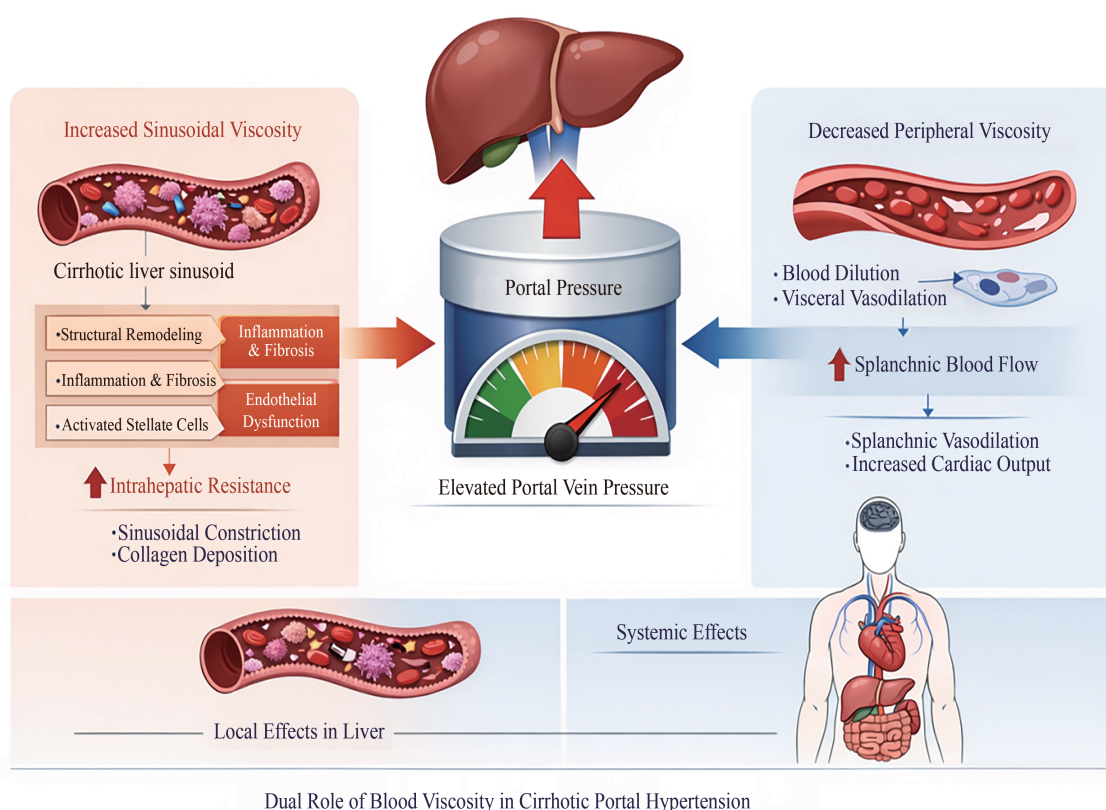


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Dual and context-dependent roles of blood viscosity in cirrhotic portal hypertension PAGE 1



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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

