

Dual and context-dependent roles of blood viscosity in cirrhotic portal hypertension

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Abstract

Portal hypertension is a major complication of cirrhosis characterized by increased intrahepatic resistance and hyperdynamic circulation. Emerging evidence suggests that hemorheological alterations may play a context-dependent dual role in this process. Increased sinusoidal blood viscosity may aggravate intrahepatic resistance, whereas decreased peripheral viscosity may facilitate splanchnic inflow and help sustain hyperdynamic circulation under specific clinical conditions. However, current evidence primarily stems from theoretical models, experimental studies, and a limited number of clinical observations, and it has not yet been established that blood viscosity is an independent upstream determinant of portal vein pressure. Therefore, this review synthesizes the existing evidence regarding the mechanistic link between blood viscosity and portal hypertension and proposes that blood viscosity be interpreted as a context-dependent modulator and amplifier of portal hypertensive pathophysiology in cirrhosis. We also discuss unresolved controversies, implications for different disease stages and specific clinical contexts, and potential directions for translational research.

Keywords: liver cirrhosis, portal hypertension, blood viscosity, hemorheology, hemodynamics

Portal hypertension is a primary consequence of liver cirrhosis and the main cause of complications such as ascites, gastroesophageal variceal bleeding, and hypersplenism ^[1]. Its pathophysiological mechanisms are complex, involving increased intrahepatic vascular resistance and elevated portal vein blood flow caused by hyperdynamic circulation, among other factors ^[2]. Currently, scoring systems that include the Child-Pugh score and the Model for End-Stage Liver Disease score are commonly used to assist in prognostic

assessment ^[3]. The primary treatment methods for liver cirrhosis include eliminating the underlying cause, surgical intervention, or using limited pharmacological strategies, mainly aimed at addressing the complications of portal hypertension ^[4, 5]. Blood rheological factors have received comparatively less attention in prevailing frameworks of portal hypertension. Yet accumulating data suggest that viscosity-related changes may influence portal hypertensive pathophysiology in more than one direction.

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Increased sinusoidal viscosity may reinforce intrahepatic resistance, whereas reduced peripheral viscosity in advanced disease or selected complication settings may favor hyperdynamic circulation and increased splanchnic inflow. These observations support the hypothesis that blood viscosity may function as a context-dependent modulator rather than a uniformly harmful or uniformly protective factor. Accordingly, this review summarizes the pathophysiological basis of viscosity changes in cirrhosis, examines the pathways through which hemorheological alterations may interact with portal hemodynamics, and discusses the strengths, limitations, and translational implications of the current evidence. The proposed dual and context-dependent framework is summarized schematically in Figure 1.

Literature search strategy

This review was informed by a structured literature search of PubMed, Web of Science, Google Scholar, and CNKI from database inception to March 2026, using combinations of the terms “cirrhosis”, “portal hypertension”, “blood viscosity”, “hemorheolog*”, “whole blood viscosity”, “plasma viscosity”, “erythrocyte deformability”, “erythrocyte aggregation”, “hyperdynamic circulation”, “platelet activation” and “sinusoidal microcirculation”. Additional relevant studies were identified through manual review of reference lists. We prioritized experimental, mechanistic, and clinical studies that directly informed the proposed framework linking blood viscosity to portal hypertensive pathophysiology. Given the narrative nature of this

