.2). All data were presented as counts with percentages for categorical variables and medians (IQRs) for continuous variables. We followed the transparent

reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guideline for development and reporting of the new model.²⁰ For variables with omission rates <20%, the mean imputation was used. χ^2 and Kruskal-Wallis tests were used when appropriate to evaluate the significance of differences in distributions between patients with recompensation, patients with gastrointestinal bleeding, patients with bacterial infection, patients with hepatic encephalopathy and patients with ascites. Indicators with $p < 0.05$ were subsequently included in the univariate logistic regression to identify the factors associated with recompensation, followed by multivariate analysis using those factors with $p < 0.05$ in the univariate logistic regression analysis.

We combined the factors in each multivariate regression analysis and used decision trees to select recompensation indicators. The decision tree algorithm selected the most relevant of these clinical variables, their position within the decision tree and their optimal cut-off values. The model was fitted using the R software (V.4.0.2) rpart package with the settings `minsplit=20` and `maxdepth=6`. A 10-fold cross-validation was used to reduce overfitting and to assess the discrimination ability of the model by estimating the corresponding sensitivity and specificity of the model and computing the overall accuracy rate along with a 95% CI for this rate (using `binom.test`) and a one-sided test to see if the accuracy is better than the 'no information rate,' which is taken to be the largest class percentage in the data.^{21 22} All tests were considered statistically significant when $p < 0.05$.

RESULTS

Baseline characteristic of patients

In the total sample of included patients, there were 553 patients with recompensation and 3400 patients with acute decompensation, including 1158 patients with gastrointestinal bleeding, 1715 patients with a bacterial infection, 104 patients with hepatic encephalopathy and 423 patients with ascites. The aetiology of liver cirrhosis in these patients was 1955 (49.5%) positive for HBV, 190 (4.8%) positive for HCV, 573 (14.5%) for alcohol abuse, 245 (6.2%) for autoimmunity and 990 (25%) for other causes. The median age was highest among the patients with ascites, while the proportion of male patients was highest among the patients with hepatic encephalopathy. The median red cell counts, platelet counts, haemoglobin, basophil percentage, eosinophil percentage, total protein, albumin, lymphocyte-to-monocyte ratio and proportion of patients with other aetiologies were highest among the patients with recompensation, while the median white cell counts, direct bilirubin, ALT, AST, γ -GT, proportion of patients with HBV infection and proportion of patients with autoimmunity were highest among the patients with bacterial infection. The proportion of patients with alcoholic cirrhosis, hypertension, diabetes, the median indirect bilirubin and ALP levels were highest among the patients with hepatic encephalopathy, while

the median NLR was highest among the patients with gastrointestinal bleeding (table 1).

Factors associated with recompensation in patients with gastrointestinal bleeding

Of the 1158 patients with gastrointestinal bleeding, multivariate logistic regression showed that alcoholic cirrhosis (OR: 0.146, 95% CI, $p=0.001$), other aetiologies (OR: 2.986, 95% CI, $p<0.001$), hypertension (OR: 0.036, 95% CI, $p<0.001$), diabetes (OR: 0.216, 95% CI, $p<0.001$), haemoglobin (OR: 1.043, 95% CI, $p<0.001$), basophil percentage (OR: 3.447, 95% CI, $p<0.001$), total protein (OR: 1.151, 95% CI, $p<0.001$) and NLR (OR: 0.843, 95% CI, $p<0.001$) were factors related to recompensation (table 2).

Factors associated with recompensation in patients with bacterial infection

Of the 1715 patients with a bacterial infection, multivariate logistic regression showed that alcoholic cirrhosis (OR: 0.129, 95% CI, $p<0.001$), autoimmune-related cirrhosis (OR: 0.445, 95% CI, $p=0.044$), hypertension (OR: 0.016, 95% CI, $p<0.001$), diabetes (OR: 0.225, 95% CI, $p<0.001$), haemoglobin (OR: 1.021, 95% CI, $p<0.001$), basophil percentage (OR: 1.752, 95% CI, $p=0.003$), total protein (OR: 1.083, 95% CI, $p<0.001$), albumin (OR: 1.125, 95% CI, $p<0.001$), ALT (OR: 0.996, 95% CI, $p=0.024$) and NLR (OR: 0.841, 95% CI, $p<0.001$) were significantly correlated with recompensation (table 3).

