A Novel Radiomics-Platelet Nomogram for the Prediction of Gastroesophageal Varices Needing Treatment in Cirrhotic Patients

Yiken Lin
   Shandong University Qilu Hospital

Lijuan Li
   Shandong Normal University School of Physics and Electronics

Dexin Yu
   Shandong University Qilu Hospital

Zhuyun Liu
   Shandong University Qilu Hospital

Shuhong Zhang
   Jinan Central Hospital Affiliated to Shandong Fisrt Medical University

Qiuzhi Wang
   Jinan Central Hospital Affiliated to Shandong University

Yueyue Li
   Shandong University Qilu Hospital

Baoquan Cheng
   Shandong University Qilu Hospital

Jianping Qiao
   Shandong Normal University School of Physics and Electronics

yanjing Gao (✉ gaoyanjing@sdu.edu.cn)
   Shandong University Qilu Hospital   https://orcid.org/0000-0001-8153-3754

Research Article

Abstract

Background and aims

Highly accurate noninvasive methods for predicting gastroesophageal varices needing treatment (VNT) are desired. Radiomics is a newly emerging technology of image analysis. This study aims to develop and validate a novel noninvasive method based on radiomics for predicting VNT in cirrhosis.

Methods

In this retrospective-prospective study, a total of 245 cirrhotic patients were divided as the training set, internal validation set and external validation set. Radiomics features were extracted from portal-phase computed tomography (CT) images of each patient. A radiomics signature (Rad-score) was constructed with the least absolute shrinkage and selection operator algorithm and 10-folds cross-validation in the training set. Combined with independent risk factors, a radiomics nomogram was built with a multivariate logistic regression model.

Results

The rad-score, consisting of 14 features from the gastroesophageal region and 5 from the splenic hilum region, was effective for VNT classification. The diagnostic performance was further improved by combining the rad-score with platelet counts, achieving an AUC of 0.987(95% CI, 0.969-1.00), 0.973(95% CI, 0.939-1.00) and 0.947(95% CI, 0.876-1.00) in the training set, internal validation set and external validation set respectively. In efficacy and safety assessment, the radiomics nomogram could spare more than 40% of endoscopic examinations with a low risk of missing VNT (<5%), and no more than 8.3% of unnecessary endoscopic examinations still be performed.

Conclusions

In this study, we developed and validated a novel, diagnostic radiomics-based nomogram which is a reliable and noninvasive method to predict VNT in cirrhotic patients.

Introduction

Gastroesophageal varices (GEV) are the principal complication of cirrhotic portal hypertension. Studies have demonstrated that GEV develops in approximately 50% of cirrhotic patients and ruptured GEV occurs in approximately 10-15% per year [1][2]. The mortality rate in cirrhotic patients with a first hemorrhage from GEV is 20%, and patients who survive the first hemorrhage without intervening are at high risk of rebleeding (greater than 60% at 1 year), with a mortality rate of approximately 33% [3].

Given to the mortality and morbidity associated with GEV, guidelines recommend that all cirrhotic patients should be screened for GEV [4,5]. Upper endoscopy is recommended as the golden standard for GEV. However, endoscopic examination is invasive. Additionally, a large proportion of cirrhotic patients do not

present with varices needing treatment (VNT), so the majority of cirrhotic patients are exposed to the risk of invasive procedure and sedation complications without detecting VNT. It would cause much useless endoscopic examination leading to the medical burden.

The 2015 Baveno VI consensus workshop proposed a noninvasive method that the patient with liver stiffness <20KPa and a platelet count >150000/mm^3 could avoid endoscopic screening safely [6]. However, the efficacy of Baveno VI criteria was criticized owing to a substantially low number of spared endoscopies (15-30%) [7–9]. Thus, researches on developing a more accurate noninvasive method are encouraging.

Computed tomography (CT) is widely applied in liver cirrhosis, vastly contributing to the diagnosis and evaluation of the complications of cirrhosis. However, the assessment is highly dependent on the experience and subjectivity of radiologists. Previous studies have attempted to quantitatively analyze CT findings by measuring varices size, liver, and spleen volume, but these radiological parameters didn't show a satisfactory performance [10–14].

