Original Article

Development and validation of a nomogram for predicting varices needing treatment in compensated advanced chronic liver disease: A multicenter study

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Abstract

Background: Only a small proportion of patients with compensated advanced chronic liver disease (cACLD) had varices needing treatment (VNT) after recommended esophagogastroduodenoscopy (EGD) screening. We aimed to create a non-invasive nomogram based on routine tests to detect VNT in cACLD patients.

Methods: The training cohort included 162 cACLD patients undergoing EGD in a university hospital, between January 2014 and September 2019. A nomogram was developed based on the independent predictors of VNT, selected using a multivariate logistic regression analysis. Thirty-three patients from eight university hospitals were prospectively enrolled as validation cohort between December 2018 and December 2019.

Results: The prevalence of VNT was 32.7% (53/162) and 39.4% (13/33) in training and validation cohorts, respectively. The univariate analysis identified six risk factors for VNT. On the multivariate analysis, four of them, i.e., gallbladder wall thickness (odds ratio [OR]: 1.23; 95% confidence interval [CI]: 0.98-1.56), spleen diameter (OR: 1.02; 95% CI: 1.00-1.04), platelet count (OR: 0.98; 95% CI: 0.97-0.99), and international normalized ratio (OR: 0.58; 95% CI: 0.06-5.84) were independently associated with VNT. Thus, a nomogram based on the four above - mentioned variables was developed, and showed a favorable performance for detecting VNT, with an area under receiver operating characteristic curve of 0.848 (95% CI: 0.769-0.927) in training cohort. By applying a cut-off value of 105 in validation cohort, 31.0% of EGD were safely spared with 3.4% of missed VNT.

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Conclusion: A nomogram based on routine clinical parameters was developed for detecting VNT and avoiding unnecessary EGD in cACLD patients.

Keywords: Compensated advanced chronic liver disease, esophagogastroduodenoscopy, nomogram, non-invasive, varices needing treatment

INTRODUCTION

The presence of gastroesophageal varices (GEV) is a frequent manifestation in patients with compensated advanced chronic liver disease (cACLD), developing at a rate of 7-8% per year.[1-4] Patients with GEV will progress from small to large varices and even experience variceal hemorrhage (VH).[1,2,5] Despite advances of therapies, the 6-week mortality of patients with VH is still as high as 15-25%.[1]

As VH risk depends on the size of the GEV and presence of red signs,[2,6] Esophagogastroduodenoscopy (EGD) screening is recommended for cirrhosis with 2-3-year intervals in patients without GEV, and 1-2-year intervals in patients with small GEV.[1,2,7,8] Once diagnosed with varices needing treatment (VNT), primary prophylaxis is needed.[1,2,9,10] Considering the huge burden of liver disease globally,[11] regular EGD screening for patients with cACLD may lead to high costs and low compliance, due to the invasiveness and lower tolerance of EGD.[1,2,12,13] Therefore, there is an urgent need to develop non-invasive models to identify patients with VNT and reduce the burden of unnecessary EGDs.[1,2,10,14,15] The study aimed to develop and validate a nomogram based on routine clinical features to identify VNT in patients with cACLD.

METHODS

Study population and design

This multicenter study included patients with cACLD from nine university hospitals in China. The training cohort enrolled eligible patients consecutively from Xingtai People's Hospital (Xingtai City, China), between January 2014 and September 2019. An external validation cohort of eligible patients was recruited from a prospective study (CHESS1801, Clinical Trials.gov identifier: NCT03749954) involving eight university hospitals (The Seventh Medical Center of PLA General Hospital, Beijing; Zhujiang Hospital, Guangzhou; The Second Affiliated Hospital of Baotou Medical College, Baotou; The First Hospital of Lanzhou University, Lanzhou; Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou; Tongji Hospital of Tongji University, Shanghai; Guangdong Second Provincial General Hospital, Guangzhou; The Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou). Data including clinical characteristics, laboratory parameters, abdominal doppler ultrasound findings, liver stiffness measurement (LSM) and EGD were collected. This study was conducted in accordance with the provisions of the Declaration of Helsinki and was approved by the institutional review boards of the involved centers. All participants provided written informed consent.

