

**Application of Hepatic and Splenic IVIM Quantitative Parameters in the Noninvasive
Prediction of High-Risk Esophagogastric Varices**

Clinical Research Protocol

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Investigator Clinical Protocol Agreement Page

Principal Investigator:

I agree to conduct this clinical study in accordance with the design and requirements of this protocol. I acknowledge that I am responsible for the implementation of this trial and agree to personally participate in or supervise the entire conduct of the clinical study.

I agree to ensure that all personnel involved in this study clearly understand their respective responsibilities and that the study staff at the trial site have access to appropriate information throughout the course of the study.

I will accept monitoring, auditing, and inspections by monitors, auditors, and the Ministry of Science and Technology of the People's Republic of China, the National Health Commission of the People's Republic of China, and the Health Department of the General Logistics Department of the Chinese People's Liberation Army, in order to ensure the quality of the study.

Abstract

Study Title	Application of Hepatic and Splenic IVIM Quantitative Parameters in the Noninvasive Prediction of High-Risk Esophagogastric Varices
Study Objectives	<p>Primary Objective:</p> <p>To evaluate the diagnostic performance of hepatic and splenic IVIM parameters in identifying high-risk esophagogastric varices.</p> <p>Secondary Objectives:</p> <ol style="list-style-type: none"> 1. To compare the diagnostic efficacy of IVIM parameters with noninvasive indices, including Baveno VI criteria, FIB-4, and APRI, in assessing esophagogastric varices. 2. To assess the reproducibility of IVIM parameters.
Study Design	Retrospective cohort study.
Study Population	Patients aged over 18 years with chronic hepatitis B–related cirrhosis.
Study Grouping	<p>According to endoscopic findings, patients will be categorized into:</p> <ol style="list-style-type: none"> 1. High-risk esophagogastric varices group 2. Non–high-risk group <p>High-risk esophagogastric varices are defined as:</p> <ol style="list-style-type: none"> 1. Medium to large varices (\geq F2 or diameter \geq 5 mm) 2. Presence of red wale signs
Inclusion Criteria	<ol style="list-style-type: none"> 1. Age \geq 18 years. 2. Clinical diagnosis of chronic hepatitis B–related cirrhosis, defined as HBsAg positivity for \geq 6 months, and meeting one of the following criteria:

	<ul style="list-style-type: none"> ● Liver biopsy confirming cirrhosis (F4 according to the METAVIR scoring system). ● Meeting at least one of the following two conditions: <ol style="list-style-type: none"> ① Endoscopic evidence of esophageal and/or gastric varices, with non-cirrhotic portal hypertension excluded; ② In the absence of endoscopy, meeting at least two of the following four criteria: Imaging findings (ultrasound, CT, etc.) suggestive of cirrhosis, including irregular liver surface and granular or nodular parenchymal changes; Liver stiffness measurement (LSM) > 12.4 kPa; ● Serum albumin < 35 g/L or prolonged prothrombin time > 3 seconds (after discontinuation of thrombolytic or anticoagulant drugs for ≥ 7 days) or decreased cholinesterase; ● Platelet count < $100 \times 10^9/L$, with no other identifiable cause. <p>3. Underwent upper gastrointestinal endoscopy for screening or evaluation.</p> <p>4. Underwent abdominal MRI including IVIM sequences within 6 months of the endoscopic examination.</p>
Exclusion Criteria	<p>1. Coexisting other chronic liver diseases.</p> <p>2. Previous portosystemic shunt procedures or splenectomy.</p> <p>3. History of upper gastrointestinal variceal treatment that may affect evaluation.</p> <p>4. Severe iron deposition in the liver or spleen.</p> <p>5. Patients with decompensated cirrhosis.</p>

	6. Presence of malignant tumors.
Primary Outcome Measure	The diagnostic performance of IVIM parameters in predicting high-risk esophagogastric varices.
Secondary Outcome Measures	<p>1. Comparison of the diagnostic efficacy of IVIM parameters with noninvasive indices, including Baveno VI criteria, FIB-4, and APRI, in assessing esophagogastric varices.</p> <p>2. Reproducibility of IVIM parameters.</p>
Planned Sample Size	150 patients.
Statistical Methods	<p>Continuous variables will be expressed as mean \pm standard deviation or median (interquartile range), as appropriate. Between-group comparisons will be performed using the Student's t-test or the Mann–Whitney U test. Categorical variables will be presented as frequency (percentage) and compared using the chi-square test or Fisher's exact test.</p> <p>The presence of high-risk esophagogastric varices will be defined as the primary outcome. The predictive performance of hepatic and splenic IVIM parameters will be evaluated by constructing receiver operating characteristic (ROC) curves. The DeLong test will be used to compare their performance with noninvasive indices, including Baveno VI criteria, FIB-4, and APRI.</p> <p>Multivariable logistic regression analysis will be conducted to develop a combined prediction model and to assess its discriminative ability. Under a predefined sensitivity threshold of $\geq 95\%$, the proportion of avoided endoscopies and the rate of missed high-risk esophagogastric varices will be calculated.</p>

	All statistical tests will be two-sided, and a P value < 0.05 will be considered statistically significant.
Expected Timeline	From February 2026 to October 2026.