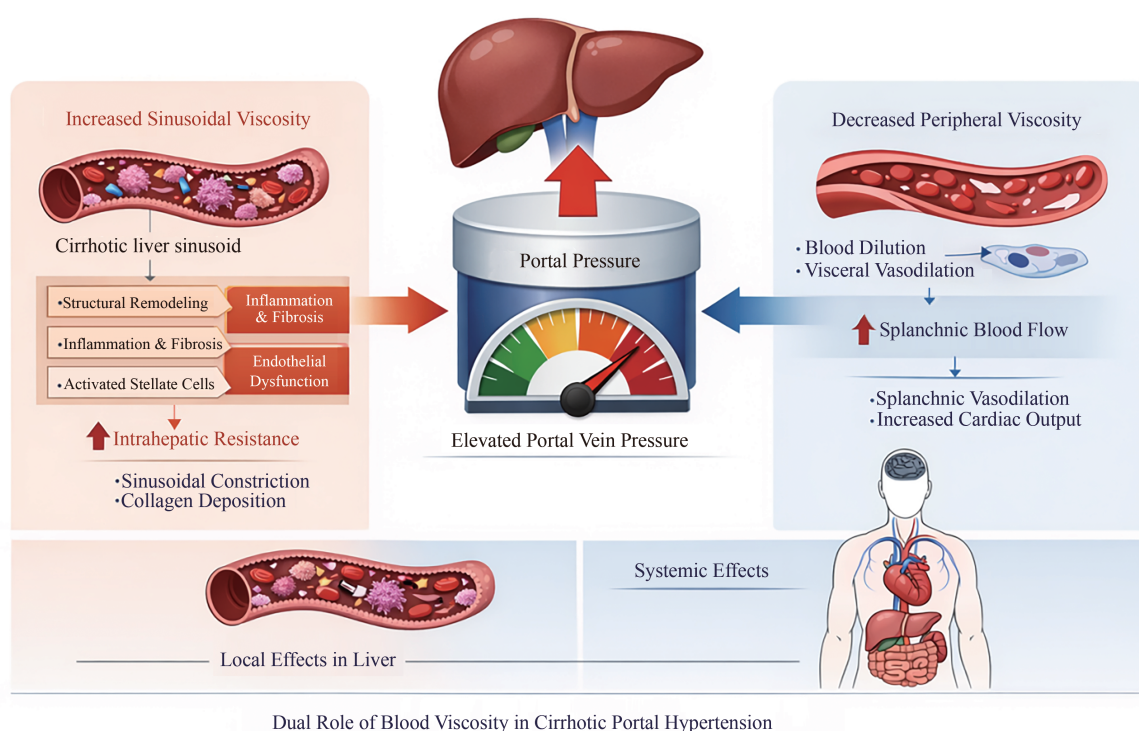


Figure 1. Conceptual schematic of the dual and context-dependent roles of blood viscosity in cirrhotic portal hypertension.

The left panel illustrates the local intrahepatic pathway, in which increased sinusoidal viscosity, together with structural remodeling, inflammation, fibrosis, endothelial dysfunction, and stellate cell activation, may reinforce intrahepatic resistance and contribute to portal pressure elevation. The right panel illustrates the systemic/peripheral pathway, in which decreased peripheral viscosity, blood dilution, and visceral vasodilation may favor increased splanchnic blood flow and sustain hyperdynamic circulation. These pathways are not mutually exclusive and may coexist across different disease stages and clinical scenarios, jointly contributing to the maintenance and amplification of portal hypertensive hemodynamics.

review, article selection was guided by relevance to mechanism, disease stage, and clinical context rather than by formal systematic-review methodology.

Blood viscosity and the pathophysiological basis of cirrhotic portal hypertension

Basic principles of blood rheology

The internal friction that impedes blood flow is referred to as the viscosity of blood, and the physical quantity used to measure this property is blood viscosity (η). Blood viscosity is a key determinant of local hemodynamic characteristics and exhibits shear thinning behavior. As the shear rate increases, blood viscosity decreases exponentially ^[6]. This property is primarily governed by the aggregation and deformability of red blood cells (RBCs) ^[7]. At high shear rates, the laminar flow phenomenon becomes prominent, RBCs are concentrated along the central axis of the bloodstream, and both rotational motion and collisions among RBCs are reduced, resulting in lower blood viscosity. Conversely, at low shear rates, RBC aggregation occurs, leading to increased blood viscosity. In addition, as the shear rate increases, the deformation of RBCs becomes more pronounced, causing the RBCs to assume shapes such as spindle, bullet, and rod forms. This reduces interference with blood flow and decreases blood viscosity. According to Poiseuille's law ($R=8 \eta L / (\pi r^4)$), an increase in blood viscosity leads to elevated vascular resistance. However, blood viscosity, through its influence on vascular wall shear stress, serves as a key regulatory factor to produce nitric oxide (NO) by endothelial nitric oxide synthase (eNOS). Therefore, in healthy individuals with intact vascular function capable of adapting to hemorheological changes, an increase in blood viscosity can promote vasodilation, thereby reducing the vascular resis-

tance that would otherwise rise due to increased blood viscosity ^[6].

