Establishment and Assessment of the Hepatic Venous Pressure Gradient using Biofluid Mechanics, Deep Convolutional Neural Network and Mixed Reality: Protocol For a Prospective, Randomised, Non-Controlled, Multicentre Study

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Abstract

Liver cirrhosis poses a significant global health burden, with clinically significant portal hypertension (CSPH), defined by a hepatic venous pressure gradient (HVPG) ≥10 mmHg, being a critical prognostic determinant. While HVPG measurement remains the gold standard, its invasive nature limits widespread clinical application. This study aimed to develop and validate a novel non-invasive virtual HVPG (vHVPG) model by integrating multi-modal data through biofluid mechanics, deep convolutional neural networks (DCNNs), and mixed reality (MR) technologies. This is a prospective, multicenter trial involving 248 patients with cirrhosis scheduled for HVPG measurement. Participants were randomly assigned 1:1 to an original cohort (model development and parameter refinement, n=124) or a validation cohort (independent model assessment, n=124). The vHVPG model was constructed using patient-specific CT, Doppler ultrasound and blood test results. DCNNs and MR technologies were employed for three-dimensional geometric reconstruction and computational fluid dynamics (CFD) analysis was used to solve the Navier-Stokes equations for blood flow simulation. The primary objective was to determine the numerical correlation between vHVPG and invasive HVPG. Secondary objectives included assessing the diagnostic accuracy of vHVPG for portal hypertension (HVPG ≥5 mmHg) and CSPH (HVPG ≥10 mmHg). Study findings will be disseminated through peer-reviewed publications and conference presentations.

Keywords: Portal hypertension, liver cirrhosis, hepatic venous pressure gradient, biofluid mechanics, deep convolutional neural network, mixed reality; noninvasive

Introduction

Liver cirrhosis is a progressive and debilitating condition that poses a significant global health burden. One of its most severe complications is portal hypertension (PH). Clinically significant portal hypertension (CSPH), defined

as a hepatic venous pressure gradient (HVPG) ≥10 mmHg, is associated with life-threatening sequelae, including variceal bleeding, ascites, and hepatic encephalopathy. Accurate assessment of portal pressure is therefore critical for risk stratification, treatment guidance, and prognostic evaluation in patients with cirrhosis.(1) Currently, HVPG measurement is the gold standard for diagnosing PH and CSPH. However, it is an invasive procedure that requires catheterization of the hepatic vein via the jugular approach. This method demands specialized expertise, carries procedural risks, and is often inaccessible outside tertiary care centers. These constraints restrict its widespread application in routine clinical practice and serial monitoring, underscoring the urgent need for reliable, non-invasive alternatives.(2)

In recent years, considerable efforts have been directed toward developing non-invasive methods for estimating portal pressure. Advances in computational modeling and artificial intelligence have opened new avenues for non-invasive hemodynamic assessment.(3) In particular, the integration of biofluid mechanics with computed tomography (CT) angiography allows for the construction of patient-specific vascular models.(4) By applying computational fluid dynamics (CFD) to simulate blood flow and pressure distribution within the portal and hepatic venous system, it is possible to derive a virtual HVPG (vHVPG). Concurrently, deep convolutional neural networks (DCNNs) are a specialized class of deep learning models exceptionally adept at processing data with a grid-like topology, such as images. In the field of medical image recognition, DCNNs have demonstrated remarkable performance, often surpassing human-level accuracy in specific diagnostic tasks. They have been successfully applied to analyze various types of medical images, including X-rays, CT scans, and MRI, for tasks such as detecting anomalies, classifying diseases, and segmenting organs or tumors.(5) U-Net architecture, in particular, has shown remarkable efficacy in automating the segmentation of complex vascular structures from medical images, thereby enhancing the reproducibility and efficiency of model construction. Meanwhile, mixed reality (MR) is an advanced immersive technology that seamlessly blends the physical and digital worlds, allowing users to interact with high-fidelity 3D holographic models in real-time while remaining fully aware of their actual surroundings. In medical imaging and surgical planning, MR revolutionizes how clinicians interpret and utilize patient-specific anatomical data. By converting traditional two-dimensional CT, MRI, or ultrasound images into interactive 3D holograms, MR provides researchers with an intuitive "X-ray vision". This technology minimizes the cognitive load required to mentally reconstruct 3D anatomy from 2D scans, thereby improving spatial awareness and precision.

