



Development and Validation of CAGIB Score for Evaluating the Prognosis of Cirrhosis with Acute Gastrointestinal Bleeding: A Retrospective Multicenter Study

Zhaohui Bai · Bimin Li · Su Lin · Bang Liu · Yiling Li · Qiang Zhu ·
Yunhai Wu · Yida Yang · Shanhong Tang · Fanping Meng · Yu Chen ·
Shanshan Yuan · Lichun Shao · Xingshun Qi

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ABSTRACT

Introduction: Acute gastrointestinal bleeding (GIB) is a major cause of death in liver cirrhosis. This multicenter study aims to develop and validate a novel and easy-to-access model for predicting the prognosis of patients with cirrhosis and acute GIB.

Zhaohui Bai, Bimin Li, Su Lin, and Bang Liu contributed equally to this work.

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Z. Bai · X. Qi (✉)
Department of Gastroenterology, General Hospital of Northern Theater Command (formerly called General Hospital of Shenyang Military Area), Shenyang, China
e-mail: xingshunqi@126.com

B. Li
Department of Gastroenterology, First Affiliated Hospital of Nanchang University, Nanchang, China

S. Lin
Liver Research Center, First Affiliated Hospital of Fujian Medical University, Fuzhou, China

B. Liu
Department of Hepatobiliary Disease, 900 Hospital of the Joint Logistics Team (formerly called Fuzhou General Hospital), Fuzhou, China

Methods: Patients with cirrhosis and acute GIB were enrolled and randomly divided into the training ($n = 865$) and validation ($n = 817$) cohorts. In the training cohort, the independent predictors for in-hospital death were identified by logistic regression analyses, and then a new prognostic model (i.e., CAGIB score) was established. Area under curve (AUC) of CAGIB score was calculated by receiver operating characteristic curve analysis and compared with Child–Pugh, model for end-stage liver disease (MELD), MELD–Na, and neutrophil–lymphocyte ratio (NLR) scores.

Results: In the training cohort, hepatocellular carcinoma (HCC), diabetes, total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT),

Y. Li
Department of Gastroenterology, First Affiliated Hospital of China Medical University, Shenyang, China

Q. Zhu
Department of Gastroenterology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China

Y. Wu
Department of Critical Care Medicine, Sixth People's Hospital of Shenyang, Shenyang, China

and serum creatinine (Scr) were independent predictors of in-hospital death. CAGIB score = diabetes (yes = 1, no = 0) \times 1.040 + HCC (yes = 1, no = 0) \times 0.974 + TBIL ($\mu\text{mol/L}$) \times 0.005 – ALB (g/L) \times 0.091 + ALT (U/L) \times 0.001 + Scr ($\mu\text{mol/L}$) \times 0.012 – 3.964. In the training cohort, the AUC of CAGIB score for predicting in-hospital death was 0.829 (95% CI 0.801–0.854, $P < 0.0001$), which was higher than that of Child–Pugh (0.762, 95% CI 0.732–0.791), MELD (0.778, 95% CI 0.748–0.806), MELD-Na (0.765, 95% CI 0.735–0.793), and NLR (0.587, 95% CI 0.553–0.620) scores. In the validation cohort, the AUC of CAGIB score (0.714, 95% CI 0.682–0.746, $P = 0.0006$) remained higher than that of Child–Pugh (0.693, 95% CI 0.659–0.725), MELD (0.662, 95% CI 0.627–0.695), MELD-Na (0.660, 95% CI 0.626–0.694), and NLR (0.538, 95% CI 0.503–0.574) scores.

Conclusion: CAGIB score has a good predictive performance for prognosis of patients with cirrhosis and acute GIB.