Radiomics is a newly emerging technology of image analysis which refers to extracting high-throughput and quantitative features from medical images, revealing the correlation between these features and the disease using data mining algorithms and statistics analysis, then builds an appropriate model with refining features [15,16]. Previous studies suggest that the potential application of radiomics in predicting VNT [17–19]. However, the previous radiomics models do not contain the esophageal and gastric radiomics features which are important evidence for the radiologist to determine the existence and severity of GEV. What's more, the efficacy and safety of radiomics model for predicting VNT are unclear.

Therefore, in this study, we aimed to develop a novel radiomics model containing the esophageal and gastric radiomics features for predicting VNT and to assess its performance in clinical application, particularly to assess its efficacy and safety.

Methods

Study design and patients

This retrospective-prospective study was performed in Qilu Hospital of Shandong University (Institution 1) and Jinan Central Hospital (Institution 2). The study design and procedures were presented in full in the study protocol (ClinicalTrials.gov: NCT04210297). Ethical committee approval was granted by the Medical Ethics Committee of involved institutions. The informed consent was waived in the training set for the retrospective analysis. All procedures involving human participants were performed following the Helsinki declaration and its later amendments.

The inclusion criteria were (1) patients who were diagnosed with liver cirrhosis [20]. (2) patients who underwent the abdominal contrast-enhanced CT examination. (3) patients who received endoscopic screening. (4) patients with written informed consent. Exclusion criteria included: (1) patients who

previously underwent endoscopic therapy, transjugular intrahepatic portosystemic shunt (TIPS), splenectomy, partial splenic embolization (PSE), hepatectomy, balloon-occluded retrograde transvenous obliteration, or liver transplantation. (2) patients with liver cancer. (3) patients with severe ascites or hepatic encephalopathy. (4) lacks abdominal contrast-enhanced CT within 1 month of endoscopy. The study design and recruitment pathways for patients in this study are shown in Fig. 1.

The training set consists of patients who were retrospectively collected in institution 1 from January 2018 to December 2019. The internal and external validation set consists of patients who were prospectively enrolled from January 2020 in institution 1 and institution 2 respectively.

Upper endoscopic examination

Every patient received an upper endoscopic examination for the screening of EV and identifying the risk of bleeding. Upper endoscopic examination was performed by experienced endoscopists. The endoscopic findings were recorded in a standard format. VNT was defined as small varices (diameter<5mm) with red signs and large varices (diameter>5mm).

Radiomics analysis

The workflow of the radiomics analysis is summarized in Figure 1 and can be divided into four steps: CT image acquisition, region of interest (ROI) segmentation, feature extraction, and radiomics signature construction.

CT image acquisition

Every patient underwent an abdominal enhanced CT scan after an overnight fast using one of the following systems: Discovery CT750 HD (GE Healthcare), Brilliance iCT (Philips Healthcare), or Sensation 16 CT (Siemens). The following parameters were used: tube voltage, 120 or 140kVp; tube current, 150–600 mAs; slice thickness, 1.25 mm; pitch, 1.375. Ultravist (2.5 mL/kg, 300 mg/mL) was injected intravenously at a rate of 3 mL/s. Arterial phase scan began at the 30s after injection, while the venous phase and delayed phase scan were started at 70 and120 s, respectively. Portal venous phase CT images were retrieved from the picture archiving and communication system (PACS).