Factors associated with recompensation in patients with hepatic encephalopathy

Of the 104 patients with hepatic encephalopathy, multivariate logistic regression showed that alcoholic cirrhosis (OR: 0.041, 95% CI, $p<0.001$), other aetiologies (OR: 3.139, 95% CI, $p=0.007$), hypertension (OR: 0.004, 95% CI, $p<0.001$), diabetes (OR: 0.101, 95% CI, $p<0.001$), haemoglobin (OR: 1.027, 95% CI, $p=0.016$), total protein (OR: 1.163, 95% CI, $p<0.001$) and albumin (OR: 1.116, 95% CI, $p=0.014$) were associated with recompensation (table 4).

Factors associated with recompensation in patients with ascites

Of the 423 patients with ascites, multivariate logistic regression showed that age (OR: 0.972, 95% CI, $p<0.001$), alcoholic cirrhosis (OR: 0.158, 95% CI, $p<0.001$), other aetiologies (OR: 2.167, 95% CI, $p<0.001$), hypertension (OR: 0.047, 95% CI, $p<0.001$), diabetes (OR: 0.255, 95% CI, $p<0.001$), total protein (OR: 1.101, 95% CI, $p<0.001$), albumin (OR: 1.131, 95% CI, $p<0.001$), ALT (OR: 0.992, 95% CI, $p=0.014$) and NLR (OR: 0.872, 95% CI, $p=0.002$) were associated with recompensation (table 5).

Tool to evaluate recompensation

A decision tree was fitted to illustrate the observed associations and to detect other specific subgroups and relationships that may not be available through multivariate regression analysis. The variables which were statistically significant in the multivariate logistic regression from