Keywords: Child–Pugh; Cirrhosis; Gastrointestinal bleeding; MELD; Prognosis

Y. Yang

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

S. Tang

Department of Gastroenterology, General Hospital of Western Theater Command, Chengdu, China

F. Meng

Department of Biological Therapy, Fifth Medical Center of PLA General Hospital, Beijing, China

Y. Chen

Difficult and Complicated Liver Diseases and Artificial Liver Center, Beijing Youan Hospital, Capital Medical University, Beijing, China

S. Yuan

Department of Gastroenterology, Xi'an Central Hospital, Xi'an, China

L. Shao

Department of Gastroenterology, Air Force Hospital of Northern Theater Command, Shenyang, China

Abbreviations

AKP	Alkaline phosphatase
ALB	Albumin
ALT	Alanine aminotransferase
AUC	Area under curve
CAGIB	Cirrhosis acute gastrointestinal bleeding
CI	Confidence intervals
GBS	Glasgow–Blatchford score
GGT	Gamma-glutamyl transpeptidase
GIB	Gastrointestinal bleeding
Hb	Hemoglobin
HCC	Hepatocellular carcinoma
HCT	Hematocrit
HE	Hepatic encephalopathy
INR	International normalized ratio
K	Potassium
MELD	Model for end-stage liver disease
Na	Sodium
NLR	Neutrophil–lymphocyte ratio
ORs	Odds ratios
PLT	Platelet
Scr	Serum creatinine
TBIL	Total bilirubin
WBC	White blood cell

INTRODUCTION

Acute gastrointestinal bleeding (GIB) is an emergency and critical clinical event [1]. The mortality of acute GIB is 6–20% in patients with cirrhosis [2–4]. The prognosis seems to be similar between patients with cirrhosis and acute variceal bleeding and those with cirrhosis and peptic ulcer bleeding [5]. It is important to accurately evaluate the prognosis in patients with cirrhosis and acute GIB. Conventional scoring systems for assessing the prognosis of patients with acute GIB mainly include Rockall score [6], Glasgow–Blatchford score (GBS) [7], and AIMS65 score [8]. However, they are not specific for patients with cirrhosis in whom gastroesophageal varices are the most frequent sources of acute GIB [9] and the severity of liver dysfunction is closely associated with patients' outcomes. On the other hand, Child–Pugh [10], model for end-stage liver disease (MELD) [11], MELD-Na [12], and neutrophil–lymphocyte

ratio (NLR) [13] scores have been widely employed for prognostic assessment in general patients with liver cirrhosis. But their predictive performances remain suboptimal in patients with cirrhosis and acute GIB.

The present work aimed to develop and validate a novel model for assessing the prognosis of patients with cirrhosis and acute GIB on the basis of the data obtained from a multicenter study.

METHODS

The present study was based on the TORCH study (NCT03846180), which was an investigator-initiated multicenter study across 13 centers from eight provinces or municipalities in China. It was carried out following the rules of the Declaration of Helsinki and was approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command (formerly General Hospital of Shenyang Military Area), which is the principal affiliation of this study. The ethical approval number was k (2019) 20. The requirement for informed written consent was waived because of the nature of this study. Briefly, we enrolled the patients with cirrhosis who were admitted because of acute GIB from January 2010 to December 2018. Age, gender, and comorbidities were not limited.

The following data were collected: age; gender; etiology of liver cirrhosis; history of GIB, diabetes, and hepatocellular carcinoma (HCC); ascites; hepatic encephalopathy (HE); and laboratory tests at admission, mainly including hemoglobin (Hb), hematocrit (HCT), white blood cell (WBC), platelet (PLT), total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), alkaline phosphatase (AKP), gamma-glutamyl transpeptidase (GGT), serum creatinine (Scr), potassium (K), sodium (Na), and international normalized ratio (INR); and in-hospital death. Child–Pugh [10], MELD [11], MELD-Na [12], and NLR [13] scores were calculated.

Random sampling was used to divide patients into training and validation cohorts with an approximate percentage of 50%. Continuous variables were expressed as mean \pm standard deviation and median (range), and categorical variables were expressed as frequency

(percentage). Difference between training and validation cohorts was compared by the non-parametric Mann–Whitney *U* test and the chi-square test. In the training cohort, logistic regression analyses were performed to identify the independent predictors associated with in-hospital death. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. An equation for predicting the death of patients with cirrhosis and acute GIB was established by merging the independent predictors with their regression coefficients. Then, receiver operating characteristic curve (ROC) analysis was performed to evaluate the predictive performance of the new equation. The area under curve (AUC) and the best cutoff value with sensitivity and specificity were calculated. The predictive performance of the new equation was also compared with other established scores (Child–Pugh [10], MELD [11], MELD-Na [12], and NLR [13] scores). All statistical analyses were performed using SPSS software version 20.0 (IBM Corp, Armonk, NY, USA) and MedCalc software version 11.4.2.0 (MedCalc Software, Mariakerke, Belgium). $P < 0.05$ was considered statistically significant.