Main Text

I . Research Background

High-risk esophageal varices represent a major complication of portal hypertension in patients with cirrhosis. Once acute variceal bleeding occurs, the mortality rate may reach approximately 35%^[1]. Currently, upper gastrointestinal endoscopy is the gold standard for diagnosing high-risk esophagogastric varices. However, as an invasive procedure, it is associated with patient discomfort, relatively high cost, and considerable time consumption, which limit its use in large-scale screening.

To reduce unnecessary endoscopic examinations, several noninvasive assessment methods have been proposed in clinical practice, including maximal spleen diameter, platelet count, platelet-to-spleen diameter ratio, aspartate aminotransferase-to-platelet ratio index (APRI), FIB-4, and the Baveno criteria^[2-5].

The latest Baveno VII consensus states that if platelet count (PLT) > 150 × 10⁹/L, liver stiffness measured by transient elastography (TE) < 20 kPa, and spleen stiffness ≤ 40 kPa, the proportion of patients who can safely avoid endoscopy can be further increased while maintaining a low rate of missed high-risk varices. In addition, magnetic resonance elastography (MRE) has been reported to be more accurate than TE in measuring liver stiffness. However, these elastography-based techniques require specialized equipment, which limits their widespread implementation^[6].

In contrast, intravoxel incoherent motion (IVIM) imaging does not require contrast agents and can separate true molecular diffusion from microcirculatory perfusion using a multi-b-value biexponential model. It provides quantitative parameters including D (related to tissue

cellular density), f (microvascular volume fraction), and D^* (associated with microcirculatory perfusion), thereby reflecting local microcirculatory and hemodynamic alterations at both hepatic and splenic levels. The development of portal hypertension is not only associated with intrahepatic fibrosis and regenerative nodules leading to microvascular remodeling, but also influenced by intrahepatic vasoconstriction. Moreover, increased portal vascular resistance may further induce splenic hemodynamic and structural changes, including fibrosis and angiogenesis^[7]. Therefore, IVIM theoretically holds significant potential for assessing high-risk esophagogastric varices.

Existing studies have demonstrated correlations between hepatic IVIM parameters and portal hypertension or esophageal varices. However, its ability to exclude high-risk esophagogastric varices remains unclear. IVIM parameters reflecting splenic microcirculatory changes have been even less systematically investigated. To date, no study has applied IVIM techniques to develop an exclusion strategy for high-risk esophagogastric varices^[8].

Based on the above background, this study aims to explore the value of hepatic and splenic IVIM imaging parameters in excluding high-risk esophagogastric varices in patients with cirrhosis, thereby providing novel imaging-based evidence for the noninvasive identification of high-risk varices.

References

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II. Study Objectives

1. Primary Objective

To evaluate the ability of hepatic and splenic IVIM parameters to identify high-risk esophagogastric varices.

2. Secondary Objectives

- To compare the diagnostic performance of IVIM with noninvasive indices, including Baveno VI criteria, FIB-4, and APRI, in assessing esophagogastric varices
- To assess the reproducibility of IVIM parameters.

III. Study Content

This retrospective study will include patients with cirrhosis or advanced chronic liver disease who have completed both upper gastrointestinal endoscopy and abdominal MRI (including IVIM sequences). According to endoscopic findings, subjects will be classified into a high-risk esophagogastric varices group and a non-high-risk group.

Hepatic and splenic IVIM parameters (D , D^* , f , and ADC) will be extracted and compared between the two groups to evaluate their predictive performance for high-risk varices. Furthermore, comparisons will be conducted with commonly used noninvasive methods, including Baveno VI criteria, FIB-4, and APRI.

In addition, correlations between IVIM parameters and the severity of varices as well as clinical indicators will be explored. Subgroup analyses will also be performed to assess the diagnostic performance of IVIM under different clinical characteristics.

IV . Study Protocol

1. Study Design

Retrospective cohort study

2. Study Population

2.1 Source of Subjects

Patients identified from the Beijing Friendship Hospital All-Disease Platform, with visits up to October 31, 2025

2.2 Inclusion Criteria

(1) Age \geq 18 years.