Table 1 Baseline characteristics of patients

Variables	Recompensation n=553	GI bleeding n=1158	Bacterial infection n=1715	HE n=104	Ascites n=423	P value
Age (years), median (IQR)	51 (44–57)	52 (45–62)	55 (46–65)	55 (46–64)	58 (49–68)	<0.001
Male gender, N (%)	356 (64.4)	810 (69.9)	1135 (66.2)	75 (72.8)	268 (63.4)	0.028
HBV, N (%)	228 (41.2)	599 (51.7)	895 (52.2)	40 (38.8)	193 (45.6)	<0.001
HCV, N (%)	32 (5.8)	65 (5.6)	74 (4.3)	7 (6.8)	12 (2.8)	0.085
Alcohol, N (%)	6 (1.1)	176 (15.2)	304 (17.7)	29 (28.2)	58 (13.7)	<0.001
Autoimmune, N (%)	24 (4.3)	50 (4.3)	141 (8.2)	3 (2.9)	27 (6.4)	<0.001
Others, N (%)	263 (47.6)	268 (23.1)	301 (17.6)	25 (24)	133 (31.4)	<0.001
Diabetes, N (%)	15 (2.7)	192 (16.6)	296 (17.3)	26 (25.2)	77 (18.2)	<0.001
Hypertension, N (%)	2 (0.4)	98 (8.5)	242 (14.1)	20 (19.4)	64 (15.1)	<0.001
Laboratory parameters, median (IQR)						
RBC ($10^{12}/L$)	4.2 (3.7–4.8)	2.8 (2.4–3.4)	3.6 (3.0–4.0)	3.3 (3.0–3.7)	3.6 (3.1–4.0)	<0.001
Haemoglobin (g/L)	134 (117–151)	80 (63–100)	110 (93–125)	106 (90–113)	110 (92–127)	<0.001
WBC ($10^9/L$)	4.5 (3.5–5.9)	4.8 (3.0–7.3)	5.0 (3.3–7.6)	4.4 (3.2–7.0)	4.0 (2.9–5.6)	<0.001
PLT ($10^9/L$)	86 (58–131)	67 (47–100)	83 (53–137)	77 (48–140)	79 (52–129)	<0.001
Basophil percentage (%)	0.4 (0.3–0.6)	0.2 (0.0–0.4)	0.2 (0.0–0.4)	0.3 (0.1–0.6)	0.3 (0.1–0.5)	<0.001
Eosinophil percentage (%)	2.2 (1.2–3.8)	1.0 (0.3–2.3)	1.2 (0.4–2.7)	1.7 (0.8–3.6)	1.8 (0.8–3.3)	<0.001
Total protein (g/L)	76.9 (72.8–80.7)	59.7 (53.4–66.2)	64.5 (58.5–71.1)	65.9 (59.0–72.0)	65.2 (59.7–71.3)	<0.001
Albumin (g/L)	41.0 (35.5–44.6)	31.3 (27.4–35.4)	30.3 (26.4–34.5)	30.0 (27.4–35.3)	31.8 (27.7–36.0)	<0.001
Direct bilirubin ($\mu\text{mol/l}$)	8.0 (5.2–13.1)	8.1 (4.8–14.5)	15.4 (7.6–46.0)	14.0 (7.6–26.1)	11.8 (6.6–24.1)	<0.001
Indirect bilirubin ($\mu\text{mol/l}$)	11.9 (8.8–17.2)	10.6 (7.0–17.2)	14.1 (8.2–27.3)	17.0 (11.2–27.0)	12.5 (7.9–21.0)	<0.001
ALT (U/L)	30.0 (22.0–46.0)	27.0 (17.7–42.2)	34.0 (20.0–74.0)	31.0 (21.2–51.5)	32.0 (18.8–57.0)	<0.001
AST (U/L)	39.0 (30.0–58.0)	37.0 (26.0–59.0)	55.0 (33.0–108.0)	50.5 (35.0–76.0)	52.9 (31.8–90.0)	<0.001
γ -GT (U/L)	42.0 (26.0–85.0)	38.9 (22.0–88.0)	71.0 (34.0–160.0)	42.4 (22.6–114.4)	66.0 (31.0–169.0)	<0.001
ALP (U/L)	110.0 (84.0–161.0)	84.0 (63.0–119.0)	121.0 (89.0–178.0)	125.5 (90.3–176.0)	125.0 (88.0–180.4)	<0.001
Neutrophil-to-lymphocyte ratio	2.1 (1.5–3.0)	4.2 (2.6–7.2)	3.7 (2.2–6.7)	2.7 (1.8–5.1)	3.2 (2.1–5.0)	<0.001
Lymphocyte-to-monocyte ratio	4.1 (3.1–5.4)	2.6 (1.7–3.9)	2.5 (1.5–3.8)	2.5 (1.5–3.7)	2.7 (1.7–4.1)	<0.001

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Gl, gastrointestinal; γ -GT, γ -glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

Table 2 Univariate and multivariate logistic regression analysis on factors associated with recompensation for patients with decompensated cirrhosis of gastrointestinal bleeding