RESULTS

Patient Selection

A total of 1682 patients with cirrhosis and acute GIB were included, of whom 865 and 817 patients were enrolled into the training and validation cohorts, respectively. Characteristics of patients are summarized in Table 1. All but the percentage of HCC were not statistically significantly different between the training and validation cohorts (Table 1).

Univariate and Multivariate Analyses in the Training Cohort

Univariate logistic regression analyses demonstrated that HCC, diabetes, hepatic C virus infection, ascites, HE, WBC, TBIL, ALB, ALT, Scr, and INR were significantly associated with in-hospital death (Table 2). Multivariate logistic regression analyses showed that HCC, diabetes,

Table 1 Characteristics of patients in training and validation cohorts

Variables	No. pts	Training cohort	No. pts	Validation cohort	<i>P</i> value
Age (years)	865	56.00 (20.00–88.00)	817	57.00 (18.00–91.00)	0.1410
		56.19 ± 12.31		57.06 ± 12.06	
Sex (male) (%)	865	615 (71.10%)	817	568 (69.50%)	0.4800
Hepatic B virus (%)	865	442 (51.10%)	817	433 (53.00%)	0.4360
Hepatic C virus (%)	865	60 (6.90%)	817	48 (5.90%)	0.3750
Alcohol abuse (%)	865	221 (25.50%)	817	199 (24.40%)	0.5730
Autoimmune liver diseases (%)	865	47 (5.40%)	817	35 (4.30%)	0.2740
History of GIB (%)	865	482 (55.70%)	817	461 (56.40%)	0.7710
History of diabetes (%)	865	164 (19.00%)	817	166 (20.30%)	0.4830
Hepatocellular carcinoma (%)	865	127 (14.70%)	817	153 (18.70%)	0.0260*
Ascites (%)	865	452 (55.30%)	817	513 (59.30%)	0.0990
Hepatic encephalopathy (%)	865	36 (4.20%)	817	40 (4.90%)	0.4690
Hemoglobin (g/L)	865	76.00 (16.00–152.00)	816	76.00 (23.00–170.00)	0.5090
		79.11 ± 24.60		78.21 ± 24.08	
Hematocrit (%)	865	23.60 (2.74–45.90)	814	23.40 (8.70–47.00)	0.3380
		24.29 ± 6.93		23.95 ± 6.78	
White blood cell (10 ⁹ /L)	865	5.81 (0.98–68.00)	815	5.63 (0.74–51.00)	0.3360
		6.75 ± 4.73		6.69 ± 4.80	
Platelet (10 ⁹ /L)	865	77.00 (4.00–827.00)	814	77.00 (2.00–846.00)	0.4890
		88.93 ± 61.38		95.42 ± 83.36	
Total bilirubin (μmol/L)	863	23.70 (4.20–518.00)	816	22.80 (2.40–449.00)	0.0680
		38.03 ± 51.14		34.01 ± 42.19	
Albumin (g/L)	846	29.00 (11.70–49.80)	797	28.80 (10.10–47.20)	0.2160
		29.07 ± 5.98		28.64 ± 5.90	
Alanine aminotransferase (U/L)	862	28.00 (3.00–2651.00)	815	26.00 (4.00–1575.00)	0.0880
		52.21 ± 147.23		41.51 ± 86.36	
Aspartate aminotransferase (U/L)	804	37.00 (6.00–3182.00)	768	35.14 (6.00–1993.00)	0.2770
		78.33 ± 216.66		64.46 ± 120.45	
Alkaline phosphatase (U/L)	843	79.78 (18.00–2344.00)	782	80.00 (18.90–1320.00)	0.3730
		110.71 ± 122.35		104.32 ± 95.26	
Gamma-glutamyl transpeptidase (U/L)	840	39.20 (2.80–2996.00)	781	41.00 (5.00–1494.90)	0.5520
		93.36 ± 190.59		85.74 ± 132.51	