This study aims to develop and validate a novel non-invasive model for predicting HVPG by leveraging advances in biofluid mechanics, deep convolutional neural network and mixed reality. We propose a prospective, multicenter trial involving patients with cirrhosis who are scheduled for HVPG measurement. The study will be conducted in two sequential stages: first, the establishment and refinement of a vHVPG model in an original cohort; and second, the independent assessment of the model's accuracy in a validation cohort. Our primary objective is to determine the numerical correlation between vHVPG and invasive HVPG, while secondary objectives include evaluating the diagnostic performance of vHVPG for detecting PH (HVPG ≥5 mmHg) and CSPH (HVPG ≥10 mmHg). We hypothesize that the integration of multi-modal data into a biomechanical model will provide a robust, non-invasive tool for quantifying portal pressure, with the potential to facilitate broader clinical adoption and dynamic monitoring in patients with cirrhosis.

Methods

Study design overview

This study is a prospective, randomised, non-controlled, multicentre trial in patients with cirrhosis.

Study population

Consecutive patients diagnosed with liver cirrhosis will be screened daily against the study's inclusion and exclusion criteria to determine eligibility. Patient recruitment commenced on 1 January 2025 and will continue until the target sample size of 248 participants is reached.

Inclusion criteria:

1. Patients at least 18 years of age.
2. Patients with cirrhosis (diagnosed by ultrasound, CT, MRI, FibrosScan or liver biopsy), scheduled for HVPG measurement.

Exclusion criteria:

1. Female patients who are pregnant or nursing.
2. Patients who are medically unstable, terminally or seriously ill, or patients whose clinical course is unpredictable.
3. Patients with clinically unstable cardiac disease, for example, congenital heart defect, arrhythmia, or uncontrolled heart failure (New York Heart Association class IV).
4. Patients with respiratory distress syndrome or clinically unstable pulmonary disease, for example, pulmonary hypertension, pulmonary emboli, pulmonary vasculitis or emphysema.
5. Patients with severe coagulation disorders.
6. Patients with unstable occlusive disease or thrombosis within the hepatic, portal or mesenteric veins.
7. Patients who are allergic to iodinated contrast.

Ethics and informed consent

This trial will be conducted in compliance with the latest version of the Declaration of Helsinki. Prior to any study-related procedures, written informed consent will be obtained from each participant, or from their legally authorized representative (legal guardian or next of kin) if the participant is incapable of providing consent themselves. All participants retain the right to withdraw from the study at any time without penalty and without prejudice to their future medical care. The study protocol, including the statistical analysis plan, informed consent forms, and case report forms, has been reviewed and approved by the Independent Ethics Committee of Shanghai Ninth People's Hospital, affiliated with Shanghai Jiao Tong University School of Medicine (Approval Numbers: SH9H-2024-T237 and SH9H-2024-T424).

Objectives

The primary objective of this study was to determine the numerical correlation between vHVPG and HVPG. The secondary objective was to determine the diagnostic accuracy of vHVPG for the diagnostics of PH and CSPH. The gold standard for the diagnosis will be the HVPG measurement.

Procedure of the study

Consecutive eligible patients will be randomly assigned in a 1:1 ratio to either the original cohort (model development) or the validation cohort (model validation). The randomization sequence will be generated using a

computer-generated random numbers table to ensure allocation concealment. This study comprises two independent, consecutive stages:

1. Model Development and Refinement (Original Cohort): For the 124 patients in the original cohort, biofluid mechanics specialists will utilize each patient's CT angiography data, blood test results (including viscosity and density), Doppler ultrasound hemodynamic parameters, and the invasive HVPG measurement to iteratively adjust the parameters of the virtual HVPG (vHVPG) model. The objective of this stage is to achieve a close numerical agreement (defined as a difference of less than 5%) between the calculated vHVPG and the measured HVPG for each patient in this cohort. Following the processing of all patients in the original cohort, the final model parameters will be frozen.
2. Model Validation (Validation Cohort): For the subsequent 124 patients in the validation cohort, the vHVPG will be calculated based on the frozen model parameters established in the first stage. Specialists will have access only to the patients' CT, blood test, and Doppler ultrasound data and will be blinded to the corresponding HVPG measurements during this calculation phase. The diagnostic accuracy of the vHVPG model will be independently assessed by comparing the predicted vHVPG values against the measured HVPG values, which serve as the gold standard.