Hemodynamic basis of portal hypertension

According to the application of Ohm's law ($\Delta P = Q \times R$) in hemodynamics, an increase in the portal vein pressure gradient (ΔP) can be attributed to an increase in resistance (R), an increase in blood flow (Q), or a combination of both ^[8]. Chronic injury leads to a series of structural and functional alterations in the liver, and changes in hepatic microcirculation result in portal hypertension ^[9]. Dysfunction of liver sinusoidal endothelial cells (LSECs), activation of hepatic stellate cells (HSCs), and alterations in the structure and function of hepatic sinusoids also trigger matrix deposition, sinusoidal contraction, and increased vascular resistance ^[4,8]. As intrahepatic vascular resistance rises, blood pressure in the splanchnic region increases, prompting visceral endothelial cells to release vasodilators, which cause mesenteric and systemic vasodilation. Ultimately, the combined effects of elevated intrahepatic resistance and hyperdynamic circulation lead to portal hypertension ^[9].

In summary, alterations in blood shear thinning, RBC deformability, RBC aggregation, and so on may exacerbate hemodynamic disturbances and contribute to disease progression in the pathogenesis of portal hypertension in liver cirrhosis.

The role of blood viscosity in cirrhotic portal hypertension

This section provides an overview of two complementary pathways: increased hepatic sinusoidal viscosity potentially reinforcing intrahepatic resistance, and decreased peripheral viscosity, together with hyperdynamic circulation, potentially favoring increased portal venous inflow (Figure 1).

Structure-driven viscosity increase

This section discusses evidence supporting the possibility that cirrhosis-associated structural remodeling may create a pro-viscous sinusoidal microenvironment, which in turn may reinforce intrahepatic resistance. The available data support biological plausibility, although they do not yet establish sinusoidal viscosity as an independent initiating determinant of portal hypertension. The primary factor contributing to the development of portal hypertension is a marked increase in intrahepatic vascular resistance to portal venous blood flow. This occurs in the early stages of chronic liver disease as a result of alterations in hepatic sinusoidal endothelial cells^[10]. According to Poiseuille's law, an increase in blood viscosity leads to an elevation in vascular resistance^[6]. The role of blood viscosity in the elevation of intrahepatic vascular resistance can be analyzed from several perspectives.

One important mechanism is the structural remodeling of the sinusoidal wall. During cirrhosis, LSEC fenestrae are reduced or lost, and the endothelial surface becomes less smooth and more irregular, a process often referred to as sinusoidal capillarization^[11,12]. These changes impair the exchange of substances between blood and hepatocytes, promote sinusoidal congestion, and increase frictional resistance to flow. As a consequence, local blood velocity and shear rate decline, favoring an increase in apparent blood viscosity within the sinusoidal lumen. In this setting, viscosity is not merely a passive blood property; rather, it is shaped by the altered microenvironment created by cirrhotic structural injury. Thus, sinusoidal remodeling and viscosity elevation may act together to reinforce intrahepatic vascular resistance.

Structural injury also affects the mechanical behavior of blood cells, particularly RBCs, thereby further am-

plifying local rheological abnormalities. Blood flow in the microcirculation is highly dependent on the deformability of RBCs, and the loss of deformability leads to an increase in blood viscosity^[6]. Researchers employed an ex vivo hepatic sinusoid model and used the immersed boundary method coupled with the lattice Boltzmann method to simulate blood flow and RBC deformation^[12]. The endothelial permeability component was set at levels (2.5×10^{-16} – 2.5×10^{-13} m²). When the endothelial permeability increased from 10^{-16} m² to 10^{-13} m², the RBC deformation index decreased by 26.7%, indicating a more circular shape. This result reflected the characteristics of intrasinusoidal microcirculation and suggested that a higher endothelial permeability coefficient leads to more stable RBC deformability. This finding holds significant biological implications in hepatic fibrosis, where endothelial capillarization tends to markedly affect RBC deformation within the sinusoidal lumen by altering endothelial permeability. Concurrently, in liver cirrhosis, hepatic sinusoids experience hypoxia due to microcirculatory disturbances. Under hypoxic conditions, cellular swelling alters the surface area-to-volume ratio, thereby reducing the deformability of cells. The decreased deformability of RBCs, meaning increased RBC rigidity, may lead to elevated blood viscosity, which in turn exacerbates portal vein pressure^[13]. At the microcirculatory level, the persistent presence of RBC aggregates may increase precapillary resistance^[6]. Similarly, in liver cirrhosis, reactive oxygen species (ROS) released from damaged hepatocytes activate Kupffer cells, initiating an inflammatory cascade reaction^[14]. These cells secrete various cytokines, including transforming growth factor- β 1, TNF- α , monocyte chemoattractant protein-1, chemokines such as CCL3 and CCL5, and other soluble mediators, thereby accelerating the progression of hepatic fibrosis^[15,16]. Concurrently, oxygen free radicals can alter the surface properties of red blood cells, changing their