Table 1 continued

Variables	No. pts	Training cohort	No. pts	Validation cohort	P value
Serum creatinine (μmol/L)	865	65.50 (7.00–372.80) 70.96 ± 31.13	817	65.00 (11.20–303.00) 70.99 ± 30.20	0.6680
Potassium (mmol/L)	864	4.10 (2.25–6.71) 4.18 ± 0.63	815	4.10 (1.85–7.37) 4.21 ± 0.69	0.4830
Sodium (mmol/L)	860	137.95 (115.00–153.90) 137.08 ± 4.69	816	137.85 (105.00–161.60) 137.19 ± 5.23	0.6360
International normalized ratio	860	1.35 (0.79–7.96) 1.45 ± 0.42	804	1.34 (0.91–4.99) 1.43 ± 0.37	0.3480
Child–Pugh score	841	8.00 (5.00–15.00) 7.91 ± 1.81	784	8.00 (5.00–13.00) 7.82 ± 1.78	0.4670
MELD score	858	7.99 (– 13.30 to 38.79) 8.85 ± 5.91	803	7.75 (– 8.13 to 33.49) 8.45 ± 5.53	0.3940
NLR score	864	5.07 (0.40–72.92) 6.36 ± 5.33	812	4.86 (0.51–179.80) 6.41 ± 7.73	0.4350
In-hospital death (%)	865	29 (3.40%)	817	23 (2.80%)	0.5240

Pts patients, *GIB* gastrointestinal bleeding, *MELD* model for end-stage liver disease, *NLR* neutrophil to lymphocyte ratio
 *Statistically significant at $P < 0.05$

TBIL, ALB, ALT, and Scr were independently associated with in-hospital death (Table 2).

($P = 0.0001$), but not between CAGIB and Child–Pugh, MELD, or MELD-Na score.

Development of CAGIB Score

A prognostic model called CAGIB (Cirrhosis Acute GastroIntestinal Bleeding) was established. $CAGIB = Diabetes (yes = 1, no = 0) \times 1.040 + HCC (yes = 1, no = 0) \times 0.974 + TBIL (\mu mol/L) \times 0.005 - ALB (g/L) \times 0.091 + ALT (U/L) \times 0.001 + Scr (\mu mol/L) \times 0.012 - 3.964$. It had an AUC of 0.829 (95% CI 0.801–0.854, $P < 0.0001$), and its best cutoff value was greater than $- 4.6646$ with a sensitivity of 78.57% and a specificity of 75.52% (Fig. 1). The AUCs of Child–Pugh, MELD, MELD-Na, and NLR scores were 0.762 (95% CI 0.732–0.791), 0.778 (95% CI 0.748–0.806), 0.765 (95% CI 0.735–0.793), and 0.587 (95% CI 0.553–0.620), respectively (Fig. 2). The difference was statistically significant between CAGIB and NLR score

Validation of CAGIB Score

In the validation cohort, the CAGIB score had an AUC of 0.714 (95% CI 0.682–0.746, $P = 0.0006$) (Fig. 3). The AUCs of Child–Pugh, MELD, MELD-Na, and NLR scores were 0.693 (95% CI 0.659–0.725), 0.662 (95% CI 0.627–0.695), 0.660 (95% CI 0.626–0.694), and 0.538 (95% CI 0.503–0.574), respectively (Fig. 4). The difference was statistically significant between CAGIB and NLR score ($P = 0.0165$), but not between CAGIB and Child–Pugh, MELD, or MELD-Na score.

DISCUSSION

Our study developed a new model (CAGIB score) for assessing the prognosis of patients

Table 2 Univariate and multivariate analyses of predictors associated with the in-hospital mortality of acute GIB in training cohort