To minimize measurement variability and potential bias, all examinations for a given patient will be conducted under standardized conditions. Patients will fast for at least 8 hours and rest supine on the examination table for a minimum of 10 minutes prior to any procedures. The Doppler ultrasound and HVPG measurement will be performed either before the contrast-enhanced CT scan or at least 24 hours afterward to avoid interference. Furthermore, the professionals performing the invasive HVPG measurements will be blinded to the results of the CT, blood tests, and Doppler ultrasound. All data collection (CT, blood tests, Doppler ultrasound, and HVPG) for each patient must be completed within a 30-day window, during which any treatments known to significantly influence HVPG values will be avoided.

The study design and procedure are shown in figure 1.

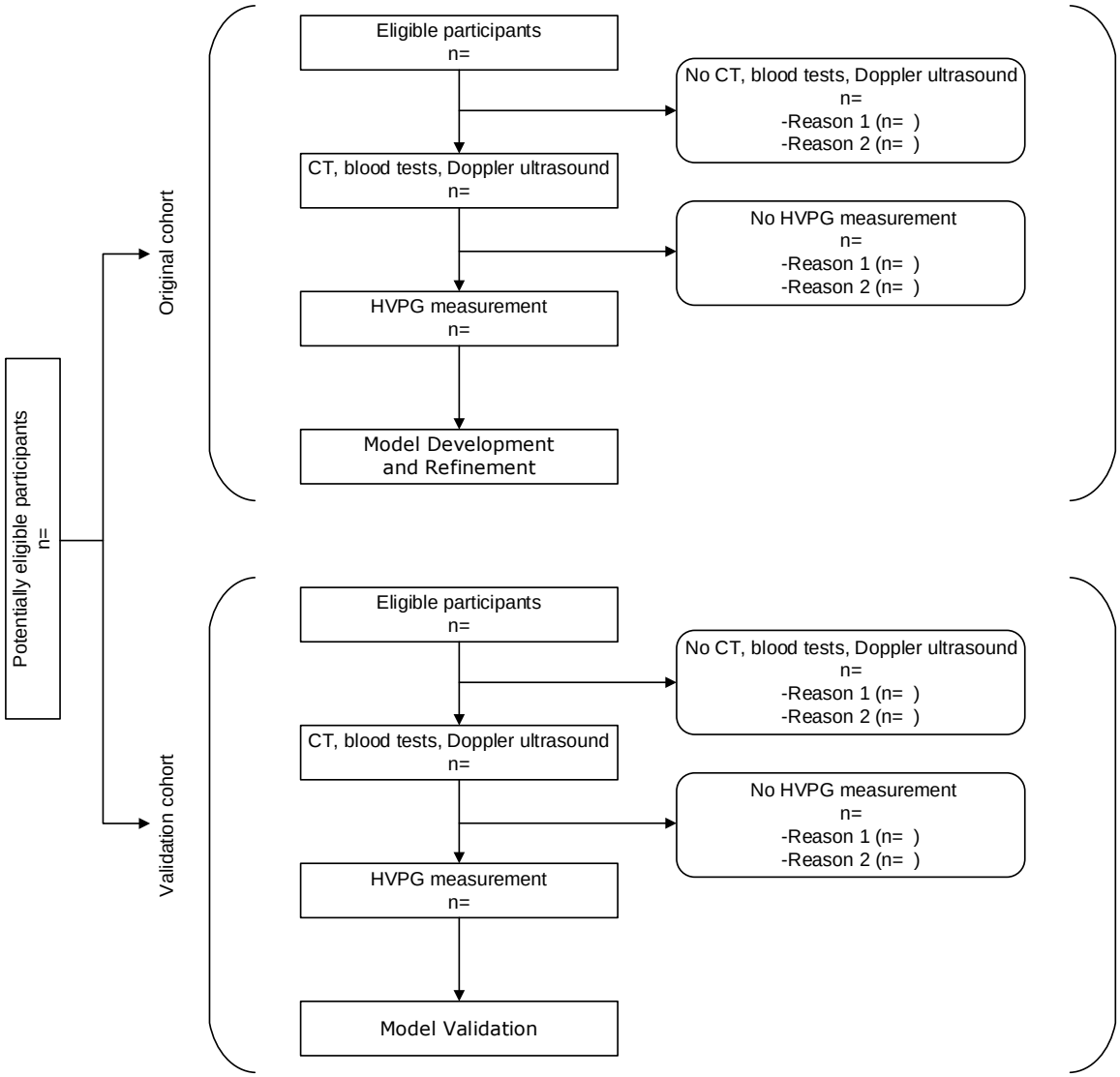

Figure 1 Study design and procedure. HVPG, hepatic venous pressure gradient.

Examination

Blood tests

Venous blood samples will be collected from the cubital vein of each patient for the measurement of blood viscosity and density. Blood viscosity will be measured using an automated blood rheology analyzer. Blood density will be determined by gravimetric analysis, specifically by weighing a 1 mL blood sample.

CT

Each patient will undergo an abdominal contrast-enhanced CT scan using multi-detector row CT scanners, performed in accordance with the study protocol.(6, 7) To standardize imaging and minimize motion artifacts, all scans will be conducted during a deep inspiration breath-hold.