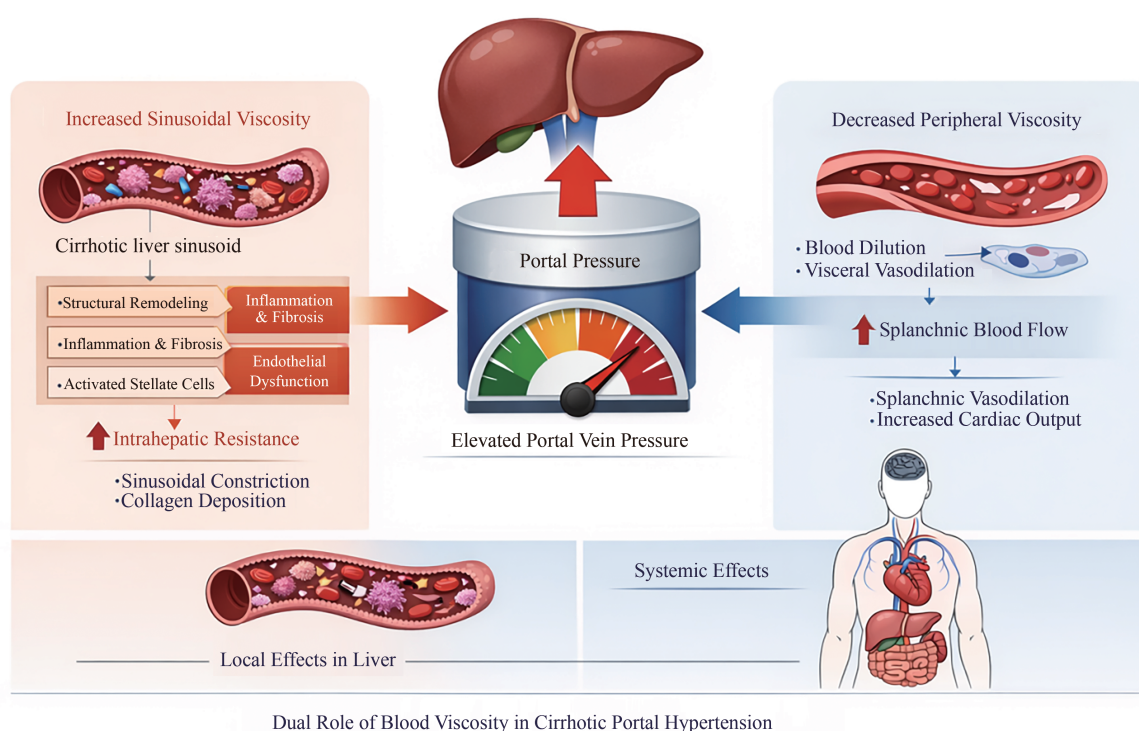


Figure 1. Conceptual schematic of the dual and context-dependent roles of blood viscosity in cirrhotic portal hypertension.

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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None.

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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Research progress and clinical applications of SERPINE1 in liver diseases: a critical review

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Abstract

SERPINE1 encodes plasminogen activator inhibitor-1 (PAI-1), a central inhibitor of tissue-type and urokinase-type plasminogen activators. By limiting plasmin generation, modulating extracellular-matrix turnover, and participating in inflammatory, metabolic, vascular, and tumor-microenvironmental processes, SERPINE1 is increasingly recognized as a context-dependent mediator in liver disease. Earlier versions of the literature often presented SERPINE1 as a uniformly pathogenic factor. A more balanced synthesis indicates that its effects depend on disease stage, cellular source, and biological context: hepatocyte- and adipose-associated PAI-1 may link metabolic stress to steatosis and insulin resistance; activated hepatic stellate cell-derived PAI-1 appears more directly related to fibrogenesis; endothelial and platelet-related PAI-1 may contribute to hypofibrinolysis and portal-vein thrombosis; and tumor- or stromal-derived PAI-1 may shape invasion, epithelial-mesenchymal transition, angiogenesis, and immune-cell recruitment in hepatocellular carcinoma. Clinical studies support an association between circulating PAI-1 and metabolic dysfunction-associated steatotic liver disease (MASLD), but most data are cross-sectional, heterogeneous, or derived from biomarker-discovery cohorts rather than definitive prospective validation. Therapeutically, PAI-1 inhibition has shown promise in cell, organoid, and animal models, particularly in steatosis and fibrotic remodeling; however, there is insufficient evidence to regard SERPINE1-targeted therapy as clinically established for liver diseases. This review critically summarizes the mechanistic, epidemiological, diagnostic, and therapeutic evidence for SERPINE1 in liver diseases, highlights unresolved controversies, and proposes a translational framework for future research.

Keywords: SERPINE1, PAI-1, MASLD, MASH, liver fibrosis, hepatocellular carcinoma, biomarker, targeted therapy

Introduction

SERPINE1, the gene encoding PAI-1, has attracted at-

tention in hepatology because it connects several processes that are central to liver disease progression: fibrinolysis, extracellular-matrix remodeling, inflammation,

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metabolic dysfunction, vascular thrombosis, and tumor progression ^[1,2]. The liver is both a metabolic organ and a hemostatic organ. Therefore, a molecule such as PAI-1 cannot be interpreted only as a fibrosis marker or only as a coagulation factor; its biological meaning changes depending on whether the dominant process is steatosis, inflammatory injury, fibrogenesis, cirrhosis-associated hemostatic imbalance, or tumor remodeling.