Variables	No. pts (all = 865)	Univariate			Multivariate		
		OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Age (years)	865	1.029	0.998–1.061	0.0670			
Sex (female vs. male)	865	1.288	0.543–3.054	0.5660			
Hepatic B virus (yes vs. no)	865	1.124	0.536–2.358	0.7570			
Hepatic C virus (yes vs. no)	865	3.778	1.476–9.670	0.0060*	2.794	0.917–8.512	0.0710
Alcohol abuse (yes vs. no)	865	1.325	0.594–2.954	0.4920			
Autoimmune (yes vs. no)	865	1.630	0.217–12.250	0.6800			
History of GIB (yes vs. no)	865	1.573	0.747–3.311	0.2330			
History of diabetes (yes vs. no)	865	2.728	1.263–5.894	0.0110*	2.824	1.127–7.079	0.0270*
Hepatocellular carcinoma (yes vs. no)	865	2.738	1.218–6.158	0.0150*	2.647	1.022–6.859	0.0450*
Ascites (yes vs. no)	865	2.707	1.091–6.718	0.0320*	1.995	0.713–5.586	0.1880
Hepatic encephalopathy (yes vs. no)	865	4.020	1.321–12.235	0.0140*	2.147	0.562–8.210	0.2640
Hemoglobin (g/L)	865	0.995	0.980–1.011	0.5280			
Hematocrit (%)	865	0.965	0.912–1.020	0.2040			
White blood cell ($10^9/L$)	865	1.054	1.005–1.104	0.0290*	1.020	0.964–1.078	0.5000
Platelet ($10^9/L$)	865	1.003	0.999–1.007	0.1580			
Total bilirubin ($\mu\text{mol/L}$)	863	1.008	1.004–1.011	< 0.0001*	1.005	1.001–1.009	0.0200*
Albumin (g/L)	846	0.874	0.815–0.936	< 0.0001*	0.912	0.840–0.989	0.0260*
Alanine aminotransferase (U/L)	862	1.002	1.001–1.003	0.0040*	1.001	1.000–1.002	0.0490*
Aspartate aminotransferase (U/L) ^b	804	1.001	1.000–1.002	0.0060*			
Alkaline phosphatase (U/L)	843	1.001	1.000–1.003	0.0750			
Gamma-glutamyl transpeptidase (U/L)	840	1.000	0.999–1.002	0.6560			
Serum creatinine ($\mu\text{mol/L}$)	865	1.012	1.005–1.018	< 0.0001*	1.012	1.004–1.020	0.0040*
Potassium (mmol/L)	864	1.323	0.765–2.289	0.3160			
Sodium (mmol/L)	860	0.940	0.877–1.007	0.0790			
International normalized ratio	860	2.320	1.310–4.110	0.0040*	1.311	0.737–2.335	0.3570
Child–Pugh score ^a	841	1.652	1.358–2.009	< 0.0001*			
MELD score ^a	858	1.149	1.095–1.205	< 0.0001*			

Table 2 continued

Variables	No. pts (all = 865)	Univariate			Multivariate		
		OR	95% CI	P value	OR	95% CI	P value
NLR score ^a	864	1.042	0.998–1.088	0.0640			

Pts patients, *GIB* gastrointestinal bleeding, *MELD* model for end-stage liver disease, *NLR* neutrophil to lymphocyte ratio

^aStatistically significant at $P < 0.05$

^a Child–Pugh score, MELD score, and NLR score are complex variables composed of many clinically significant variables, so they were not included in the multivariate analysis

^b Aspartate aminotransferase and alanine aminotransferase had a potential collinearity for assessing liver dysfunction, so we excluded the aspartate aminotransferase in multivariate analysis

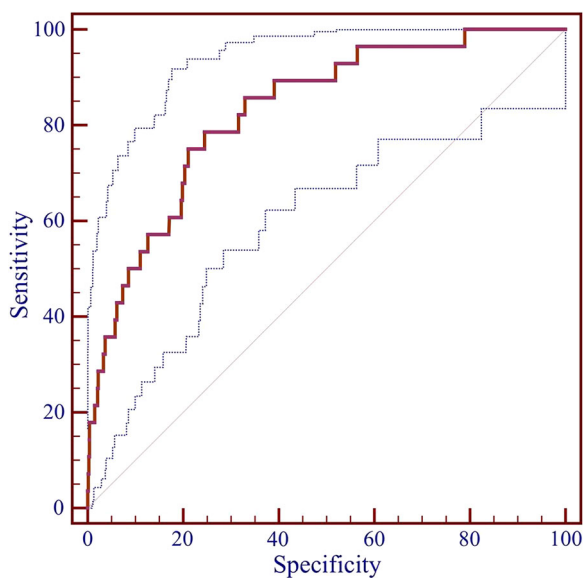


Fig. 1 ROC curve of CAGIB score for predicting the in-hospital death of patients with cirrhosis and acute GIB in the training cohort