tendency to aggregate, which enhances RBCs aggregation and increases intrahepatic vascular resistance^[17].

Platelet (PLT) activation and micro-thrombosis provide another structural mechanism by which viscosity-related resistance may be reinforced. Research findings^[18–21] have shown that in patients with liver cirrhosis, plasma levels of thrombin, von Willebrand factor, and soluble P-selectin are elevated. PLT become activated and release procoagulant substances, leading to the formation of micro-thrombi. In addition, PLT in patients with liver cirrhosis produce large amounts of isoprostanes, which are chemically stable eicosanoids derived from the interaction between arachidonic acid and ROS generated by NADPH oxidase 2. These isoprostanes promote PLT aggregation by activating platelet membrane glycoprotein IIb/IIIa, thereby increasing blood viscosity, obstructing hepatic sinusoids, and elevating blood flow resistance. Simultaneously, various bioactive molecules released by activated PLT recruit inflammatory cells to the liver, causing necrotizing inflammation and fibrosis. In addition to inducing immune-mediated liver injuries, PLT also reduce hepatic sinusoid microcirculation by secreting serotonin^[22].

Emerging mechanobiological evidence further suggests that increased tissue stiffness and pressure transmission within the fibrotic liver may create a self-reinforcing loop. As fibrosis progresses, hepatic compliance decreases, sinusoidal pressure rises, and abnormal mechanical stress is transmitted to neighboring endothelial and non-parenchymal cells^[23]. Researchers have used in vitro experiments and animal models to measure portal vein pressure with a digital blood pressure analyzer. The results showed that in congestive liver disease, when endothelial cells are subjected to tensile stress, the Piezo1-Notch1 receptor-Hes/Hey signaling pathway is activated. This pathway can lead

to micro-thrombosis formation and an increase in hydrostatic pressure, which may ultimately create a positive feedback loop that exacerbates the progression of portal hypertension^[24].

Taken together, currently available evidence supports the possibility that cirrhosis-associated structural remodeling may create a pro-viscous sinusoidal micro-environment characterized by capillarization, reduced shear space, impaired RBC transit, PLT activation, and micro-thrombotic obstruction. These factors may jointly increase local blood viscosity and resistance, suggesting that structural-driven viscosity increase may represent an important contributor to the initiation and progression of portal hypertension.

Hemodynamic-driven viscosity amplification

In addition to structural abnormalities, hemodynamic disturbances can amplify the effects of altered blood viscosity and help sustain portal hypertension once it has developed. Portal hypertension is determined by both resistance and blood flow, as illustrated by the hemodynamic application of Ohm's law ($\Delta P = Q \times R$)^[8]. Although structural remodeling is central to the initial rise in intrahepatic resistance, the subsequent changes in blood flow velocity, shear conditions, and systemic vascular tone may further magnify viscosity-related abnormalities. In this sense, blood viscosity may not only be structurally increased within the cirrhotic liver but also functionally amplified by abnormal hemodynamic conditions.

A key mechanism is the reduction in sinusoidal blood flow velocity and shear rate. In cirrhosis, endothelial dysfunction, reduced NO bioavailability, increased release of vasoconstrictors, and hepatic stellate cell contraction all contribute to heightened sinusoidal resistance. As intrahepatic resistance rises, blood flow

within the distorted sinusoidal network becomes slower and more heterogeneous. Because blood is a shear-thinning fluid, a reduction in shear rate itself tends to increase blood viscosity ^[6]. This may create a vicious cycle in which elevated resistance slows blood flow, lower flow increases apparent viscosity, and the resulting viscosity increase may further augment resistance. Therefore, under cirrhotic conditions, hemorheological abnormalities are not static but dynamically intensified by low-shear intrahepatic flow.