The terminology of steatotic liver disease has recently changed. In accordance with the 2023 multisociety Delphi consensus, the term metabolic dysfunction-associated steatotic liver disease (MASLD) is used in this review, and metabolic dysfunction-associated steatohepatitis (MASH) is used for the inflammatory and fibrosing phenotype previously referred to as NASH ^[3]. When describing older studies, NAFLD/NASH is retained only when it appears in the original study design or title. This approach avoids both historical confusion and unnecessary inconsistency.

The purpose of this revised review is not simply to list studies. Instead, it organizes the evidence around three questions. First, in which cells and disease stages is SERPINE1 most likely to be mechanistically relevant? Second, which clinical claims are supported by human evidence, and which remain preclinical or exploratory? Third, how can SERPINE1 be integrated into biomarker panels, imaging strategies, and therapeutic development without overstating the current evidence?

Biological Basis of SERPINE1/PAI-1 in Liver Disease

Core fibrinolytic and extracellular-matrix functions

PAI-1 is the major physiological inhibitor of tissue-

type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). By suppressing tPA/uPA activity, PAI-1 reduces conversion of plasminogen to plasmin, thereby limiting fibrinolysis and pericellular proteolysis ^[1]. In liver injury, this function has two competing consequences. On one side, reduced plasmin activity can impair extracellular-matrix degradation and favor fibrotic remodeling. On the other side, in acute injury or advanced cirrhosis, excessive fibrinolysis can contribute to bleeding risk; in such settings, PAI-1 may have a compensatory or protective function.

This duality explains why SERPINE1 should not be interpreted as a uniformly harmful gene. A practical example is useful: in chronic MASH fibrosis, persistently high PAI-1 from activated hepatic stellate cells (HSCs) may act like a “brake” on matrix clearance, allowing scar tissue to accumulate. In acute liver injury with hemorrhagic tendency, the same brake may prevent uncontrolled fibrinolysis and protect vascular integrity. The biological direction therefore depends on the dominant pathological process rather than on SERPINE1 expression alone.

Metabolic and hepatocellular axis

Metabolic stress can induce SERPINE1 expression through insulin, glucose, free fatty acids, inflammatory cytokines, and adipose-liver crosstalk ^[1,4,5]. Experimental work indicates that PAI-1 is not merely associated with metabolic dysfunction but may also influence lipid-related transcriptional programs in the liver ^[4]. In this context, SERPINE1 may link obesity, insulin resistance, dyslipidemia, and hepatic steatosis.

Evidence from mouse models supports a relationship between PAI-1 inhibition and reduced hepatic steatosis. However, an important study of the PAI-1 inhibitor

TM5441 showed attenuation of hepatic steatosis without prevention of progressive MASH-related fibrosis [6]. This distinction is critical. It suggests that SERPINE1 may contribute to lipid accumulation and metabolic stress while not being sufficient, by itself, to determine all downstream inflammatory and fibrotic outcomes.

Hepatic stellate cell and fibrogenic axis

Activated HSCs are a major source of extracellular matrix during liver fibrosis. Recent single-nucleus transcriptomic and chromatin-accessibility analyses of human MASLD and MASH livers identified SERPINE1 among activated HSC-enriched genes with increased expression and accessibility [7]. Importantly, this work linked activated HSC-derived PAI-1 to fibrogenic programs and tested genetic or pharmacological targeting approaches in experimental systems. These data strengthen the mechanistic argument that the HSC-specific source of SERPINE1 matters.

The TGF- β /Smad pathway provides a plausible molecular bridge between HSC activation and SERPINE1 expression. TGF- β can induce SERPINE1 transcription, and increased PAI-1 may reduce matrix degradation by limiting plasmin-mediated proteolysis. Nevertheless, this should be described as a disease-promoting loop in experimental and fibrotic contexts, not as an established universal mechanism across all liver diseases.

Immunometabolism and coagulation-inflammation crosstalk

SERPINE1 also participates in the interface between inflammation and coagulation. Inflammatory mediators such as TNF- α , IL-6, LPS, and NF- κ B-related signaling can increase PAI-1 expression [1,5]. In MASLD,

this creates a plausible link between adipose inflammation, hepatic steatosis, systemic insulin resistance, and a prothrombotic state. In cirrhosis, however, hemostasis is rebalanced rather than simply procoagulant or anticoagulant, so single biomarkers must be interpreted cautiously.