Variables	Univariate analysis		Multivariate analysis	
	Or (95% CI)	P value	Or (95% CI)	P value
Age (years), median (IQR)	0.990 (0.983 to 0.998)	0.017	1.003 (0.988 to 1.019)	0.693
Male gender, N (%)	0.776 (0.626 to 0.962)	0.021	0.971 (0.643 to 1.466)	0.888
HBV, N (%)	0.655 (0.533 to 0.804)	<0.001	1.037 (0.565 to 1.903)	0.906
Alcohol, N (%)	0.061 (0.027 to 0.139)	<0.001	0.146 (0.048 to 0.446)	0.001
Autoimmune, N (%)	1.005 (0.611 to 1.654)	0.983		
Others or unknown, N (%)	2.445 (1.980 to 3.018)	<0.001	2.986 (1.631 to 5.466)	<0.001
Diabetes, N (%)	0.140 (0.082 to 0.240)	<0.001	0.216 (0.099 to 0.473)	<0.001
Hypertension, N (%)	0.039 (0.010 to 0.160)	<0.001	0.036 (0.006 to 0.215)	<0.001
Laboratory parameters, median (IQR)				
RBC ($10^{12}/L$)	6.511 (5.438 to 7.795)	<0.001	0.892 (0.559 to 1.425)	0.633
Haemoglobin (g/L)	1.060 (1.055 to 1.066)	<0.001	1.043 (1.030 to 1.056)	<0.001
WBC ($10^9/L$)	0.937 (0.907 to 0.967)	<0.001	0.998 (0.930 to 1.070)	0.950
PLT ($10^9/L$)	1.004 (1.002 to 1.005)	<0.001	0.999 (0.997 to 1.002)	0.716
Basophil percentage (%)	6.804 (4.763 to 9.720)	<0.001	3.447 (1.981 to 5.997)	<0.001
Eosinophil percentage (%)	1.179 (1.133 to 1.227)	<0.001	1.016 (0.959 to 1.075)	0.593
Total protein (g/L)	1.240 (1.214 to 1.266)	<0.001	1.151 (1.118 to 1.185)	<0.001
Albumin (g/L)	1.244 (1.217 to 1.272)	<0.001	1.005 (0.964 to 1.049)	0.798
Direct bilirubin ($\mu\text{mol/l}$)	0.998 (0.994 to 1.002)	0.371		
Indirect bilirubin ($\mu\text{mol/l}$)	0.999 (0.990 to 1.008)	0.845		
ALT (U/L)	0.999 (0.997 to 1.001)	0.212		
AST (U/L)	0.999 (0.998 to 1.000)	0.125		
γ -GT (U/L)	1.000 (0.999 to 1.000)	0.477		
ALP (U/L)	1.002 (1.001 to 1.004)	<0.001	1.000 (0.999 to 1.002)	0.663
Neutrophil-to-lymphocyte ratio	0.652 (0.612 to 0.695)	<0.001	0.843 (0.770 to 0.923)	<0.001
Lymphocyte-to-monocyte ratio	1.142 (1.095 to 1.191)	<0.001	0.975 (0.893 to 1.066)	0.582

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ -GT, γ -glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

gastrointestinal bleeding group, bacterial infection group, hepatic encephalopathy group and ascites group were combined, and a decision tree was employed to determine the index correlations with recompensation in patients with decompensated cirrhosis. The most relevant indicator of recompensation selected by the decision tree model was albumin, with a threshold of 40 g/L (figure 1). Total protein, haemoglobin, basophil percentage, ALT, NLR and diabetes were also selected to subsequently distinguish patients. The overall accuracy rate of the model was 0.92 (0.91–0.93), with high specificity (86.9%) and sensitivity (92.6%).

If a patient with decompensated cirrhosis has serum albumin equal to or greater than 40 g/L, total protein equal to or greater than 72 g/L, basophil percentage equal to or greater than 0.07, NLR less than 5, haemoglobin equal to or greater than 104 g/L, and has no history of diabetes, then he/she has 89% probability to

be discriminated as being recompensation. This is an example of an interpretation from figure 1.

DISCUSSION

Recompensation is a special phase of decompensated liver cirrhosis. After a period of effective treatment, the liver function can meet the patients' daily activities, and there will be no complications related to decompensated liver cirrhosis.⁴ Until now, there has been a lack of a comprehensive evaluation index to identify patients with a 'recompensation advantage.' In this study, we analysed the recompensation-related factors of different complications of decompensated liver cirrhosis and combined these factors to establish a decision tree based on the presence of several routine laboratory indicators and comorbidities. It has demonstrated that albumin, total protein, haemoglobin, basophil percentage, ALT, NLR and

Table 3 Univariate and multivariate logistic regression analysis on factors associated with recompensation for patients with decompensated cirrhosis of bacterial infection