Region of interest (ROI) segmentation and feature extraction

The liver at the porta hepatis level, the spleen at splenic hilum level, and the level from the lower esophagus to gastric fundus were selected as the ROI. ROI was delineated manually by two radiologists (reader 1: Dexin Yu and reader 2: Zhuyun Liu with 20 and 3 years of clinical experience in abdominal CT interpretation respectively) using the ITK-SNAP 3.8 (www.itksnap.org). The two radiologists were blinded to the endoscopic findings. Radiomic features were extracted from each ROI using the MATLAB 2018b (MathWorks, Natick, USA) by utilizing the open-source radiomics feature extraction package. Textural and non-textural feature extractions were conducted. Image normalization including Wavelet bandpass filtration, isotropic resampling, and quantization of gray level was performed before radiomic features

extraction. For each ROI, 10324 radiomic features were extracted and a total of 30972 radiomic features were extracted from each patient. More information about radiomics features extraction methodology is shown in Supplementary information.

The inter-observer and intra-observer reliability were analyzed with 30 randomly chosen cases from the training set, two radiologists repeated ROI segmentation and feature extraction twice on those cases with a one-month interval. The reliability was calculated by using the intra-class correlation coefficient (ICC), both intra-observer and inter-observer ICC values greater than 0.75 were regarded as robust reliability and reproducibility.

Feature selection andRadiomics signature construction

The least absolute shrinkage and selection operator (LASSO) logistic regression method was used to select the most effective predictive features from the training set. The LASSO logistic regression model was used with tuning penalty parameter lambda(λ) that was conducted by 10-fold cross-validation based on minimum criteria. A formula was generated using a linear combination of selected features that were weighted by their respective LASSO coefficients; the formula was then used to calculate a radiomics signature (Rad-score) for each patient to predict the risk of VNT.

Radiomics nomogram construction

The Rad-scores and the clinical variables were tested in univariate logistic regression analysis in the training set. All variables with $P < 0.05$ were entered into the multivariate logistic regression analysis. A radiomics nomogram was then constructed according to the multivariate logistic regression model.

Statistical analysis

Differences of clinical characteristics between the training set and the validation set as well as between the VNT group and non-VNT group in their respective datasets were assessed using independent sample t-test or Mann-Whitney U-test. The optimal cut-off value for Rad-score was determined using Youden's index in the training set, which maximizes the sum of sensitivity and specificity. The predictive accuracy of the radiomics signature was quantified by the area under the receiver operator characteristic (ROC) curve (AUC) in both training and validation sets. The likelihood ratio test with a backward stepwise selection was applied to the multivariate logistic regression model. Additionally, a decision curve analysis was performed to evaluate the clinical usefulness and net benefits of the developed radiomics nomogram. Statistical analysis was performed using the R software (version 3.6.2, R Project for Statistical Computing, http://www.r-project.org). Two-sided P-values less than 0.05 were considered statistically significant.

Results

Study Population

A total of 245 cirrhotic patients from two institutions were included in this study. 111 patients retrospectively collected from institution 1 were taken as the training set, 71 patients prospectively enrolled from institution 1 were used as the internal validation sets and 63 patients prospectively enrolled from institution 2 were used as the external validation set. Baseline characteristics of the study population were outlined in Table 1.

Radiomic features selection and radiomics signature development

After extracting features from ROIs, 30972 radiomics features were retrieved from patients in the training set and reduced to 19 potential predictors with 14 features from the gastroesophageal region and 5 from the splenic hilum region using the LASSO regression analysis. The radiomics signature (Rad-score) calculation formula is shown in Supplementary materials. The intra-observer ICCs ranged from 0.883 to 0.990 and the inter-observer ICCs ranged from 0.839 to 0.935, indicating favorable intra- and inter-observer feature extraction reproducibility.

Diagnostic performance of the rad-score for VNT

The rad-score showed a good diagnostic performance for identifying VNT in cirrhotic patients with the AUC of 0.983 (95% CI, 0.964 to 1.00) in the training set. And the rad-score yielded the AUC of 0.970 (95% CI, 0.930 to 1.00) and 0.932(95% CI, 0.853 to 1.00) in internal and external validation sets, respectively (Supplementary Figure S1). There was a significant difference between the rad-scores (median [standard deviation]) of the Non-VNT and VNT patient groups in the training set (0.753 [0.116] vs. 0.292 [0.150], respectively, $P < 0.001$), this difference was confirmed in internal validation sets (0.216 [0.152] vs. 0.664 [0.148], respectively, $P < 0.001$) and external validation sets (0.326 [0.176] vs. 0.761 [0.185], respectively, $P < 0.001$).