Newer work has begun to connect SERPINE1 with neutrophil extracellular traps, HSC-neutrophil communication, and early fibrosis prediction in MASLD [8]. These studies are valuable because they move beyond the older “PAI-1 equals fibrosis” model and instead position SERPINE1 within an immunothrombotic network. However, most NET-related data remain discovery-stage and require prospective validation before routine clinical use (Figure1).

Tumor microenvironment in HCC

In hepatocellular carcinoma (HCC), SERPINE1 should be discussed as a tumor-microenvironment and invasion-related molecule rather than as a simple diagnostic marker. Experimental and bioinformatic studies suggest that PAI-1 may influence epithelial-mesenchymal transition, migration, invasion, angiogenesis, and immune-cell recruitment [9,10]. For example, CAF-derived miR-642a-3p has been reported to modulate HCC cell migration, invasion, and EMT through SERPINE1-related mechanisms [9].

Because several SERPINE1 studies are cancer-type specific, citation accuracy is essential. Evidence from gastric cancer, colorectal cancer, or pan-cancer analyses cannot be used as direct proof for HCC unless it is clearly labeled as indirect or hypothesis-generating. In this revised manuscript, HCC statements are supported by HCC-specific literature or are explicitly described as extrapolations requiring validation.

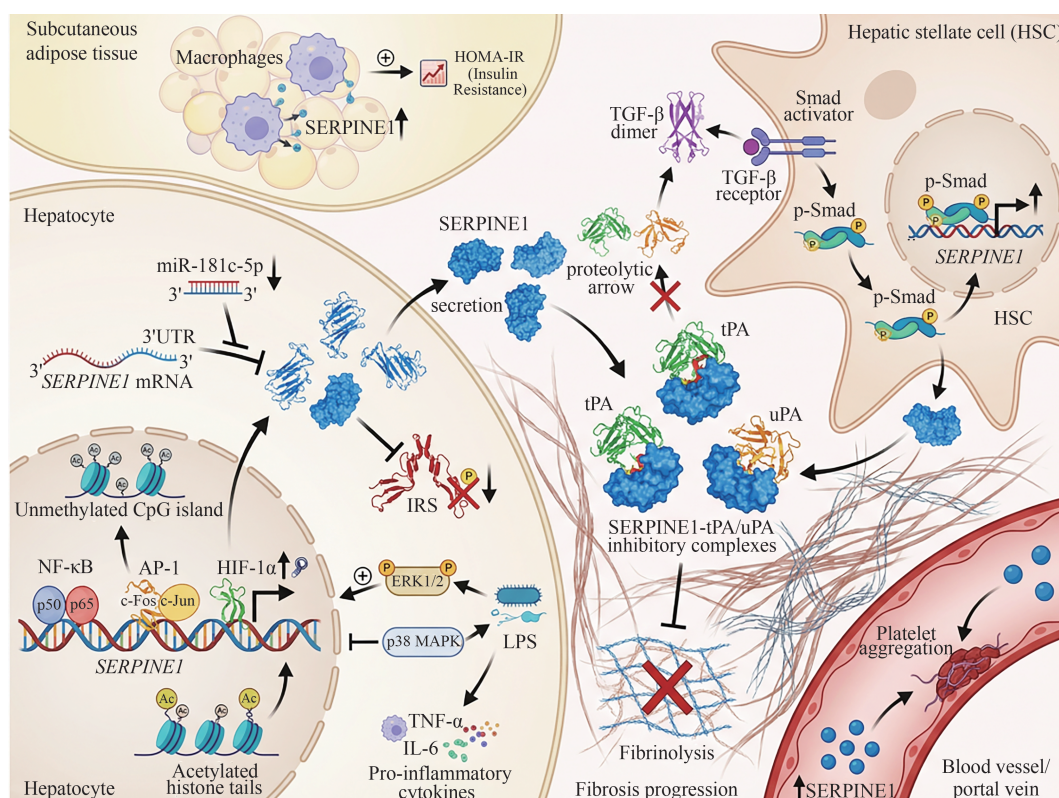


Figure 1. Fundamental theoretical basis of SERPINE1 in the field of liver diseases.