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years), median (IQR)	0.988 (0.982 to 0.994)	<0.001	0.997 (0.985 to 1.008)	0.575
Male gender, N (%)	0.923 (0.755 to 1.129)	0.437		
HBV, N (%)	0.643 (0.529 to 0.780)	<0.001	0.698 (0.386 to 1.263)	0.235
Alcohol, N (%)	0.051 (0.023 to 0.115)	<0.001	0.129 (0.050 to 0.337)	<0.001
Autoimmune, N (%)	0.506 (0.325 to 0.789)	0.003	0.445 (0.202 to 0.979)	0.044
Others or unknown, N (%)	2.672 (2.191 to 3.260)	<0.001	1.793 (0.965 to 3.330)	0.065
Diabetes, N (%)	0.134 (0.079 to 0.227)	<0.001	0.225 (0.120 to 0.423)	<0.001
Hypertension, N (%)	0.022 (0.005 to 0.089)	<0.001	0.016 (0.004 to 0.071)	<0.001
Laboratory parameters, median (IQR)				
RBC ($10^{12}/L$)	1.000 (0.997 to 1.002)	0.816		
Haemoglobin (g/L)	1.040 (1.035 to 1.045)	<0.001	1.021 (1.014 to 1.028)	<0.001
WBC ($10^9/L$)	0.913 (0.885 to 0.942)	<0.001	0.972 (0.919 to 1.027)	0.311
PLT ($10^9/L$)	0.999 (0.998 to 1.000)	0.063		
Basophil percentage (%)	2.656 (2.086 to 3.381)	<0.001	1.752 (1.218 to 2.521)	0.003
Eosinophil percentage (%)	1.068 (1.041 to 1.097)	<0.001	1.012 (0.971 to 1.056)	0.567
Total protein (g/L)	1.159 (1.142 to 1.176)	<0.001	1.083 (1.062 to 1.104)	<0.001
Albumin (g/L)	1.267 (1.240 to 1.294)	<0.001	1.125 (1.093 to 1.158)	<0.001
Direct bilirubin ($\mu\text{mol/l}$)	0.977 (0.972 to 0.983)	<0.001	0.995 (0.989 to 1.000)	0.059
Indirect bilirubin ($\mu\text{mol/l}$)	0.974 (0.966 to 0.982)	<0.001	1.011 (0.998 to 1.024)	0.093
ALT (U/L)	0.994 (0.992 to 0.996)	<0.001	0.996 (0.992 to 0.999)	0.024
AST (U/L)	0.992 (0.990 to 0.994)	<0.001	0.999 (0.997 to 1.002)	0.532
γ -GT (U/L)	0.998 (0.997 to 0.998)	<0.001	0.999 (0.998 to 1.000)	0.110
ALP (U/L)	0.998 (0.997 to 0.999)	0.001	1.000 (0.999 to 1.002)	0.865
Neutrophil-to-lymphocyte ratio	0.723 (0.685 to 0.763)	<0.001	0.841 (0.785 to 0.901)	<0.001
Lymphocyte-to-monocyte ratio	1.004 (0.996 to 1.012)	0.322		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ -GT, γ -glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

diabetes is associated with recompensation for patients with decompensated cirrhosis. The level of albumin was the most important indicator. The algorithm generally had good accuracy with high specificity and sensitivity.

The proposed decision tree included three liver function indexes (albumin, total protein and ALT). Many studies have suggested a correlation between albumin and the prognosis of cirrhosis, with low serum albumin concentration being an important factor in the poor prognosis of cirrhosis.^{23–25} For patients with alcohol-related liver disease on the liver transplantation waiting list, model for end-stage liver disease score <20 and albumin ≥ 32 g/L at entry were found to be the optimum cut-off points for predicting withdrawal from the transplantation list after recompensation.¹¹ Long-term use of albumin has a low hospital admission rate and mortality due to tension ascites or complications, such as hepatic encephalopathy, spontaneous peritonitis, bacterial infections other than spontaneous peritonitis, renal insufficiency,

type 1 hepatorenal syndrome and side effects caused by potential diuretics, such as hyponatraemia and hyperkalaemia.^{24 25} In our study, the cut-off value of albumin was 40 g/L, which was consistent with the results of the ANSWER study and indicated that only sufficient albumin concentrations can play a protective role.²⁴ ALT is generally considered to be an indicator of liver damage due to steatosis and inflammatory responses.²⁶ Severe impairment of liver function may lead to the risk of hepatic encephalopathy.²⁷