Doppler Ultrasound

An abdominal Doppler ultrasound examination will be performed on each patient to measure the inner diameters, blood flow direction, and blood flow velocity in key vessels, including the inferior vena cava, hepatic veins, portal vein, and its main branches, following established recommendations.(8-10) The examination will utilize a color Doppler ultrasound system equipped with a 3–5 MHz transducer. Imaging parameters will be optimized to ensure

the acquisition of high-quality images. The 12 specific measurement positions are detailed in Figure 2. Each measurement will be obtained during a deep inspiration breath-hold, using an insonation angle of 45° to 55°. All measurements will be performed in at least duplicate and subsequently averaged. To ensure measurement reliability, both intra-observer and inter-observer variability will be maintained below 10%.

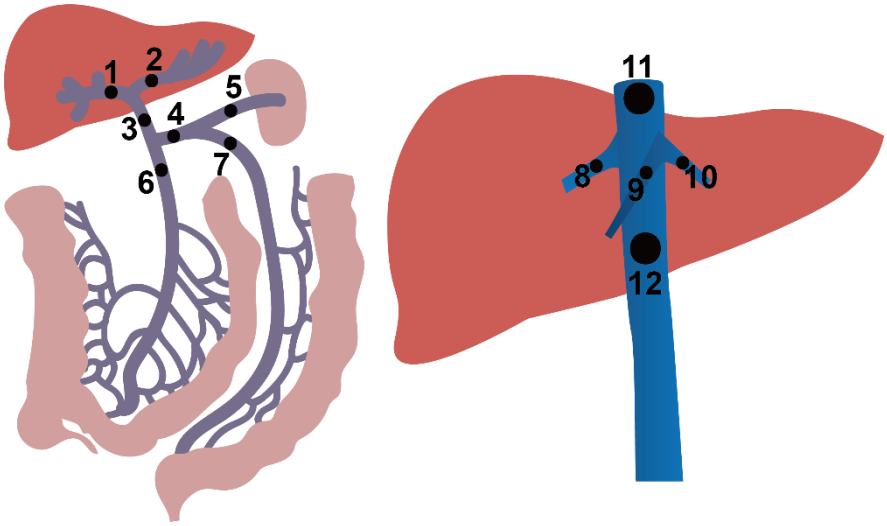

Figure 2 Ultrasound measurement positions. 1, right branch of the portal vein; 2, left branch of the portal vein; 3, the portal vein; 4, proximal part of the splenic vein; 5, distal part of the splenic vein; 6, the superior mesenteric vein; 7, the inferior mesenteric vein; 8, the right hepatic vein; 9, the middle hepatic vein; 10, the left hepatic vein; 11, the suprahepatic inferior vena cava; 12, the infrahepatic inferior vena cava.