Evidence across major liver disease categories

MASLD and MASH

Among liver diseases, MASLD/MASH provides the strongest rationale for studying SERPINE1 because metabolic dysfunction, adipose inflammation, steatosis, fibrogenesis, and vascular risk converge in this condition. Human studies generally show higher circulating PAI-1 levels in individuals with steatotic liver disease, particularly in populations with obesity or insulin resistance^[5,11,12]. However, the magnitude and interpretation of this association vary by diagnostic method, population characteristics, and adjustment for adiposity and metabolic risk factors.

A recent FibroScan-based cross-sectional study in apparently healthy individuals with overweight or obesity found that circulating PAI-1 correlated with liver steatosis and, to a lesser extent, fibrosis^[11]. The au-

thors emphasized the need for longitudinal trials to clarify causality. This is a useful model for cautious writing: PAI-1 may be associated with steatosis and metabolic risk, but cross-sectional data cannot prove that SERPINE1 independently drives disease progression in humans.

In MASH fibrosis, the strongest mechanistic evidence now comes from multi-omics and single-cell approaches that localize SERPINE1 to activated HSC programs^[7]. This shifts the review from a descriptive biomarker narrative to a source-specific model: circulating PAI-1 may reflect combined hepatic, adipose, endothelial, and inflammatory inputs, whereas HSC-derived PAI-1 may be more directly relevant to fibrogenesis.

Alcohol-related liver disease, viral hepatitis, and cirrhosis

Alcohol-related liver disease shares several pathological

features with MASLD, including steatosis, inflammation, oxidative stress, and fibrosis. Experimental models and older mechanistic work suggest that PAI-1 may participate in alcohol-induced steatosis and fibrin deposition ^[13,14]. Nevertheless, the clinical evidence base is less mature than in MASLD, and the role of PAI-1 may differ across early steatosis, alcoholic hepatitis, advanced cirrhosis, and hyperfibrinolytic states.

In viral hepatitis and cirrhosis, SERPINE1 should be considered within a broader hemostatic and fibrotic network. Studies of the PAI-1 4G/5G polymorphism in HCV-related cirrhosis or HCC have produced inconsistent results ^[15,16]. Some populations show associations with thrombosis or disease risk, whereas others show no significant relationship. Therefore, SERPINE1 polymorphisms should be described as candidate modifiers rather than validated clinical predictors.

Portal-vein thrombosis (PVT) is particularly relevant because MASLD-related cirrhosis is associated with a prothrombotic phenotype, and PAI-1 contributes to hypofibrinolysis ^[16–18]. However, PVT is multifactorial, involving portal-flow reduction, endothelial dysfunc-

tion, inflammation, platelet activation, inherited thrombophilia, and cirrhosis severity. PAI-1 should therefore be framed as one component of thromboinflammatory risk, not as a standalone determinant.

HCC

In HCC, SERPINE1 is relevant to tumor biology, but the clinical role remains unsettled. HCC-specific studies suggest that PAI-1 can be linked with tumor grade, immune microenvironment features, invasion, and EMT-related programs ^[9,10]. These observations support further investigation of SERPINE1 as part of molecular or immunohistochemical panels (Table 1).

At the same time, HCC biomarker development is a demanding clinical field. A marker must improve diagnosis, risk stratification, or treatment selection beyond established clinical variables, imaging, alpha-fetoprotein, and current molecular models. Most SERPINE1-HCC studies are retrospective, bioinformatic, or mechanistic. Thus, the evidence supports hypothesis generation and panel development, but not the conclusion that SERPINE1 alone is ready for routine HCC diagnosis or therapeutic decision-making.

Table 1. Context-specific interpretation of SERPINE1 in liver diseases.