Our study found that regardless of whether there was gastrointestinal bleeding, the level of haemoglobin in patients with decompensated liver cirrhosis was a relevant factor for recompensation. Anaemia is another factor that has been recently characterised as a predictor of poor outcomes in patients with cirrhosis, including ACLF occurrence in outpatients with liver cirrhosis, and hepatocellular carcinoma induced death.^{28–32} Bothou *et al* found that a low level of haemoglobin was a strongly

Table 4 Univariate and multivariate logistic regression analysis on factors associated with recompensation for patients with decompensated cirrhosis of hepatic encephalopathy

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years), median (IQR)	0.982 (0.963 to 1.000)	0.051		
Male gender, N (%)	0.675 (0.423 to 1.077)	0.099		
HBV, N (%)	1.105 (0.718 to 1.700)	0.650		
Alcohol, N (%)	0.028 (0.011 to 0.070)	<0.001	0.041 (0.011 to 0.146)	<0.001
Autoimmune, N (%)	1.512 (0.447 to 5.118)	0.506		
Others or unknown, N (%)	2.382 (1.503 to 3.776)	<0.001	3.139 (1.366 to 7.214)	0.007
Diabetes, N (%)	0.083 (0.042 to 0.163)	<0.001	0.101 (0.034 to 0.302)	<0.001
Hypertension, N (%)	0.015 (0.003 to 0.066)	<0.001	0.004 (0.001 to 0.027)	<0.001
Laboratory parameters, median (IQR)				
RBC (10 ¹² /L)	4.336 (3.126 to 6.014)	<0.001	0.698 (0.309 to 1.574)	0.386
Haemoglobin (g/L)	1.038 (1.030 to 1.047)	<0.001	1.027 (1.005 to 1.049)	0.016
WBC (10 ⁹ /L)	0.965 (0.900 to 1.035)	0.319		
PLT (10 ⁹ /L)	1.001 (0.998 to 1.004)	0.529		
Basophil percentage (%)	1.399 (0.750 to 2.611)	0.292		
Eosinophil percentage (%)	1.026 (0.954 to 1.103)	0.491		
Total protein (g/L)	1.183 (1.144 to 1.223)	<0.001	1.163 (1.095 to 1.234)	<0.001
Albumin (g/L)	1.249 (1.195 to 1.304)	<0.001	1.116 (1.022 to 1.219)	0.014
Direct bilirubin (µmol/L)	0.991 (0.985 to 0.996)	0.001	1.014 (0.997 to 1.031)	0.105
Indirect bilirubin (µmol/L)	0.964 (0.948 to 0.981)	<0.001	0.984 (0.954 to 1.015)	0.308
ALT (U/L)	0.998 (0.994 to 1.002)	0.440		
AST (U/L)	0.997 (0.994 to 0.999)	0.012	0.995 (0.989 to 1.000)	0.054
γ-GT (U/L)	0.999 (0.999 to 1.000)	0.161		
ALP (U/L)	0.997 (0.996 to 0.999)	0.005	0.997 (0.994 to 1.000)	0.044
Neutrophil-to-lymphocyte ratio	0.867 (0.804 to 0.935)	<0.001	0.918 (0.835 to 1.009)	0.075
Lymphocyte-to-monocyte ratio	1.517 (1.321 to 1.742)	<0.001	1.066 (0.864 to 1.315)	0.551

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, γ-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

and independent predictor of hospital admission in outpatients with decompensated liver cirrhosis.³³ The mean value of haemoglobin reported by Bothou *et al* was 134 g/L. Anaemia can predict the development of ACLF in outpatients with cirrhosis, the median value was 108 g/L.²⁹ Thus, improving anaemia is a therapeutic target for maintaining the stability of decompensated liver cirrhosis, and it is very probable that for patients with cirrhosis even mild anaemia should be treated. The pathophysiology of patients with liver cirrhosis may be related to anaemia, which leads to arterial hypotension and tachycardia, resulting in circulatory dysfunction. However, the specific mechanism needs to be investigated in future studies.