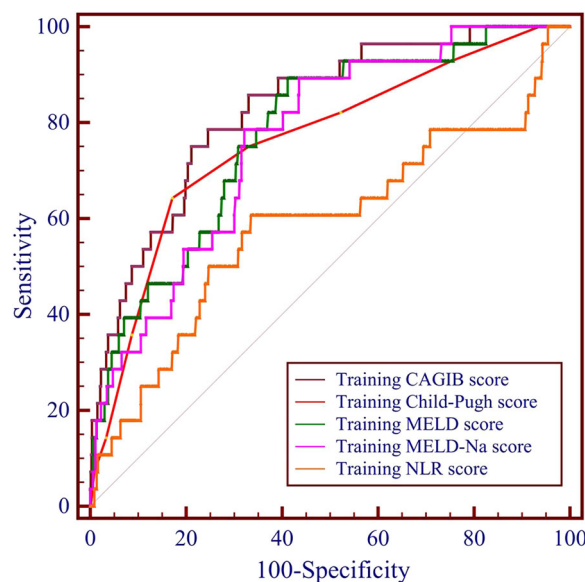


Fig. 2 Comparison of predictive performance of CAGIB score with Child–Pugh, MELD, MELD-Na and NLR scores in the training cohort. Brown line refers to the CAGIB score, red line refers to the Child–Pugh score, green line refers to the MELD score, purple line refers to the MELD-Na score, and orange line refers to the NLR score

with cirrhosis and acute GIB. Our study has the following notable features: (1) the data was obtained from multiple institutions in China; (2) a large number of patients were included; (3) the variables used for this model were readily available in clinical practice; (4) CAGIB score had a greater predictive performance than other conventional models in both training and validation cohorts; and (5) the predictive performance of CAGIB score was further validated.

CAGIB score includes two clinical variables (i.e., diabetes and HCC). Diabetes is a worldwide pandemic with a prevalence of 9.4% in the USA [14] and 11.6% in China [15]. Increasing

evidence suggests a close relationship between diabetes and outcomes of liver disease. Diabetes increased the risks of liver cancer and chronic liver diseases [16–18] and was also associated with an increased risk of mortality in patients with cirrhosis [19]. Our previous single-center study also showed that diabetes was significantly associated with the prognosis of patients with cirrhosis and acute upper GIB, which is consistent with our current study [20]. On the other hand, HCC is one of the most common

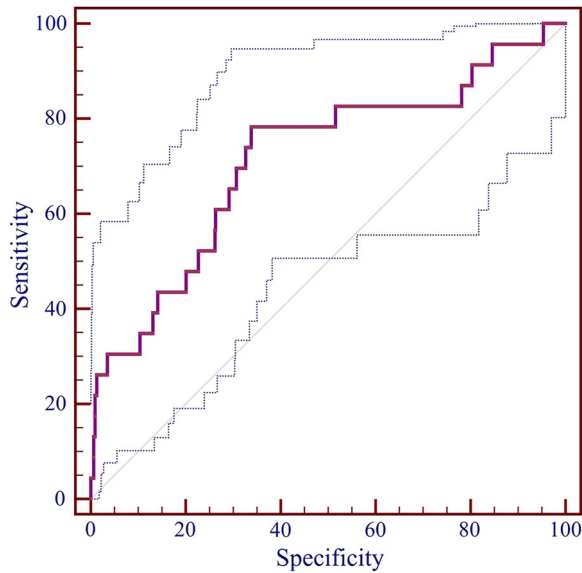


Fig. 3 ROC curve of CAGIB score for predicting the in-hospital death of patients with cirrhosis and acute GIB in the validation cohort