Context	Likely dominant source	Major biological link	Current evidence level	Clinical caution
MASLD / early steatosis	Hepatocytes, adipose tissue, endothelium	Lipid metabolism, insulin resistance, systemic inflammation	Human association plus animal models	Cross-sectional data do not prove causality
MASH fibrosis	Activated hepatic stellate cells	TGF- β -related activation, ECM deposition, reduced matrix degradation	Single-cell/multi-omics plus experimental validation	Needs prospective human validation
Cirrhosis and PVT	Endothelium, platelets, injured liver, inflammatory cells	Hypofibrinolysis and thromboinflammation	Clinical association and mechanistic plausibility	PVT is multifactorial; PAI-1 alone is insufficient
Acute liver injury	Endothelium, inflammatory and parenchymal cells	Limitation of excessive fibrinolysis and bleeding	Experimental evidence	Potential protective role must be acknowledged
HCC	Tumor cells, CAFs, stromal and immune cells	EMT, invasion, angiogenesis, immune crosstalk	HCC-specific studies plus bioinformatic evidence	Not a standalone diagnostic marker

Diagnostic and risk-assessment applications

Circulating PAI-1 as a biomarker

Circulating PAI-1 has potential value as a biomarker because it captures information from several disease-relevant compartments: adipose tissue, hepatocytes, HSCs, endothelium, platelets, and inflammatory cells. This broad origin is both an advantage and a limitation. It may help detect systemic metabolic and thromboinflammatory stress, but it also reduces organ specificity.

Meta-analytic and clinical studies indicate that serum or plasma PAI-1 is often elevated in adult NAFLD/MASLD, especially in biopsy-proven or imaging-confirmed disease ^[11,12]. However, diagnostic performance varies across cohorts, and PAI-1 is influenced by age, sex, obesity, diabetes, circadian rhythm, inflammation, and medications. Therefore, PAI-1 should be evaluated as part of multi-marker panels rather than promoted as a single definitive diagnostic test.

Biomarker claims should also distinguish diagnosis, staging, prognosis, and monitoring. An association with steatosis does not automatically imply reliable staging of fibrosis; a correlation with fibrosis does not prove prediction of future decompensation; and a decrease after intervention does not necessarily mean PAI-1 is a causal therapeutic target. Clear separation of these endpoints improves scientific rigor.

Integration with imaging and clinical scores

The most realistic clinical application is integration

with existing noninvasive tools such as FIB-4, transient elastography, controlled attenuation parameter, magnetic resonance-based fat quantification, or inflammatory-metabolic panels. SERPINE1-related markers may improve performance when they add biological information not captured by aminotransferases, platelet count, age, body mass index, glycemic indices, or imaging.

Recent biomarker-discovery studies combining transcriptomics, single-cell analysis, serum validation, and clinical variables suggest that SERPINE1 may contribute to early fibrosis prediction in MASLD ^[8]. Such work is promising because it combines mechanism with clinical measurement. Nonetheless, before clinical adoption, external validation, calibration, decision-curve analysis, cost-effectiveness, and threshold reproducibility are required.

Genetic polymorphisms

The SERPINE1 promoter 4G/5G variant is biologically plausible because it can influence PAI-1 expression. However, liver-disease association studies have produced inconsistent results across ethnic groups, disease etiologies, and control definitions ^[15,16,19]. These inconsistencies likely reflect modest effect sizes, small samples, population stratification, environmental modification, and interaction with metabolic or viral risk factors.

Accordingly, polymorphism data should not be overinterpreted. It is appropriate to state that SERPINE1 genetic variants may modify susceptibility or thrombotic phenotype in selected populations, but current evidence does not support routine SERPINE1 genotyping for MASLD, fibrosis, cirrhosis, or HCC risk assessment.

Therapeutic implications

Preclinical PAI-1 inhibition

PAI-1 inhibitors such as TM5441, TM5275, TM5614, and related compounds have been used to test whether PAI-1 is a modifiable contributor to metabolic and fibrotic liver injury ^[4,6,20]. In preclinical models, PAI-1 inhibition can improve steatosis, metabolic parameters, or fibrotic readouts. TM5275, for example, attenuated hepatic fibrosis in rat models of metabolic syndrome-associated fibrosis through suppression of activated HSCs ^[20].

However, the evidence is not uniformly positive. TM5441 attenuated hepatic steatosis but did not prevent progressive MASH-related fibrosis in mice ^[6]. This finding should be highlighted rather than minimized because it demonstrates that SERPINE1 biology is disease-stage and endpoint dependent. It also prevents overstatement of therapeutic potential.