At the systemic and splanchnic levels, hyperdynamic circulation further contributes to this amplification process. As resistance within the liver increases, upstream pressure rises and stimulates the release of vasodilators, particularly NO, from the splanchnic and systemic endothelium ^[9]. This leads to enhanced vasodilation and increased cardiac output, resulting in hyperdynamic circulation that further augments blood flow to the viscera and liver ^[25,26]. Researchers investigated the mechanism underlying the upregulation of eNOS in a biliary cirrhosis rat model. Three types of rat models were established: a biliary cirrhosis model (36 rats), a portal vein stenosis model (32 rats), and a sham-operated control group (30 rats). Three parallel groups receiving propranolol treatment were also included. Propranolol was administered to rats with liver cirrhosis to reduce cardiac output and decrease shear stress. The results showed that systemic vasodilation primarily depended on shear stress-related upregulation of eNOS ^[27]. Increased shear stress may therefore enhance NO production and further aggravate vasodilation, forming another positive feedback loop ^[28]. Although this pathway does not directly increase blood viscosity, it amplifies the hemodynamic consequences of viscosity-related resistance by increasing portal venous inflow.

A further aspect of hemodynamic-driven amplification

is the reduction in peripheral blood viscosity, particularly in advanced cirrhosis. According to Poiseuille's law, lower blood viscosity reduces vascular resistance. Evidence primarily derives from small-sample clinical or animal/theoretical studies. Peripheral cytopenia caused by hypersplenism and inflammatory response in patients with advanced liver cirrhosis can affect the hyperdynamic circulatory state. In a cross-sectional study including 42 patients with cirrhotic variceal bleeding and 44 matched non-bleeding patients, the results showed that patients with advanced liver cirrhosis had reduced RBC hematocrit and PLT counts, as well as decreased RBC aggregation ^[29]. Another retrospective analysis of clinical data from 183 patients with cirrhotic portal hypertensive splenomegaly complicated by peripheral cytopenia demonstrated that splenomegaly and hypersplenism were the main causes of peripheral cytopenia. The larger the spleen volume, the more blood cells were phagocytosed by spleen macrophages, leading to lower peripheral blood cell counts and consequently reduced peripheral vascular resistance. This hemodynamic change may exacerbate the hyperdynamic circulatory state ^[30]. A randomized controlled trial (RCT) was conducted to investigate the effects of rifaximin on endotoxemia and thrombocytopenia in patients with alcoholic liver cirrhosis ^[31]. Thirteen patients with alcoholic liver cirrhosis received rifaximin treatment at a dose of 1,200 mg/d for four weeks and were compared with ten patients in the control group. The results showed that rifaximin improved thrombocytopenia by reducing endotoxin levels. These findings suggest that peripheral cytopenia is associated with inflammatory responses. During anti-inflammatory treatment, the increase in blood cell counts also elevates peripheral blood viscosity, thereby alleviating the hyperdynamic circulatory state.

In addition, the hemodilution effect during gastrointestinal bleeding in liver cirrhosis may exacerbate the

hyperdynamic circulatory state by reducing blood viscosity, although this effect is likely to be context-dependent and may coexist with compensatory vascular responses. When esophageal and gastric variceal bleeding in liver cirrhosis leads to anemia, a large amount of tissue fluid shifts into the blood vessels, resulting in hemodilution and a decrease in hematocrit, which in turn reduces whole blood viscosity^[32]. In parallel, plasma globulin levels increase, but fibrinogen decreases significantly, and the combined effect leads to a reduction in plasma viscosity^[33]. In one study, ex vivo blood or plasma substitutes were infused into normal rats and portal hypertension rat models (a total of 32 rats) that had experienced blood loss to investigate the effects of reduced blood viscosity on the hyperdynamic circulation, portal vein pressure, and vascular geometry. The results showed that although rapid infusion of low-viscosity fluids could reduce peripheral resistance, it aggravated the hyperdynamic circulation and might lead to an increase in portal pressure. Twenty-four hours after infusion, contraction of portal collateral vessels was observed in the experimental group, which might represent a compensatory reaction of the body to the hyperdynamic circulation. Therefore, during acute bleeding in portal hypertension, slow volume resuscitation is more conducive to hemodynamic adaptation and helps prevent the worsening of hyperdynamic circulation^[34].