The inclusion criteria were: (a) age 18-75 years; (b) confirmed liver cirrhosis based on biopsy or clinical findings; (c) absence of previous decompensating events, including ascites, VH, hepatic encephalopathy or jaundice; (d) the interval between EGD and routine laboratory tests, abdominal ultrasound and LSM was within 90 days; and (e) with written informed consent. The exclusion criteria were: (a) prior splenectomy or cholecystectomy surgery; (b) history of inflammatory cholecystitis, severe cardiovascular or kidney disease; (c) coexistence of malignancies including hepatocellular carcinoma; (d) under non-selective beta-blockers treatment; and (e) pregnant women.

Laboratory parameters

Laboratory assessments included platelet count (PLT), albumin, total bilirubin, international normalized ratio (INR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and prothrombin time. Child-Pugh score was calculated as previously described.[6]

Doppler ultrasound procedure

Abdominal Doppler ultrasound was performed by two experienced sonographers. Patients fasted for 8 hours before ultrasound, and all measurements were conducted with the participants lying supine and breathing normally by using a 3.5-MHz transducer (LOGIQ S7 Expert Ultrasound System, GE Healthcare, Fairfield, CT; LOGIQ S8 Ultrasound System, GE Healthcare, Fairfield, CT; HD 15 Ultrasound System, Philips Healthcare, Reedsville, PA; iU22 Ultrasound System, Philips Healthcare, Reedsville, PA). The gallbladder wall thickness (GBWT) was measured as previously described.[16] Spleen diameter (SD) was defined as the maximum spleen bipolar diameter.[17] Portal vein diameter (PV) was defined as the maximum diameter of PV in hepatic hilum.[18] All measurements were performed in triplicate, and then averaged, expressing the results in millimeters (mm).

Liver stiffness measurement

LSM was conducted with FibroScan® (Echosens, Paris, France) in a fasting state. LSM values were obtained as previously described and expressed in kilopascals (kPa).[19] LSM required at least 10 successful measurements, and then, the median value was taken as representative. The reliable criteria was defined as at least 10 measurements with an interquartile range (IQR)/median ≤30%.[20]

Calculation of non-invasive indicators

The non-invasive indicators were calculated according to formulas: AST-to-ALT ratio (AAR) = AST (U/L) / ALT (U/L); AST-to-PLT ratio index (APRI) = [(AST / upper limit of normal) × 100] / PLT ($\times 10^9$/L); PLT-to-SD ratio (PSR) = PLT ($\times 10^9$/L) × 100/SD (mm); The Baveno VI criteria was defined as follows: LSM <20 kPa and PLT >150,000 /mm^3.[2,21-23]

EGD procedure

VNT were defined as large varices (diameter >5 mm), or small varices (diameter <5 mm) with red sign, and non-VNT were defined as no varices or small varices without red signs.[2,7,10] Patients were accordingly classified as VNT group or non-VNT group by experienced endoscopists.

Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median (interquartile range), and compared using unpaired two-tailed Student's t-test, or the Kruskal–Wallis test, as appropriate. Categorical data were expressed as numbers (percentages), and compared using the c2 test or the Fisher's exact test as appropriate. Univariate logistic regression analysis was used to identify the risk factors for VNT. All variables associated with VNT at a significant level were included into a multivariate logistic model. Backward elimination was done to remove uninformative variables from the model, based on the lowest Akaike information criterion. A nomogram was formulated based on the results of multivariate logistic regression analysis, using the "rms" package of R Language (version 3.5.3, *http://www.r-project.org/*). The best nomogram cut-off was calculated to maximally rule out patients with VNT (corresponding to a low risk [< 5%] of missed VNT).[22] Receiver operating characteristic curve (ROC) was used to evaluate the discrimination of the model. The diagnostic performance of the model was assessed using the area under ROC curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive values. $P < 0.05$ was considered as statistically significant. All analyses were performed using the R Language software (version 3.5.3, http://www.r-project.org/).