NLR is a novel indicator of systemic inflammation and has recently been reported to predict the outcome of patients with decompensated cirrhosis.^{34–36} The PREDICT study indicated that patients with stable decompensated cirrhosis had less systemic inflammation compared with

pre-ACLF patients who exhibited systemic inflammation with rapid progression (leading to the development of ACLF and death within 90 days) and unstable decompensated cirrhosis patients who were readmitted at least once during 90 days but did not progress to ACLF.²¹ Our research indicated that the NLR was markedly higher in patients with acute decompensated cirrhosis with gastrointestinal bleeding, bacterial infection and ascites compared with that in patients with recompensation. An NLR equal to or greater than five is more likely to be classified as acute decompensated liver cirrhosis. These findings clearly suggest that the systemic inflammatory response is predictive of a poor prognosis. Therefore, clinicians should pay significant attention to the prevention of infections, which could avoid secondary complications (further development of decompensation, recurrent infections, ACLF and death) of cirrhosis.³⁷

Basophils may induce and expand inflammation by producing specific cytokines and proteases and are

Table 5 Univariate and multivariate logistic regression analysis on factors associated with recompensation for patients with decompensated cirrhosis of ascites

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years), median (IQR)	0.960 (0.950 to 0.971)	<0.001	0.972 (0.957 to 0.988)	<0.001
Male gender, N (%)	1.045 (0.803 to 1.360)	0.742		
HBV, N (%)	0.836 (0.648 to 1.079)	0.169		
Alcohol, N (%)	0.069 (0.029 to 0.162)	<0.001	0.158 (0.057 to 0.437)	<0.001
Autoimmune, N (%)	0.665 (0.378 to 1.171)	0.158		
Others or unknown, N (%)	1.682 (1.297 to 2.180)	<0.001	2.167 (1.444 to 3.251)	<0.001
Diabetes, N (%)	0.125 (0.071 to 0.221)	<0.001	0.255 (0.121 to 0.538)	<0.001
Hypertension, N (%)	0.020 (0.005 to 0.084)	<0.001	0.047 (0.010 to 0.226)	<0.001
Laboratory parameters, median (IQR)				
RBC ($10^{12}/L$)	3.017 (2.485 to 3.662)	<0.001	1.017 (0.653 to 1.583)	0.942
Haemoglobin (g/L)	1.034 (1.028 to 1.040)	<0.001	1.009 (0.996 to 1.021)	0.174
WBC ($10^9/L$)	0.992 (0.977 to 1.007)	0.298		
PLT ($10^9/L$)	1.000 (0.998 to 1.002)	0.919		
Basophil percentage (%)	2.221 (1.519 to 3.246)	<0.001	1.706 (0.995 to 2.923)	0.052
Eosinophil percentage (%)	1.059 (1.012 to 1.107)	0.012	1.016 (0.950 to 1.087)	0.637
Total protein (g/L)	1.174 (1.149 to 1.200)	<0.001	1.101 (1.071 to 1.131)	<0.001
Albumin (g/L)	1.228 (1.196 to 1.262)	<0.001	1.131 (1.083 to 1.183)	<0.001
Direct bilirubin ($\mu\text{mol/l}$)	0.987 (0.982 to 0.993)	<0.001	0.998 (0.992 to 1.005)	0.611
Indirect bilirubin ($\mu\text{mol/l}$)	0.984 (0.973 to 0.996)	0.007	1.013 (0.996 to 1.031)	0.143
ALT (U/L)	0.995 (0.993 to 0.998)	<0.001	0.992 (0.985 to 0.998)	0.014
AST (U/L)	0.995 (0.992 to 0.997)	<0.001	1.004 (0.998 to 1.010)	0.171
γ -GT (U/L)	0.998 (0.997 to 0.999)	<0.001	0.999 (0.998 to 1.000)	0.060
ALP (U/L)	0.998 (0.997 to 0.999)	0.002	1.000 (0.998 to 1.002)	0.801
Neutrophil-to-lymphocyte ratio	0.773 (0.724 to 0.827)	<0.001	0.872 (0.799 to 0.951)	0.002
Lymphocyte-to-monocyte ratio	1.379 (1.279 to 1.486)	<0.001	1.019 (0.929 to 1.117)	0.693