HVPG Measurement

The hepatic venous pressure gradient (HVPG) will be measured by experienced operators in accordance with established standards.(11) Under local anesthesia, the right internal jugular vein will be cannulated. A 5.5-French balloon-tipped catheter connected to a pressure monitoring system will then be advanced into the right or middle hepatic vein. The wedged hepatic venous pressure (WHVP) will be recorded after balloon inflation to occlude the hepatic vein, with occlusion confirmed by the absence of reflux upon manual contrast injection. The free hepatic venous pressure (FHVP) will be measured with the catheter tip positioned freely in the hepatic vein, approximately 3 cm from its junction with the inferior vena cava. Pressure tracings will be recorded continuously until stable readings are obtained (≥60 seconds for WHVP and ≥20 seconds for FHVP), with the patient resting quietly and breathing normally to prevent artifacts. WHVP will be measured at least three times. All pressure tracings will be permanently saved for independent review and artifact exclusion. The HVPG will be calculated as the difference between the average WHVP and the average FHVP (HVPG = WHVP - FHVP).

Computation

Geometry

After obtaining CT images in Digital Imaging and Communications in Medicine (DICOM) format, automated vascular segmentation was implemented using a deep learning framework based on convolutional neural networks. Specifically, we employed a U-Net architecture, which has demonstrated exceptional performance in medical image segmentation tasks due to its encoder-decoder structure with skip connections that preserve spatial information across network layers. The model was pretrained and could significantly reduce the requirement for

large annotated medical datasets while maintaining high segmentation accuracy. Following segmentation, vessel tracing and anatomical labeling were performed using a conditional random field (CRF) framework to incorporate both local image features and spatial relationships between vascular structures. The annotated two-dimensional vascular segments were reconstructed into stereolithography (STL) formatted three-dimensional geometric models using surface rendering and volume rendering techniques. This model is then imported into Unity 3D, which is a development platform widely used for creating MR applications. After spatial registration and alignment by using fiducial markers or surface matching algorithms, the aligned model is rendered through an MR headset.

Following the reconstruction of the three-dimensional geometric model of the blood vessel, mesh generation was performed using ANSYS Meshing software to discretize the computational domain for subsequent computational fluid dynamics analysis in ANSYS Fluent software. The vascular geometry was imported, and a predominantly tetrahedral mesh was generated to accommodate the complex anatomical structure. Finally, the boundaries were explicitly defined, marking the inlet, outlet, and vessel wall surfaces, and the mesh was exported in a format compatible with ANSYS Fluent software.

Boundary conditions

Biofluid mechanics specialists will calculate the blood flow velocity at the boundaries of the main blood vessels according to the blood flow direction and the blood flow velocity (measured by Doppler ultrasound), the inner diameter (obtained from the STL format files) and the principle of mass conservation.

The Navier-Stokes equations

Blood is modeled as an incompressible, Newtonian fluid, an assumption that is reasonable for flow simulations in large vessels where shear rates are sufficiently high. The flow is governed by the incompressible Navier-Stokes equations as follows:

Formula 1: $$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \vec{v}) = S_m$$

Formula 2: $$\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial x}(\rho v_x) + \frac{\partial}{\partial r}(\rho v_r) + \frac{\rho v_r}{r} = S_m$$

Formula 3: $$\frac{\partial}{\partial t}(\rho E) + \nabla \cdot (\vec{v}(\rho E + p)) = \nabla \cdot \left(k_{eff} \nabla T - \sum_j h_j \vec{J}_j + \left(\bar{\bar{\tau}}_{eff} \cdot \vec{v}\right)\right) + S_h$$

Formula 4: $$E = h - \frac{p}{\rho} + \frac{v^2}{2}$$

Formula 5: $$\frac{\partial}{\partial t}(\rho \vec{v}) + \nabla \cdot (\rho \vec{v} \vec{v}) = -\nabla p + \nabla \cdot (\bar{\bar{\tau}}) + \rho \vec{g} + \vec{F}$$

Formula 6: $$\bar{\bar{\tau}} = \mu \left[(\nabla \vec{v} + \nabla \vec{v}^T) - \frac{2}{3} \nabla \cdot \vec{v} I\right]$$

ρ: density; v: velocity; S_m: mass added to the continuous phase; x: axial coordinate; r: radial coordinate; v_x: axial velocity; v_r: radial velocity; h: enthalpy value; p: static pressure; $\bar{\bar{\tau}}$: stress tensor; $p\vec{g}$: gravitational body force; $\vec{F}$: external body force; μ: molecular viscosity; I: unit tensor.