Radiomics nomogram development and validation

For univariate analysis, the rad-score, platelet counts, albumin, and spleen diameters were found significantly associated with VNT. When multiple logistic regression analyses were performed, the rad-score and platelet counts remained significant for VNT (Table 2). Then, a radiomics nomogram for predicting VNT was constructed using the above regression coefficients (Figure 2). The calibration curve and a nonsignificant Hosmer-Lemeshow test statistic ($P = 0.49$) showed good calibration in training sets. The calibration curve was confirmed in the internal and external validation sets with a nonsignificant Hosmer-Lemeshow test statistic $P = 0.29$ and $P = 0.33$ respectively (Figure 3A). The radiomics nomogram showed favorable predictive efficacy with AUC of 0.987 (95% CI, 0.969-1.00), which confirmed with AUC of 0.973 (95% CI, 0.939-1.00) and 0.947 (95% CI, 0.876-1.00) in internal validation set and external validation set respectively (Figure 3B). Compared to other noninvasive methods that were proposed in previous researches, the radiomics nomogram still showed the highest diagnostic performance.

To evaluate the clinical usefulness of our radiomics nomogram, decision curve analysis (DCA) was applied in this study (Figure 3C). The DCA curve indicated that if the threshold probability for a patient or

a doctor is within a range from 0 to 0.95, the radiomics nomogram adds more benefit than either the treat-all-patients or the treat-none strategies. Within this range, the radiomics nomogram also was better than the PSR which showed a good performance in predicting VNT in previous studies.

Efficacy and safety assessment

Furthermore, we evaluated the efficacy and the safety of the radiomics nomogram for the prediction of VNT in cirrhotic patients. As shown in Table 3, the radiomics nomogram could spare 42.3%, 49.3%, and 44.4% endoscopies with a low risk of VNT missed (< 5%) and no more than 8.3% of unnecessary endoscopic examinations still be performed in the training set, internal validation set, and external validation set, respectively. When compared to the radiologist, the radiomics nomogram was more accurate than radiologist interpretation, especially in the discrimination of mild varices. In our study, the radiologist could classify 13 patients among 27 patients with mild varices correctly while the radiomics nomogram could classify 23 patients correctly.

Discussion

Although the endoscopic examination is recommended as the golden diagnostic standard for VNT, compliance with endoscopic screening recommendations is limited owing to its invasive procedure and the need for sedation. Thus, in recent years noninvasive methods for VNT detection have been highlighted. In this study, we developed and validated a diagnostic, noninvasive, radiomics-based nomogram for the prediction of VNT in cirrhosis.

Radiomics has been recognized as an emerging image analysis technology in clinical disease assessment. A prospective multicenter study developed a radiomics model that showed good performance in the prediction of patients with HVPG > 10mmHg [19]. And following studies used similar radiomics methods to predict gastroesophageal varices needing treatment and varices rebleeding [18,21], but the results were not satisfying. When predicting HVPG and GEV by analyzing an abdominal CT image, the main difference between them is that GEV is visualized. However, the former radiomics model lacked radiomics features from gastroesophageal ROI. In our study, we developed an improved radiomics model containing the esophageal and gastric radiomics features and this radiomics nomogram showed excellent performance in the prediction of VNT in cirrhotic patients.

For the construction of rad-score, 19 potential predictors with 14 features from the gastroesophageal region and 5 from the splenic hilum region were obtained. Major of potential predictors are from the gastroesophageal region which confirmed that gastroesophageal radiomics features are more important. However, none of the hepatic features while 5 splenic features were selected by LASSO analysis. This finding may result from the prevalence of splenomegaly is over 50% in our study and the extra-hepatic factors contribute more to the rise of portal pressure. Recent studies suggested that splenomegaly may be superior to liver fibrosis in the prediction of VNT [22−27]. Our data also showed that PSR which reflects the splenomegaly performed a better diagnostic ability than liver fibrosis-associated parameters such as APRI and FIB-4.