(2) Clinical diagnosis of chronic hepatitis B–related cirrhosis, defined as HBsAg positivity for \geq 6 months, and meeting the following criteria:

- Liver biopsy confirming cirrhosis, defined as F4 according to the METAVIR scoring system
- Meeting at least one of the following two conditions: ①Endoscopic evidence of esophageal and/or gastric varices, with non-cirrhotic portal hypertension excluded; ②In the absence of endoscopy, meeting at least two of the following four criteria: Imaging findings (ultrasound, CT, etc.) suggestive of cirrhosis, including irregular liver surface and granular or nodular parenchymal changes; Liver stiffness measurement (LSM) > 12.4 kPa; Serum albumin < 35 g/L, or prolonged prothrombin time > 3 seconds (after discontinuation of thrombolytic or anticoagulant drugs for ≥ 7 days), or decreased cholinesterase; Platelet count $< 100 \times 10^9/L$, without other identifiable causes.

(3) Underwent upper gastrointestinal endoscopy for screening or evaluation.

(4) Underwent abdominal MRI including IVIM sequences within 6 months of the endoscopic examination.

2.3 Exclusion Criteria

- (1) Coexisting other chronic liver diseases.
- (2) Previous portosystemic shunt procedures or splenectomy.
- (3) History of upper gastrointestinal variceal treatment that may affect evaluation.
- (4) Severe iron deposition in the liver or spleen.
- (5) Decompensated cirrhosis.
- (6) Presence of malignant tumors.

3. Study Procedures

3.1 Assessments

- (1) Demographic data: sex and age.
- (2) Hematological parameters: complete blood count, coagulation function, and liver function tests.
- (3) Imaging examinations: liver stiffness measurement (LSM), MRI sequences, and upper gastrointestinal endoscopy

4. Study Endpoints

4.1 Primary Endpoint:

The primary study endpoint is the presence of high-risk esophagogastric varices

4.2 Secondary Endpoints:

- (1) Correlation between IVIM parameters and the severity of varices.
- (2) Correlation between IVIM parameters and commonly used noninvasive indices.
- (3) Reproducibility analysis of IVIM parameters

5. Study Assessments and Definitions

5.1 High-Risk Esophagogastric Varices

High-risk esophagogastric varices will be determined based on endoscopic findings and defined as meeting any of the following criteria:

- (1) Medium or large varices ($\geq F2$ or diameter ≥ 5 mm) ;
- (2) Presence of red wale signs

6. Sample Size Determination

Using endoscopic findings as the gold standard, this study aims to evaluate the noninvasive predictive value of hepatic and splenic IVIM imaging parameters for high-risk esophagogastric varices. Based on previous literature, hepatic and splenic IVIM parameters have demonstrated a moderate to high effect size (approximately 0.8) in distinguishing patients with and without high-risk varices.

Referring to similar imaging studies, assuming a significance level of $\alpha = 0.05$ and statistical power of $1 - \beta = 0.9$, the required total sample size is estimated to be approximately 120–140 patients.

Considering that this is a retrospective study and that some cases may have suboptimal image quality or incomplete data, a total of 150 patients will ultimately be included to ensure adequate statistical power and model stability. This sample size is sufficient to meet the statistical requirements of the primary study objective.

V. Statistical Analysis

Continuous variables will be expressed as mean \pm standard deviation or median (interquartile range) after testing for normality. Categorical variables will be presented as frequencies and percentages. Between-group comparisons will be performed using the independent sample t-test or Mann-Whitney U test, depending on data distribution, and chi-square or Fisher's exact test will be used for categorical variables.

The primary outcome variable is the presence of high-risk esophagogastric varices. Receiver operating characteristic (ROC) curves will be calculated for hepatic and splenic IVIM parameters to assess their diagnostic performance. Additionally, comparisons with commonly used noninvasive indices will be made.

A multivariable logistic regression model will be used to construct a combined IVIM prediction model. Under the condition of sensitivity $\geq 95\%$, the proportion of avoided endoscopies and the rate of missed high-risk esophagogastric varices will be calculated for different models. The stability of the model will be internally validated through bootstrap resampling (B=1000 times), and the bias-corrected AUC will be obtained.

Correlation analysis will also be conducted to explore the relationships between IVIM parameters and the grading of varices, platelet count, liver stiffness, FIB-4, APRI, and other noninvasive indices. All tests will be two-sided, and a P value < 0.05 will be considered statistically significant.

VI. Ethical Considerations

Ethical review: This study must comply with the Declaration of Helsinki and relevant clinical research regulations in China. The clinical research protocol must be reviewed and approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University, before the study begins.

VII. Informed Consent and Confidentiality of Study Information

The clinical information of patients in this study will be collected through the Beijing Friendship Hospital All-Disease Platform, and de-identified (anonymized) data will be exported from the clinical big data platform. The information obtained will not include identifiable subject information such as names, phone numbers, ID numbers, or registration numbers. As the information cannot be used to identify or contact the subjects, a waiver of informed consent is requested.

VIII. Protocol Amendments

Once this protocol has been approved by the Ethics Committee, any major modifications during the study's implementation will be documented in an "Amendment to the Protocol" written by the principal investigator. The amendment will be signed and submitted to the Ethics Committee for approval before it can be implemented