At the same time, reduced blood viscosity should not be interpreted as uniformly deleterious in all clinical settings. Experimental microcirculatory studies suggest that tissue perfusion depends on a dynamic balance among viscosity, oxygen-carrying capacity, and shear-dependent endothelial responses, implying that both excessive hemoconcentration and excessive hemodilution may be unfavorable^[35]. In cirrhosis, this trade-off becomes particularly relevant during acute variceal bleeding: although anemia and hemodilution

may transiently reduce flow resistance and support systemic perfusion, excessive restoration of hemoglobin may increase portal pressure and potentially favor rebleeding^[36,37]. Consistent with this view, current guidance recommends conservative packed RBC transfusion with a target hemoglobin of 7–8 g/dL, rather than aggressive correction^[1]. These observations support the possibility that the clinical effects of hypoviscosity are biphasic and context-dependent rather than uniformly harmful. However, no cirrhosis-specific study has yet defined an optimal blood-viscosity “window”, and this concept should therefore be regarded as a heuristic framework rather than a clinically actionable target.

Overall, this framework suggests that once portal hypertension is established, low-shear intrahepatic flow, splanchnic vasodilation, increased cardiac output, and reduced peripheral vascular resistance may collectively magnify viscosity-related abnormalities and thereby help sustain portal hypertensive hemodynamics.

Time-course perspective

From a temporal perspective, changes in blood viscosity are not linear but are regulated by multiple factors, including hepatic functional reserve, portal venous hemodynamics, systemic inflammation, and coagulation-fibrinolysis imbalance^[38]. In the pre-cirrhotic stage, although hepatic dysfunction is relatively mild, blood viscosity may already begin to show a mild hyperviscosity state. A retrospective study conducted by some researchers demonstrated that whole blood viscosity in the pre-cirrhotic stage was significantly higher than that in advanced cirrhosis^[39]. This early alteration may be associated with microcirculatory changes occurring during hepatic inflammation and fibrosis. As chronic liver disease progresses, hepatic impairment

worsens, portal hypertension becomes more pronounced, and the changes in blood viscosity become increasingly complex. Rheological testing has shown that patients with decompensated cirrhosis exhibit a significant decrease in viscosity, approaching the characteristics of a Newtonian fluid, along with a reduction in elastic modulus, indicating a loss of blood elasticity ^[32]. In addition, patients with decompensated liver disease often present with systemic inflammatory response and endotoxemia. These inflammatory responses lead to visceral vasodilation, such as in the mesentery, and renal vasoconstriction, which subsequently reduce the glomerular filtration rate and result in regional microcirculatory disturbance ^[40]. Meanwhile, the imbalance of the coagulation-fibrinolysis system caused by liver disease keeps patients in a prethrombotic state, increasing the risk of thrombosis ^[41]. Therefore, the decrease in blood viscosity in patients with decompensated cirrhosis does not indicate the disappearance of thrombotic risk. However, most of the existing evidence is derived from cross-sectional or retrospective studies rather than from individual evolution trajectories that have been fully validated by longitudinal studies.

Clinical implications

From a clinical perspective, the significance of hemorheological alterations is best interpreted across three partially overlapping contexts: disease stage, complication state, and treatment intervention. In compensated or earlier-stage disease, hemorheological abnormalities may remain more mechanistic than actionable, because clinical decision-making is still driven primarily by established portal hypertension assessment tools. By contrast, in advanced or decompensated cirrhosis, viscosity-related changes may become more clinically relevant through their interaction with anemia, inflammation, hyperdynamic circulation, and

thrombo-inflammatory imbalance. This context-based framework may help identify where hemorheological assessment is biologically informative, clinically relevant, or still premature.

The emerging mechanistic role of blood viscosity in portal hypertension raises an important translational question: should hemorheological assessment be incorporated into clinical practice? At present, clinical pathways still rely primarily on validated tools such as hepatic venous pressure gradient (HVPG), liver stiffness, platelet-based algorithms, spleen stiffness, endoscopy, and Doppler-derived hemodynamic assessment, whereas blood viscosity remains insufficiently standardized and clinically validated ^[1].