In our study, the 19-features-based rad-score was found to be effective for VNT classification, this rad-score could stratify patients into non-VNT and VNT group with an AUC of 0.983 (95% CI, 0.964 to 1.00), 0.970 (95% CI, 0.930 to 1.00) and 0.932(95% CI, 0.853 to 1.00) in the training set, internal validation set and external validation set respectively. Next, we considered clinical risk factors, a multivariate logistic regression analysis for accessible clinical parameters indicated that platelet count was a significant predictive factor distinct from rad-score. The diagnostic performance was further improved by combining the rad-score with platelet counts, achieving an AUC of 0.987(95% CI, 0.969-1.00), 0.973(95% CI, 0.939-1.00) and 0.947(95% CI, 0.876-1.00) in the training set, internal validation set and external validation set respectively. Although the AUC was mild improvement when rad-score combined with the platelet count, the combined nomogram could reduce the risk of missing VNT and unneeded endoscopies in the following evaluation. When compared to other noninvasive methods that were comprehensively validated in previous studies such as PSR, APRI, and FIB-4, both rad-score and radiomics nomogram showed better performance in the prediction of VNT.

Although our radiomics nomogram showed excellent discrimination and calibration, it could not represent favorable clinical usefulness. Previous studies seldom assess the clinical usefulness and safety of the VNT-prediction radiomics model. In this study, we applied decision curve analysis and the result suggested that our radiomics nomogram could derive good net benefit in clinical application. Furthermore, our radiomics nomogram could spare more than 40% of endoscopic examinations with a low risk of missing VNT, and no more than 8.3% of unneeded endoscopies still be performed.

Previous studies demonstrated that radiologists could distinguish VNT with an accuracy of nearly 90% by analyzing portal-phase abdominal CT images [28]. In our study, the accuracy of medical image reports was 90.1%, 87.3%, and 84.1% in the training set, internal validation set, and external validation set, respectively. This result suggested radiologist interpretation may be unstable owing to the subjectivity and experience of radiologists. Additionally, it may be difficult for the radiologist to distinguish the mild varices and VNT sometimes. Compared to radiologist interpretation, the radiomics nomogram yielded a robust accuracy and better performance in the classification of mild varices and VNT overall.

Compared to previous studies reporting the radiomics model for detecting VNT, our study has the following advantages. Firstly, our study has a larger study population and validated our radiomics model in an independent external population, which improved test power and predictive ability. Secondly, we analyzed not only hepatic and splenic features but also gastroesophageal features, which contributes to a better diagnostic performance than the previous radiomics model. Additionally, our study has more detailed validation in efficacy and safety assessment which previous studies lacked.

Some limitations of our study should be discussed. One of the potential criticisms is our training set was collected retrospectively and not large, so we prospectively enrolled more patients as the validation set to reduce the related deviation. Another shortage of our study was that we only performed liver stiffness measurement in those patients who were hardly diagnosed with cirrhosis according to clinical presentation, blood tests, or medical images. Only a total of 42 patients with liver stiffness measurement

were enrolled in the internal and external validation set, so we did not evaluate the comparison of radiomics nomogram and Baveno VI criteria.

Conclusion

In this study, we developed and validated a novel, diagnostic radiomics-based nomogram which is a reliable and noninvasive method to predict VNT in cirrhotic patients.

Abbreviations

GEV, gastroesophageal varices; VNT, varices needing treatment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; AKP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; HGB, hemoglobin; PLT, platelet count; AFP, alpha-fetoprotein; INR, international normalized ratio; HBV, hepatitis B virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; NPV, negative predictive value; ACC, accuracy; SD, standard deviation; ROC, receiver operator characteristic; AUC, area under the curve; PSR, platelet-spleen ratio; APRI, AST-to-platelet ratio index; FIB-4, fibrosis-4 score.