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ -GT, γ -glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; PLT, platelet count; RBC, red blood cell count; WBC, white blood cell count.

related to T helper 2 immune responses.^{38 39} However, their role in decompensated liver cirrhosis has rarely been reported. Our study found that the increase in the basophil percentage is an evaluation index of recompensation, especially for the occurrence of gastrointestinal bleeding or bacterial infection. We speculate that basophils may regulate local and systemic inflammatory responses and shape innate and adaptive immune responses to prevent acute decompensation, but the specific mechanism needs further study.

Diabetes is closely related to complications of liver cirrhosis. Diabetes may be related to an increased risk for the existence of covert hepatic encephalopathy and the development of overt hepatic encephalopathy in patients with liver cirrhosis.⁴⁰ Uncontrolled diabetes is associated with an increased risk of infection, an enhanced propensity for renal insufficiency, and a variety of other related complications.⁴¹ Diabetes increases the risk of rehospitalisation within 30 or 90 days for patients with

decompensated cirrhosis.^{42 43} These results are in line with our study that diabetes is a risk indicator for acute decompensation, and patients with decompensated cirrhosis without diabetes are more likely to have recompensation.

The strengths of our study

As far as we know, this was the first study for including patients who did not experience acute decompensation within 1 year as recompensation. Compared with the previous study, the patient's condition was stable for a longer period of time. Furthermore, we combined logistic regression and decision tree to screen recompensation indexes, and proposed cut-off values of different indicators, which was more convenient for clinical application.

LIMITATIONS

Our study has several limitations. First, since our study of factors associated with recompensation in cirrhosis

Figure 1 Decision tree plot for identifying recompensated cirrhosis. Each node shows the percentage of patients classified and their probability of recompensation (also represented by the colours and colour intensity). The blue colour represents acute decompensated cirrhosis. The green colour represents recompensated cirrhosis. The intensity of the colour indicates the accuracy of the classification of each category, the more intense the colour, the higher the accuracy.

is unique, there were no other cohorts that could available for external validation. We will conduct a prospective study to further evaluate the effectiveness of this new model. Second, we did not compare known models, such as the Child-Turcotte-Pugh, model for end-stage liver disease, or chronic liver failure-consortium acute decompensation scores. Because our model neither includes subjective clinical symptoms, such as hepatic encephalopathy and the severity of ascites, nor indicators that cannot be detected in community hospitals, such as international normalised ratio. We only included the most widely used laboratory indicators and comorbidities. The study from the real world makes our indicators easier to apply in clinical and even community hospitals. Besides, we performed 10-fold cross-validation to reduce overfitting of the model. Third, these thresholds have not yet been validated in the external cohort. Therefore, the difference between these cut-off values may be related to the difference in the prevalence of cirrhosis among the studied populations.

CONCLUSIONS

This study showed the level of albumin, total protein, haemoglobin, basophil percentage, ALT, NLR and the history of diabetes is related to recompensation in patients with decompensated cirrhosis. The decision tree algorithm identified albumin with a threshold of 40 g/L as the indicator that most influenced the occurrence of recompensation. The knowledge of recompensated indicators may help support the development of different prevention strategies to reduce the incidence of acute decompensation.

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Data availability statement Data are available on reasonable request. The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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