A more realistic near-term role for hemorheological assessment may therefore be selective rather than universal, and particularly relevant in high-risk settings. One such scenario is the peri-splenectomy setting, where postoperative increases in viscosity and platelet count may contribute to portal vein system thrombosis (PVST). In this setting, hemorheological assessment may be explored as an adjunct to early PVST risk stratification rather than as a routine monitoring tool for all patients ^[39]. Another relevant setting is acute variceal bleeding, where the key clinical issue is the balance among anemia, portal pressure, and transfusion strategy rather than normalization of viscosity per se. Contemporary evidence supports a restrictive packed RBC transfusion strategy in acute variceal bleeding, which has been associated with lower rates of rebleeding and mortality ^[42]. This indicates that the primary risk lies in excessive overcorrection at either end, rather than in “low viscosity” alone.

Therapeutically, blood viscosity may be modifiable, but the current evidence is still insufficient to support viscosity-targeted treatment in routine practice.

Experimental cirrhosis studies showed that pentoxifylline reduced portal pressure together with blood viscosity and improved whole-blood filterability ^[43]. Recent meta-analytic evidence suggests that statins may modestly reduce portal pressure in cirrhosis, but these studies evaluated portal-pressure reduction rather than viscosity-guided therapy itself ^[44]. Region-specific exploratory evidence also suggests that certain anti-fibrotic traditional Chinese medicine formulations, such as Fuzheng Huayu, may improve fibrosis-related parameters in chronic liver disease, and a multicenter randomized trial has been designed to evaluate its adjunctive role in portal hypertension with HBV-related cirrhosis ^[45]. However, direct evidence that such interventions confer a validated dual benefit on both hemorheology and portal-pressure control in routine clinical management remains limited. Thus, blood viscosity is best viewed at present as a complementary mechanistic biomarker that may refine risk interpretation in selected scenarios, rather than as a standalone biomarker or validated intervention target. A cirrhosis-specific optimal blood-viscosity “window” has not been established, and no clinically validated viscosity target is currently available for routine management.

Controversies and challenges

Despite its mechanistic plausibility, the blood-viscosity hypothesis remains limited by unresolved questions of causality, measurement, and clinical translation.

Causality dilemma

Whether blood viscosity is a driver of portal hypertension or merely a downstream epiphenomenon remains unresolved. The core pathophysiology of portal hypertension in liver cirrhosis lies in the increased intrahepatic vascular resistance and the hyperdynamic circulation of the extrahepatic splanchnic system. Within

this framework, alterations in hemorheology are biologically plausible, although they have not been confirmed as an independent upstream determinant of portal vein pressure. The reverse direction is also plausible: pathological pressure and altered shear conditions may themselves remodel the phenotype of sinusoidal endothelial cells and microvascular behavior, thereby secondarily modifying rheological characteristics. For example, researchers obtained liver tissue samples from patients with hepatitis B through hepatic biopsy, and the results showed that these patients exhibited hepatic microcirculatory disturbance, suggesting that changes in blood viscosity within the microcirculation may precede the onset of liver cirrhosis ^[46]. Therefore, the existing literature supports an association rather than causality.

Measurement bias

The second point of contention concerns the measurement itself. Blood viscosity is highly dependent on hematocrit, the composition of plasma proteins, RBC aggregation, RBC deformability, temperature, storage conditions, sampling time, and the shear rate range used in testing. Significant variations may occur across different testing platforms and clinical conditions. This methodological instability leads to two consequences. First, data from different studies are difficult to compare, particularly when measurements at low and high shear rates are not reported separately. Second, whole blood viscosity estimated by formula may underestimate the effects of RBC aggregation and deformability ^[47]. Therefore, some inconsistencies in the literature may arise from measurement heterogeneity rather than true biological differences.