Declarations

Data availability

All data included in this study are available upon request by contact with the corresponding author.

Ethical approval

Ethical committee approval was granted by the Medical Ethics Committee of involved institutions. All procedures involving human participants were performed following the Helsinki declaration and its later amendments. No animal participants was used for this manuscript.

Informed consent

The informed consent was obtained from all patients enrolled as the validation sets and was waived in the training set for the retrospective analysis. All authors reviewed and approved the final version of the manuscript.

Clinical trials registration

NCT04210297

Authors' contributions

Study design: Yiken Lin, Yanjing Gao and Jianping Qiao.

Data collection: Yiken Lin, Qiuzhi Wang and Shuhong Zhang

Technical support: Lijuan Li, Jianping Qiao. Dexin Yu and Zhuyun Liu

Statistical analysis of data: Yiken Lin

Manuscript writing: Yiken Lin

Critical revision of the manuscript: Yanjing Gao, Baoquan Chen and Yueyue Li

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Conflicts of interest

All authors declare no conflict of interest.

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Tables

Table 1. Baseline characteristics of patients in the training set, internal validation set and external validation set.

Characteristics	Training set (n=111)	Internal validation set (n=71)	External validation set (n=63)
Age (years)	54 (11)	56 (11)	58 (10)
Child-Pugh class, n (%)			
A	90 (81.1%)	59 (83.1%)	54 (85.7%)
B	18 (16.2%)	10 (14.1%)	7 (11.1%)
C	3 (2.7%)	2 (2.8%)	2 (3.2%)
Etiology, n (%)			
HBV	86 (77.5%)	53 (74.6%)	32 (50.8%)
Alcohol	12 (10.8%)	4 (5.6%)	22 (34.9%)
PBC	7 (6.3%)	8 (11.3%)	5 (7.9%)
Others	6 (5.4%)	6 (8.5%)	4 (6.3%)
Varices, n (%)			
No	37 (33.3%)	29 (40.8%)	22 (34.9%)
Low risk	12 (10.8%)	8 (11.3%)	7 (11.1%)
VNT	62 (55.9%)	34 (47.9%)	34 (54.0%)
ALT(U/L)	36.0 (32.2)	34.8 (45.7)	29.4 (21.1)
AST (U/L)	43.0 (35.2)	41.7 (49.4)	35.9 (23.9)
GGT (U/L)	67.9 (80.8)	67.3 (116.2)	105.4 (177.3)
AKP (U/L)	99.2 (55.6)	99.2 (55.9)	81.0 (31.1)
TBIL (μmol/L)	23.9 (35.7)	18.2 (11.8)	19.4 (11.7)
ALB(g/L)	39.7 (6.4)	39.8 (5.6)	37.0 (5.5)
HGB (g/L)	118.6 (31.7)	112.7 (28.5)	109.3 (29.8)
PLT (x10^9/L)	117 (61.0)	109 (59.8)	107 (74.0)
AFP (ng/ml)	6.13 (11.7)	3.85 (3.3)	5.76 (10.3)
INR	1.22 (0.11)	1.19 (0.15)	1.17 (0.16)
Spleen diameters (cm)	13.3 (3.6)	13.0 (3.6)	12.6 (3.2)

Data are shown as median (standard deviation)

Abbreviations: HBV, hepatitis B virus; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; AKP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; HGB, hemoglobin; PLT, platelet count; AFP, alpha-fetoprotein; INR, international normalized ratio.

Table 2. Univariate and multivariate analysis of factors associated with the presence of VNT in cirrhotic patients.