Establishment, improvement and assessment of the vHVPG model

Use the ANSYS FLUENT software to solve the Navier-Stokes equations (formulas 1–6) and to get the simulated blood pressure on each volume grid. The virtual HVPG will be calculated from the difference between virtual portal pressure (vPP) and virtual hepatic venous pressure (vHVP), namely, vHVPG = vPP − vHVP. Compare the virtual and measured HVPGs. If they do not match well (their difference greater than 5%), then modify the parameters of the model until the virtual and measured HVPGs match well (their difference less than 5%). After

applying this process to each patient in the original cohort, freeze the model parameters and finalize the model improvement.

Use the FLUENT software to solve the Navier-Stokes equations and calculated the vHVPG of each patient in the validation cohort and compare the virtual and measured HVPGs.

Sample size calculation

The sample size for this study was calculated using PASS software version 19.0.1, (NCSS, LLC, USA). The "Bland-Altman Method for Assessing Agreement in Method Comparison Studies" procedure was used.(12) This method requires specifying the confidence level for the limits of agreement (set at 95%), the confidence level for the CI of these limits (also 95%), and the maximum allowable difference (set at 3.0 mmHg). The anticipated mean difference (0.184 mmHg) and standard deviation of differences (1.163 mmHg) between vHVPG and HVPG measurements were derived from prior canine experiments. Based on these parameters, the analysis indicated that a sample size of 112 subjects would provide 80% statistical power to demonstrate agreement between the two measurement methods. To account for an anticipated 10% attrition rate or exclusion due to protocol deviations, the target recruitment was set at 124 patients per cohort, resulting in a total sample size of 248 patients.

Statistical Analysis Plan

Discrete variables will be summarised by frequencies and percentages and analysed by the χ^2 test. Continuous variables will be checked for normal distribution and summarised by either mean and SD or median and IQR as appropriate. Comparison of continuous variables will be performed by using Student's t-test or analysis of variance for normally distributed variables and the Mann-Whitney U test or the Kruskal-Wallis test for non-normally distributed variables as appropriate.

The primary analysis, assessing the agreement between the novel virtual HVPG (vHVPG) and the invasive gold standard HVPG in the validation cohort, will be conducted primarily using the Bland-Altman method.(13) A Bland-Altman plot will be constructed by plotting the differences between vHVPG and HVPG against their averages for each subject. The bias will be defined as the mean of these differences. The 95% limits of agreement (LOA) will be calculated as the bias ± 1.96 times the standard deviation (SD) of the differences. The 95% confidence intervals (CIs) for both the bias and the LOA will be calculated to assess their precision . To supplement the Bland-Altman analysis, the numerical relationship will also be quantified using the intraclass correlation coefficient, Lin's concordance correlation coefficient and allowable total error and limits for erroneous results zones for agreement measurement.

The diagnostic performance of vHVPG for detecting portal hypertension (PH, defined as HVPG ≥5 mmHg) and clinically significant portal hypertension (CSPH, defined as HVPG ≥10 mmHg) will be evaluated in the validation cohort. This assessment will include sensitivity, specificity, false-positive rate, false-negative rate, positive predictive value (PPV), negative predictive value (NPV), overall diagnostic accuracy, and the Youden index. The likelihood ratios for positive and negative test results (LR+ and LR-) will also be calculated. The agreement between vHVPG-based and HVPG-based classifications will be further quantified using Cohen's kappa statistic. Receiver operating characteristic (ROC) curves will be generated, and the area under the ROC curve (AUC) will be computed to summarize the overall discriminatory ability of vHVPG. The diagnostic accuracy of vHVPG will also be compared with the diagnostic accuracy of other published non-invasive methods.(2, 14)

All tests of significance will be at the 5% significance level. Analyses will be conducted using SPSS Statistics V.24.0, NCSS Statistical Software V.19.0.1 (NCSS, LLC, USA) and MedCalc Statistical Software V.18.11, (MedCalc Software bvba, Belgium).