RESULTS

Patient characteristics

For the training cohort, 283 eligible patients were screened, of whom 121 were excluded. A total of 162 patients (107 males, mean age 52 years; age range 24-78 years) were included in the final analysis [Figure 1]. For the validation cohort, 33 eligible participants (27 males, mean age 52 years; age range 35-74 years) were collected from 8 external university hospitals [Figure 1]. VNT were observed in 67 (34.4%) of 195 patients, of whom 53 (32.7%) and 14 (42.4%) were in the training and validation cohort, respectively. Hepatitis B-related cirrhosis

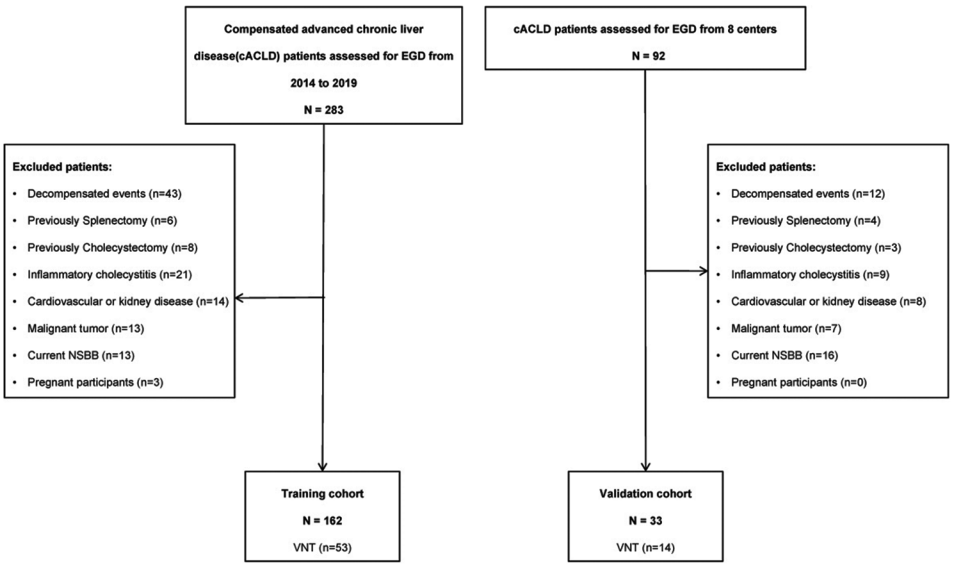

Figure 1: Flow chart of patient enrollment

Table 1: Baseline characteristics of the included patients

Variable	*n*	Overall	Training	Validation
Age (in years)	195	51.8±10.9	51.8±11.4	52.1±8.15
Gender	195			
Male		134 (68.7%)	107 (66.0%)	27 (81.8%)
Female		61 (31.3%)	55 (34.0%)	6 (18.2%)
Body mass index	152	24.1 (21.9-26.1)	23.7 (21.6-26.0)	24.4 (22.9-26.1)
Etiology				
Hepatitis B virus	195	139 (71.3%)	117 (72.2%)	22 (66.7%)
Hepatitis C virus		7 (3.59%)	5 (3.09%)	2 (6.06%)
Primary biliary cirrhosis		4 (2.05%)	2 (1.23%)	2 (6.06%)
Alcohol		5 (2.56%)	0 (0.00%)	5 (15.2%)
Other		40 (20.5%)	38 (23.5%)	2 (6.06%)
Child-Pugh class				
A	168	135 (80.4%)	106 (78.5%)	29 (87.9%)
B		33 (19.6%)	29 (21.5%)	4 (12.1%)
Alanine aminotransferase, U/L		34.5 (23.0-64.0)	37.0 (24.5-69.0)	24.0 (17.0-46.1)
Aspartate aminotransferase, U/L	156	39.0 (26.0-70.0)	41.0 (26.0-79.0)	32.0 (26.0-53.6)
Albumin, g/L	170	39.0 (36.0-43.8)	40.1 (36.1-44.1)	37.0 (33.0-39.4)
Total bilirubin, μmol/L	169	22.5 (16.5-35.6)	24.6 (17.1-41.0)	17.8 (11.3-21.3)
Prothrombin time, s	168	12.3 (11.4-13.7)	12.0 (11.2-13.4)	13.6 (12.7-15.5)
International normalized ratio	167	1.14 (1.05-1.26)	1.15 (1.05-1.27)	1.11 (1.03-1.25)
Platelet count, ×10^9/L	163	96.5 (65.5-137)	89.0 (63.0-132)	116 (75.0-161)
Gallbladder wall thickness, mm	168	4.00 (2.50-5.60)	4.00 (2.32-5.75)	4.20 (3.00-5.50)
Spleen diameter, mm	195	120 (101-141)	120 (97.2-140)	121 (108-152)
Portal vein diameter, mm	192	12.0 (10.0-14.0)	12.0 (10.0-14.0)	11.2 (10.2-13.2)
Liver stiffness measurement, kPa	72	12.1 (9.07-19.3)	11.6 (8.70-17.4)	12.1 (9.50-22.2)

n, number

was found in 133 (82.1%) patients in the training cohort and in 22 (66.7%) patients in the validation cohort. Baseline characteristics are summarized in Table 1.