Translational gap and safety considerations

The current therapeutic literature should be described as preclinical and translational, not as established clinical therapy for liver diseases. Claims of phase II efficacy or routine clinical benefit should be removed unless supported by a verified liver-disease trial. At present, the most defensible conclusion is that PAI-1 inhibition is a promising strategy requiring rigorous clinical testing.

Safety is a central issue. Because PAI-1 regulates fibrinolysis, systemic inhibition could theoretically increase bleeding risk, especially in patients with advanced cirrhosis, thrombocytopenia, portal hypertension, varices, or altered coagulation balance. Liver-directed delivery, cell-specific targeting, partial inhibi-

tion, or patient selection may be required to widen the therapeutic window.

Combination and precision strategies

Combination therapy should be framed as a research direction rather than a proven clinical strategy. In MASLD/MASH, SERPINE1-targeted approaches could theoretically complement interventions that reduce metabolic stress, such as weight loss, incretin-based therapies, lipid-lowering strategies, or anti-inflammatory approaches. In fibrosis, PAI-1 inhibition may need to be paired with therapies targeting HSC activation, TGF- β signaling, matrix cross-linking, or immune-cell recruitment.

In HCC, SERPINE1 may be more relevant as a tumor-microenvironment marker than as a direct single-drug target. Its association with EMT, CAF signaling, angiogenesis, and immune infiltration suggests potential value in stratifying tumor biology or identifying combinations with anti-angiogenic therapy and immunotherapy. These possibilities remain exploratory and require HCC-specific validation.

Controversies and future directions

Reconciling pathogenic and protective roles

The most important controversy is the apparent contradiction between pathogenic and protective roles of PAI-1. This contradiction can be resolved by using a context model. In chronic metabolic injury, high SERPINE1 may amplify steatosis, HSC activation, and matrix persistence. In acute injury or hyperfibrinolytic states, PAI-1 may reduce bleeding and preserve tissue integrity. In cancer, PAI-1 may support invasion and immune remodeling, but effects can vary with tumor stage and stromal composition.

Future studies should therefore report not only PAI-1 expression but also the disease stage, cellular source, compartment measured, and endpoint. For example, serum PAI-1 in an obese patient with early MASLD is not biologically equivalent to HSC-specific SERPINE1 in MASH fibrosis or stromal PAI-1 in HCC.

Multi-omics, single-cell technologies, and spatial biology

Emerging technologies can address several weaknesses in the existing literature. Single-cell and single-nucleus sequencing can identify which cell populations express SERPINE1 in different disease stages. Chromatin-accessibility data can reveal regulatory programs that activate SERPINE1. Spatial transcriptomics and multiplex immunohistochemistry can show whether SERPINE1-expressing cells are located near fibrotic septa, inflammatory aggregates, vascular structures, or invasive tumor fronts.

These methods are particularly important because circulating PAI-1 is biologically nonspecific. A high plasma level may reflect adipose inflammation, endothelial activation, hepatic production, platelet release, or tumor-associated stroma. Multi-omics approaches

can deconvolute these sources and help determine when SERPINE1 is a driver, a marker, or a compensatory response.

Proposed research priorities

First, prospective cohorts should test whether PAI-1 improves prediction of fibrosis progression, decompensation, PVT, or HCC beyond established clinical and imaging models. Second, disease-stage-specific studies should compare simple steatosis, MASH without advanced fibrosis, advanced fibrosis, cirrhosis, and HCC rather than pooling heterogeneous cases. Third, therapeutic studies should use endpoints that distinguish steatosis improvement from fibrosis regression and vascular safety.

Fourth, HCC studies should avoid borrowing conclusions from non-liver cancers unless clearly labeled as indirect evidence. Fifth, SERPINE1 polymorphism studies should be interpreted with attention to ancestry, metabolic status, viral etiology, sample size, and gene-environment interactions. Finally, clinical trial design should consider bleeding risk, cirrhosis severity, portal-hypertension status, and the possibility that partial or cell-specific inhibition may be safer than systemic blockade (Table 2).

Table 2. Translational evidence and recommended wording.