Discussion

It is a truth acknowledged that PH is a critical syndrome because it may cause severe complications, including gastro-oesophageal variceal haemorrhage, hepatic encephalopathy and ascites.(15) This prospective, multicenter study aimed to develop and validate a novel non-invasive model for predicting the hepatic venous pressure gradient (HVPG) in patients with liver cirrhosis by integrating biofluid mechanics, deep convolutional neural network and mixed reality. In previous experiments, we made a model of PP assessment by using biofluid mechanics in canines and found out a strong correlation between simulated PP and measured PP.(16) We then applied this model to several portal hypertensive patients who underwent portosystemic shunts or splenectomy with periesophagogastric devascularisation and came up with similar results.(17) These findings proved our biofluid mechanics-based method to be feasible. The primary findings of this study are expected to demonstrate a strong numerical correlation between the virtual HVPG (vHVPG) and the invasive HVPG measurement. If validated, the vHVPG model could represent a significant advancement in the non-invasive assessment of portal hypertension, addressing a critical clinical need for a safer, more accessible alternative to the invasive gold standard.(18)

The proposed model's strength lies in its multi-modal approach, which synthesizes anatomical data from CT angiography, functional flow parameters from Doppler ultrasound, and individualized blood viscosity and density measurements. This integration likely allows for a more comprehensive simulation of portal and hepatic venous system hemodynamics compared to previous models that relied on static anatomical data or simplified assumptions.(19) The use of deep convolutional neural network, specifically a U-Net architecture, for automated segmentation of the complex portal and hepatic vasculature is a key innovation that enhances reproducibility and reduces manual intervention bias. Furthermore, the integration of MR technology offers a transformative potential for intuitive, three-dimensional interaction with the computational models, which could significantly improve the understanding of complex vascular relationships for preoperative planning and intraoperative guidance. The study's two-stage design - initial model development and refinement followed by independent validation in a distinct cohort - strengthens the robustness of the findings and minimizes overfitting.

Interpreting the results will require careful comparison with existing non-invasive methods for assessing portal hypertension. The vHVPG model, based on direct hemodynamic simulation, may offer a more specific reflection of portal pressure and could potentially outperform previous studies. The statistical plan, which includes Bland-Altman analysis for agreement, intraclass correlation coefficient, and ROC analysis for diagnostic accuracy, will provide a comprehensive assessment of the model's performance against the well-defined benchmarks of PH (HVPG ≥5 mmHg) and CSPH (HVPG ≥10 mmHg).(20)

Several potential limitations of this study must be acknowledged. First, the model's performance is contingent on the quality of the input imaging and Doppler ultrasound data. Variations in scanner protocols, patient breath-holding compliance, or operator technique during ultrasound could introduce variability. While standardized protocols are in place to mitigate this, it remains a practical consideration. Second, the biofluid mechanics model assumes blood is a Newtonian fluid, which is a simplification of its true rheological properties, particularly in

low-flow states or diseased vessels. This assumption might affect pressure estimation accuracy in some patients. Third, the study population, though multi-center, may have specific characteristics, and the generalizability of the model to all cirrhotic patients, such as those with extensive portosystemic collaterals or prior interventions, requires further investigation. The exclusion of patients with unstable thrombosis or severe coagulation disorders also means the model's applicability in these subgroups is not established.

Despite these limitations, the successful development and validation of the vHVPG model would have profound clinical implications. It could facilitate widespread, repeated assessment of portal pressure, enabling earlier detection of CSPH, improving risk stratification, and monitoring response to pharmacologic therapy in both tertiary and non-tertiary care settings. Future research directions should include external validation in more diverse populations, longitudinal studies to assess the model's utility in tracking disease progression or treatment response over time, and technical refinements to incorporate non-Newtonian fluid dynamics and automate the Doppler ultrasound data integration further.

In conclusion, this study proposes a rigorous methodology for creating a non-invasive HVPG estimation tool. By leveraging advances in biofluid mechanics and deep learning, the vHVPG model holds the promise of transforming the clinical management of patients with cirrhosis and portal hypertension by making a crucial hemodynamic parameter more accessible.

Conflicts of Interest

None.

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