Risk factors for VNT

In the training cohort, PLT (odds ratio [OR]: 0.975; 95% confidence interval [CI]: 0.964 -0.986, $P < 0.001$), INR (OR: 11.353; 95% CI: 1.812-71.131, $P = 0.009$), SD (OR: 0.975; 95% CI: 0.964-0.986, $P < 0.001$), PV diameter (OR: 0.975; 95% CI: 0.964-0.986, $P < 0.001$), and GBWT (OR: 0.975; 95% CI: 0.964-0.986, $P < 0.001$) showed significant association with VNT [Table 2]. On multivariate analysis, with results reported as OR (95% CI), GBWT (1.23 [0.98-1.56]), SD (1.02 [1.00-1.04]), PLT (0.98 [0.97-0.99]), and INR (0.58 [0.06-5.84]) were obviously associated with VNT [Table 3]. A nomogram for individual risk estimation of VNT was built based on the multivariate logistic regression model in the training cohort [Figure 2a].

Performance of nomogram

After excluding patients without key data, such as ALT, AST, INR, PLT, PT, we included 110 patients for further analysis in the training cohort. The nomogram demonstrated a good accuracy in predicting VNT, with an AUC of 0.848 (95% CI, 0.769-0.927, Figure 2b). According to the ROC curves of the nomogram, the best cut-off was a score of 105. By applying the cut-off value, the nomogram showed a favorable predictive performance for VNT detection with sensitivity, specificity,

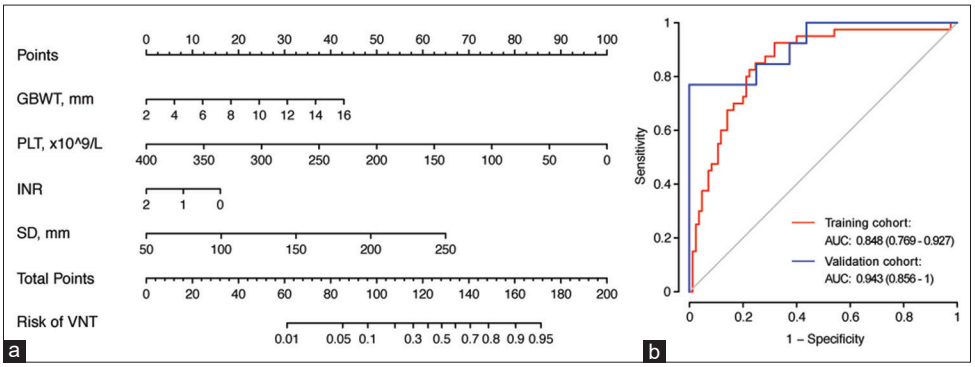

Figure 2: Nomogram to predict the presence of VNT. (a) The nomogram maps the predicted risk of VNT on a scale of 0-200. For each factor, a vertical line is drawn upwards to note down the corresponding points (i.e., PLT 200 × 10^9/L = 50 points). This is repeated for each factor ending with a total score that corresponds to a predicted probability of VNT at the bottom of the nomogram. (b) ROC curves of the nomogram in estimating the presence of VNT in the training cohort ($n = 110$) and the validation cohort ($n = 28$). VNT- varices needing treatment; ROC-receiver operating characteristic; AUC-area under ROC curve

Table 2: Performance of non-invasive markers for prediction of VNT in the training cohort