Translational gap

Intrasinusoidal viscosity cannot be directly measured

in routine clinical practice. The central hypothesis of this review concerns sinusoidal hemorheology, yet sinusoidal viscosity is not a clinical variable that can currently be measured at the bedside. Contemporary diagnostic pathways for portal hypertension rely on HVPG and endoscopy as reference standards, with increasing use of non-invasive tools such as liver stiffness, platelet count, and spleen stiffness ^[48]. By contrast, the most direct approaches to sinusoidal flow behavior remain preclinical, including intravital imaging, liver-on-a-chip systems, and computational or microfluidic models. These tools are mechanistically informative, but they are not interchangeable with clinical measurement ^[49,50]. The current generation of models cannot simultaneously reproduce the spatial heterogeneity, multicellular crosstalk, dynamic fibrosis, collateral circulation, inflammatory activation, and stage-specific hemodynamics of clinical cirrhosis. Thus, the field currently faces a translational problem.

Longitudinal HVPG studies have not yet validated the hypothesis that viscosity is associated with portal vein pressure. Even if viscosity is mechanistically relevant, its clinical significance remains uncertain unless it correlates with temporal changes in portal venous pressure. To date, no human longitudinal study has demonstrated, through serial HVPG measurements, the validity of blood viscosity as a causal or predictive biomarker. This represents a major evidence gap, indicating that without hemodynamic validation of temporal association, viscosity cannot be translated from a mechanistic concept into a clinically reliable biomarker.

There is a lack of direct RCT evidence for viscosity-targeted therapy, and its treatment transformation remains limited. Emerging randomized evidence suggests that in patients with specific types of liver cirrho-

sis complicated by severe portal hypertension, adjunctive treatment with statins can reduce the HVPG and improve endothelial dysfunction. Recent meta-analyses have shown a modest short-term benefit in portal venous pressure ^[44]. However, these studies evaluated strategies aimed at reducing portal venous pressure rather than viscosity-targeted therapy itself. Although some studies have indicated that statins may enhance RBC deformability and decrease RBC aggregation, thereby reducing blood viscosity and improving microcirculation, viscosity was neither the primary therapeutic target nor an essential intermediate biomarker in these investigations ^[51,52]. Therefore, the assertion that “correction of viscosity can improve portal hypertension” still lies beyond the scope of current clinical trial evidence.

Poiseuille’s law remains a useful teaching framework, but it becomes insufficient when used as the dominant explanatory model for cirrhotic portal hypertension. Blood is a non-Newtonian, shear-thinning suspension rather than an ideal Newtonian fluid, and low-shear conditions are precisely the setting in which rheological complexity becomes most relevant ^[6]. More importantly, the portal system in cirrhosis is not a rigid tube: it is a dynamically remodeling vascular network shaped by fibrosis, sinusoidal collapse, endothelial signaling, hepatic stellate cell contraction, collateralization, and extrahepatic circulatory adaptation ^[53]. Under these conditions, pressure cannot be understood as a passive function of viscosity and radius alone. Recent mechanobiology and computational studies reinforce this point. Pathological hydrodynamic pressure can directly alter sinusoidal endothelial phenotype and generate circulating biomarkers associated with portal hypertension, while computational models suggest that patient-specific venous remodeling and collateral sensitivity may substantially shape pressure-flow relationships and clinical trajectories ^[54]. These findings

do not invalidate Poiseuille's law; rather, they show that an exclusive dependence on it risks oversimplifying a biologically active, multiscale disease process. For this reason, blood viscosity should be interpreted as one component of a broader mechanobiological system, not as a self-sufficient explanation for portal hypertension.

Summary

Collectively, changes in both local and systemic blood viscosity within the hepatic sinusoid may play dual and interactive roles in the development of portal hypertension. At the sinusoidal level, structural remodeling and microenvironmental alterations may increase local flow resistance by favoring a hyperviscous milieu. At the systemic level, hemodilution and vasodilation under hyperdynamic conditions may reduce peripheral vascular resistance and facilitate portal venous inflow. Rather than establishing viscosity as a proven primary cause of portal hypertension, these observations support its role as a context-dependent hemorheological modulator that may amplify pressure-generating mechanisms across different stages and clinical settings.

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Author contributions

Caiyi He contributed to the conception and design of the study, data collection, data analysis, and manuscript drafting. Zhongjie Hu supervised the study, provided critical revisions to the manuscript, and approved the final version for publication. Both authors read and approved the final manuscript.

Conflicts of interest

All authors declare no conflicts of interest.

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