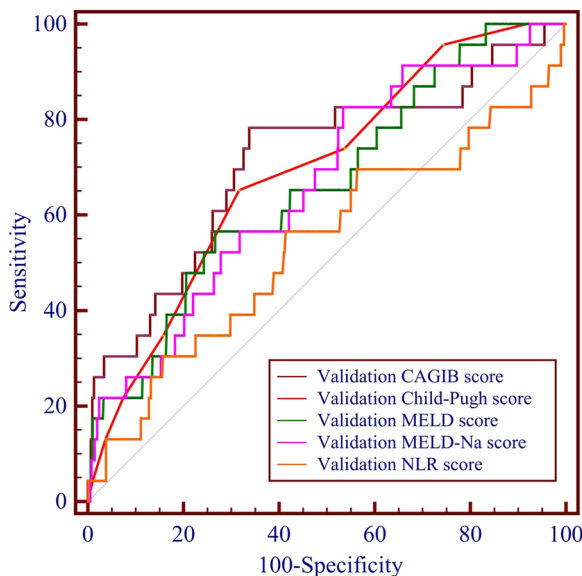


Fig. 4 Comparison of predictive performance of CAGIB score with Child–Pugh, MELD, MELD–Na and NLR scores in the validation cohort. Brown line refers to the CAGIB score, red line refers to the Child–Pugh score, green line refers to the MELD score, purple line refers to the MELD–Na score, and orange line refers to the NLR score

causes of cancer-related death [21]. And 80% of HCC patients have liver cirrhosis [22]. HCC can further aggravate portal pressure due to tumor

compression and tumor thrombus formation and is considered as the independent predictor of death and re-bleeding in patients with cirrhosis and GIB [9, 23–25].

CAGIB score also includes four laboratory variables (i.e., TBIL, ALB, Scr, and ALT). Inclusion of TBIL, ALB, and Scr into this new model is easily understood, because they are important components of conventional scoring systems (i.e., MELD and Child–Pugh scores). Notably, a rapid increase in Scr level is often an acute critical condition indicating decreased kidney perfusion in patients with cirrhosis developing an acute GIB episode. Indeed, regardless of acute GIB, renal failure increases the mortality sevenfold in patients with cirrhosis [26]. In patients with cirrhosis and acute GIB, acute kidney injury is also an independent predictor for death [5, 27]. Besides, our study found that an increased ALT level was another independent predictor. In patients with cirrhosis and massive GIB, nearly all organs, including liver, are in an ischemic state after acute blood loss [28]. Hypoxic hepatitis, which is characterized by a rapid rise in serum aminotransferases due to liver cell necrosis by mitochondrial damage and DNA fragmentation [29], can be frequently observed in patients with cirrhosis and variceal bleeding [30] and negatively influence the patients' outcomes [31].

A major limitation was that CAGIB score could not be compared with conventional scoring systems for GIB, such as Rockall, GBS, and AIMS65 scores, because not all patients underwent endoscopy. Second, for some patients, the source of GIB was unclear due to lack of the relevant endoscopy data. Thus, the association of sources of acute GIB with the mortality was not explored in the current study. Third, the stage of HCC was not extracted in our study. Fourth, the potential heterogeneity in the treatment selection among the participating centers should be acknowledged.

CONCLUSIONS

We developed and validated the CAGIB score to predict the in-hospital death of patients with cirrhosis and acute GIB. A CAGIB score of greater than -4.6646 suggested a high risk of

in-hospital death in liver cirrhosis with acute GIB. On the basis of the CAGIB score, physicians may also pay attention to the management of diabetes, improvement of liver and renal function, and supplementation of human albumin solution for patients with cirrhosis and acute GIB.

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Authorship Contributions. Zhaohui Bai: collected the data, analyzed the data, performed the statistical analysis, and drafted manuscript. Bimin Li, Su Lin, Bang Liu, Yiling Li, Qiang Zhu, Yunhai Wu, Yida Yang, Shanhong Tang, Fanping Meng, Yu Chen, Shanshan Yuan, and Lichun Shao: collected the data, analyzed the data, and gave critical comments. Xingshun Qi: conceived the work, wrote the study protocol, reviewed the literature, gave critical comments, and revised the manuscript. All authors reviewed and approved the paper.

Disclosures. All authors, including Zhaohui Bai, Bimin Li, Su Lin, Bang Liu, Yiling Li, Qiang Zhu, Yunhai Wu, Yida Yang, Shanhong Tang, Fanping Meng, Yu Chen, Shanshan Yuan, Lichun Shao, and Xingshun Qi, have nothing to disclose.

Compliance with Ethics Guidelines. The present study was carried out following the rules of the Declaration of Helsinki and approved by the Medical Ethical Committee of the General Hospital of Northern Theater Command (formerly General Hospital of Shenyang Military Area), which is the principal affiliation of this

study. The ethical approval number was k(2019) 20. Considering the nature of this observational study, the patients' written informed consent was waived by the ethics committee.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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