Variable	*n*	AUC	OR	95%CI	*P*
Age (in years)	162	0.519	0.998	0.969-1.027	0.884
Gender, female vs. male	162	0.528	1.281	0.645-2.544	0.478
Body mass index	119	0.505	0.997	0.924-1.075	0.931
Etiology:	162	0.538			
HCV vs. HBV			3.243	0.52-20.242	0.208
PBC vs. HBV			0	0 - Inf	0.989
Other vs. HBV			1.124	0.518-2.441	0.767
Child-Pugh class, B vs. A	135	0.521	0.773	0.311-1.919	0.579
Alanine aminotransferase, U/L	123	0.511	1.003	0.998-1.007	0.262
Aspartate aminotransferase, U/L	137	0.486	1	0.997-1.003	0.993
Albumin, g/L	136	0.519	0.996	0.94-1.056	0.895
Total bilirubin, μmol/L	135	0.560	1.002	0.994-1.01	0.619
Prothrombin time, s	135	0.636	1.229	1.032-1.464	0.021
International normalized ratio	131	0.694	11.353	1.812-71.131	0.009
Platelet count, 10^9/L	135	0.798	0.975	0.964-0.986	< 0.001
Gallbladder wall thickness, mm	162	0.742	1.476	1.236-1.763	< 0.001
Spleen diameter, mm	162	0.772	1.039	1.023-1.054	< 0.001
Portal vein diameter, mm	162	0.700	1.331	1.145-1.547	< 0.001
Liver stiffness, kPa	43	0.542	1.017	0.919-1.125	0.745

VNT-varices needing treatment; *n*-number; OR-odds ratio; CI-confidence interval; AUC-area under the receiver operating characteristic curve; HBV-hepatitis B virus; HCV-hepatitis C virus; PBC-primary biliary cirrhosis; Inf-infinite

positive predictive value (PPV) and negative predictive value (NPV) of 0.950, 0.541, 0.494 and 0.958, respectively [Table 4]. Compared to other non-invasive indicators, the nomogram exhibited the highest predictive performance for VNT. The cut-off values, sensitivity, specificity, PPV and NPV of non-invasive indicators including PSR, APRI, AAR, GBWT, SD, PV, PT, INR, and PLT for VNT, in training cohort, are summarized in Table 4.

Validation of nomogram

Twenty-eight patients were included in the validation cohort after excluding patients without key data (PT, INR, SD, PV). The nomogram exhibited a satisfactory performance for VNT with an AUC, sensitivity, specificity, PPV and NPV of 0.943, 0.923, 0.563, 0.632 and 0.900, respectively [Table 4]. We further compared the performance of the nomogram with other non-invasive indicators for predicting VNT. As a result, the nomogram still showed the highest performance for VNT [Table 4]. The AUCs, cut-off values, sensitivity, specificity, PPV and NPV of non-invasive indicators for VNT , in the validation cohort, are summarized in Table 4.

Performance for avoiding unnecessary EGD

In 41 patients with LSM in the training cohort, the Baveno VI criteria spared 19.5% of EGDs, but with a risk of missed VNT of 12.5%. While in 29 patients with LSM in the validation cohort, the Baveno VI criteria could avoid 17.2% unnecessary EGDs with no VNT missed. By applying a cut-off value of 105 for nomogram, 38.4% of patients in the training cohort could avoid unnecessary EGDs, with 4.2% of missed VNT. Results were further confirmed in the prospective validation cohort, safely sparing 31.0% of unnecessary EGDs (3.4% VNT missed).

Table 3: Multivariate logistic regression analysis of VNT presence in the training cohort

Variable	β	OR	95% CI	*P*
Gallbladder wall thickness	0.21	1.233	0.976-1.558	0.079
Spleen diameter	0.022	1.022	1.003-1.042	0.022
Platelet count	-0.017	0.983	0.971-0.995	0.007
International normalized ratio	-0.548	0.578	0.057-5.839	0.642

VNT, varices needing treatment; OR, odds ratio; CI, confidence interval

DISCUSSION

In this multicenter study, we developed a nomogram based on four routine parameters (GBWT, SD, PLT and INR), and further validated its performance for non-invasive detection of VNT, in patients with cACLD. As expected, the nomogram showed a favorable performance with AUCs of 0.848 and 0.943 in training and validation cohorts, respectively.

Regarding the four components (GBWT, INR, PLT and SD) of the nomogram, decreased PLT and enlarged SD are the common clinical manifestations of patients with cACLD, which were widely used in non-invasive models for portal hypertension.[14,17,24] INR is a critical index for worsening liver function and one of the indicators of both Child-Pugh score and Model for End-Stage Liver Disease.[25] GBWT has been reported to correlate with the severity of portal hypertension and presence of GEV.[26-31] By using the practical nomogram, clinicians can quickly and reliably predict VNT. Besides, the nomogram maintained a superior performance of VNT, in comparison to other non-invasive predictors.