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Rad-score	5.806 (2.828-11.917)	<0.001	5.383 (2.466-11.753)	<0.001
Age, years	0.612 (0.270-1.386)	0.239	NA	NA
ALT(U/L)	0.985 (0.969-1.002)	0.087	NA	NA
AST (U/L)	0.992 (0.979-1.004)	0.190	NA	NA
GGT (U/L)	0.996 (0.990-1.002)	0.166	NA	NA
AKP (U/L)	1.000 (0.993-1.007)	0.956	NA	NA
TBIL (μmol/L)	0.999 (0.989-1.010)	0.892	NA	NA
ALB(g/L)	0.836 (0.773-0.903)	<0.001	NA	NA
PLT (x10^9/L)	0.981 (0.973-0.990)	<0.001	0.985 (0.971-0.999)	0.031
INR, median (SD)	1.258 (0.873-1.813)	0.219	NA	NA
Spleen diameters(cm)	1.258 (0.873-1.813)	<0.001	NA	NA

Abbreviations: OR, Odds ratio; 95%CI, confidence internal; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; AKP, alkaline phosphatase; TBIL, total bilirubin; ALB, albumin; PLT, platelet count; INR, international normalized ratio.

Table 3. The efficacy and safety of different noninvasive methods.

A. Training set

Methods		Spared endoscopy	Unneeded endoscopy	VNT missed	Accuracy
Nomogram	(cut-off 0.386)	47/111 (42.3%）	3/64 (4.7%)	1/47 (2.1%)	107/111 (96.4%)
Rad-score	(cut-off 0.483)	45/111 (40.5%)	5/66 (7.6%)	1/45 (2.2%)	106/111 (95.5%)
Radiologists		56/111 (50.5%)	4/55 (7.3%)	7/56 (12.5%)	100/111 (90.1%)
PSR	(cut-off 10.5)	42/111 (37.8%)	15/69 (21.7%)	8/42 (19.0%)	88/111 (79.3%)
APRI	(cut-off 0.301)	50/111 (45.0%)	16/61 (26.2%)	17/50 (34.0%)	78/111 (70.3%)
FIB-4	(cut-off 3.33)	53/111 (47.7%)	10/58 (17.2%)	14/53 (26.4%)	87/111 (78.4%)

B. Internal validation set

Methods	Spared endoscopy	Unneeded endoscopy	VNT missed	Accuracy
Nomogram	35/71 (49.3%)	3/36 (8.3%)	1/35 (2.9%)	67/71 (94.4%)
Rad-score	38/71 (53.5%)	3/33 (9.1%)	4/38 (10.5%)	64/71 (90.1%)
Radiologists	28/71 (39.4%)	9/43 (20.9%)	0/28 (0%)	62/71 (87.3%)
PSR	25/71 (35.2%)	14/46 (30.4%)	4/25 (16.0%)	53/71 (74.7%)
APRI	33/71 (46.5%)	12/38 (31.6%)	10/33 (30.3%)	49/71 (69.0%)
FIB-4	29/71 (40.9%)	14/42 (33.3%)	8/29 (27.6%)	49/71 (69.0%)

C. External validation set

Methods	Spared endoscopy	Unneeded endoscopy	VNT missed	Accuracy
Nomogram	28/63 (44.4%)	2/35 (5.7%)	1/28 (3.6%)	60/63 (95.2%)
Rad-score	29/63 (46.0%)	3/34 (13.9%)	3/29 (10.3%)	57/63 (90.5%)
Radiologists	23/63	8/40 (20.0%)	2/23	53/63

	(36.5%)		(8.7%)	(84.1%)
PSR	20/63 (31.4%)	11/43 (25.6%)	2/20 (10%)	50/63 (79.4%)
APRI	29/63 (46.0%)	14/34 (41.2%)	14/29 (48.3%)	35/63 (55.6%)
FIB-4	26/63 (41.3%)	14/37 (37.8%)	11/26 (42.3%)	38/63 (60.3%)

Abbreviations: VNT. Varices needing treatment; NPV, negative predictive value; Accuracy = the number of correctly classified patients / the number of total patients; Spared endoscopy = the number of patients who were classified as non-VNT group by noninvasive methods; Unneeded endoscopy = the number of non-VNT patients / the number of patients who were classified as VNT group by noninvasive methods; VNT missed = the number of VNT patients / spared endoscopy; PSR, platelet-spleen ratio; APRI, AST-to-platelet ratio index; FIB-4, fibrosis-4 score.