In our study, the proportion of VNT was 34.4% (67/195). EGD screening for a large proportion of patients without

Table 4: Comparison predictive performance of VNT among different non-invasive indicators

Indicator	Training cohort (*n*=110)						Validation cohort (*n*=28)				
	Cut-off	SEN	SPE	PPV	NPV	AUC (95% CI)	SEN	SPE	PPV	NPV	AUC (95% CI)
Nomogram in current study	105	0.950	0.541	0.494	0.958	0.848 (0.769-0.927)	0.923	0.563	0.632	0.9	0.943 (0.856-1)
Other non-invasive indicators											
PSR	0.648	0.857	0.76	0.625	0.919	0.823 (0.738-0.909)	0.667	0.875	0.8	0.778	0.927 (0.836-1)
Platelet count	83.5	0.829	0.68	0.547	0.895	0.785 (0.694-0.877)	0.667	0.812	0.727	0.765	0.906 (0.801-1)
Spleen diameter	126.5	0.771	0.693	0.54	0.867	0.776 (0.686-0.865)	0.833	0.75	0.714	0.857	0.893 (0.776-1)
GBWT	3.55	0.886	0.547	0.477	0.911	0.756 (0.662-0.851)	0.917	0.375	0.524	0.857	0.724 (0.532-0.916)
INR	1.155	0.771	0.707	0.551	0.869	0.743 (0.641-0.844)	0.5	0.688	0.545	0.647	0.732 (0.543-0.921)
Portal vein diameter	11.5	0.8	0.613	0.491	0.868	0.726 (0.625-0.827)	0.583	0.562	0.5	0.643	0.646 (0.438-0.853)
Prothrombin time	12.85	0.629	0.827	0.629	0.827	0.71 (0.597-0.824)	0.917	0.562	0.611	0.9	0.766 (0.587-0.944)
APRI	0.981	0.857	0.453	0.423	0.872	0.655 (0.549-0.761)	0.583	0.688	0.583	0.688	0.74 (0.553-0.926)
AAR	1.895	1	0.16	0.357	1	0.548 (0.435-0.662)	0.167	0.875	0.5	0.583	0.635 (0.418-0.853)

VNT, varices needing treatment; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic curves; CI, confidence interval; PSR, platelets-to-spleen diameter ratio; APRI, The AST-to-platelet count ratio index; AAR, AST-to-ALT ratio; GBWT, gallbladder wall thickness; INR, international normalized ratio

VNT may increase unnecessary costs and risks.[1,2,17] The Baveno VI consensus recommends that patients with cirrhosis who have a LSM <20 kPa and platelet count >150,000/mm^3 have a very low risk of VNT, and thus, can safely avoid screening EGDs.[2,8] In the ANTICIPATE cohort, 14% patients met the Baveno VI criteria for not performing EGD, with a risk of missing VNT of 3%.[32] In our validation cohort, the Baveno VI criteria could only spare 17.2% unnecessary EGDs. Thus, the shortcoming of the Baveno VI criteria is related to avoid only 15-25% unnecessary EGDs.[33,34] Although studies have improved the cut-off values of LSM and PLT, the rate of spared EGDs was still limited.[35-37] Therefore, a more accurate non-invasive tool is needed to improve risk stratification of GEV in patients with cACLD.[1,2,38] Compared to the Baveno VI criteria, our nomogram (with a cut-off value £105) showed a favorable performance for identifying VNT and avoided a larger proportion (38.4 and 31.2%) of unnecessary EGDs, with a low rate of missing VNT. More importantly, the nomogram required only routine parameters without extra costs and discomfort, which could benefit more patients with cACLD.

Our study has several limitations. First, considering the retrospective nature of the training cohort, part of the data was incompletely recorded. Nevertheless, the prospective multicenter validation cohort added the value of the nomogram. Besides, with the limited data of LSM it failed to compare our nomogram with the Baveno VI criteria accurately. A large-scale, prospective cohort with available recommended non-invasive models for VH is Therefore, needed.

CONCLUSION

We developed and validated a nomogram based on routine clinical parameters (GBWT, SD, PLT and INR) for detecting VNT and avoiding unnecessary EGD safely, in patients with cACLD.

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Conflicts of interest

There are no conflicts of interest.

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