Topic	Supported statement	Avoid overstating	Recommended wording
MASLD biomarker	PAI-1 is often elevated and associated with steatosis/metabolic risk.	PAI-1 is a validated standalone diagnostic test.	PAI-1 may contribute to multi-marker risk stratification after external validation.
MASH fibrosis	HSC-derived SERPINE1 is implicated in fibrogenic programs.	SERPINE1 alone determines fibrosis progression.	SERPINE1 is a mechanistically plausible component of fibrogenic HSC networks.
PVT/cirrhosis	PAI-1 contributes to hypofibrinolytic tendency.	High PAI-1 alone predicts PVT.	SERPINE1 should be considered within broader thromboinflammatory risk models.
HCC	SERPINE1 relates to EMT, stromal signaling, and immune microenvironment in HCC studies.	Gastric-cancer evidence proves HCC prognosis.	HCC-specific validation is required for diagnostic or prognostic claims.
Therapy	PAI-1 inhibitors show preclinical promise.	Clinical efficacy is established.	PAI-1 inhibition remains experimental for liver disease and requires safety-focused trials.

Conclusion

SERPINE1/PAI-1 is best understood as a context-dependent hub linking fibrinolysis, extracellular-matrix remodeling, metabolic stress, inflammation, vascular dysfunction, and tumor-microenvironmental remodeling in liver diseases. The strongest current evidence supports its association with MASLD/MASH biology, particularly steatosis, metabolic inflammation, activated HSC programs, and fibrogenesis. In cirrhosis and PVT, SERPINE1 belongs to a broader thromboinflammatory network rather than serving as a stand-alone predictor. In HCC, SERPINE1 is a plausible marker of stromal and invasive biology, but its clinical use remains exploratory. Therapeutic targeting of PAI-1 is promising but remains largely preclinical; future studies must define patient selection, disease stage, cellular source, treatment endpoint, and bleeding safety. A critical, source-specific, and evidence-graded approach will be essential for translating SERPINE1 research into clinically useful biomarkers or therapies.

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Inflammation-associated hepatocellular carcinoma: a revised comprehensive review from pathogenesis to precision prevention and treatment

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Abstract

Hepatocellular carcinoma (HCC) develops predominantly on the background of chronic liver inflammation. This revised review focuses on how different etiologies-metabolic dysfunction-associated steatotic liver disease (MASLD, formerly non-alcoholic fatty liver disease), viral hepatitis, alcohol-related liver disease, and cholestatic or autoimmune liver disorders-converge on common inflammatory programs while retaining distinct immuno-metabolic and carcinogenic features. We summarize mechanistic evidence linking persistent hepatocyte injury to activation of NF- κ B, IL-6/JAK/STAT3, TLR4/MyD88, COX-2/PGE2, oxidative stress, endoplasmic reticulum stress, ferroptosis, and stromal remodeling, and further discuss how these pathways reprogram macrophages, T lymphocytes, liver sinusoidal endothelial cells, hepatic stellate cells, and hepatic progenitor cells within the tumor microenvironment. Emphasis is placed on the translational bridge from mechanism to clinic, including inflammation-related serum markers, radiomics-clinical nomograms, model development methods, validation metrics, and pathways for clinical implementation. We also critically discuss unresolved issues, including the dual role of regulatory T cells in MASLD/metabolic dysfunction-associated steatohepatitis (MASH), etiology-specific differences in immunotherapy biomarkers, and the challenge of distinguishing causality from association in gut microbiome-HCC studies. Finally, we outline therapeutic strategies that target inflammatory signaling and the immune microenvironment, from immune checkpoint inhibitors and rational local-systemic combinations to pathway-directed small molecules, cell therapy, and nucleic acid delivery platforms. Together, these advances support a precision framework for risk stratification, early detection, and individualized intervention in inflammation-associated HCC.

Keywords: hepatocellular carcinoma, chronic liver inflammation, tumor microenvironment, immunotherapy

Introduction

Hepatocellular carcinoma remains one of the leading

causes of cancer-related death worldwide and typically emerges through a long natural history of chronic liver injury, fibrosis, cirrhosis, and malignant transformation.

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Inflammation is not merely an accompanying phenomenon; it is a biologically active driver of genomic instability, compensatory proliferation, angiogenesis, immune evasion, and treatment resistance^[1,2].

Compared with prior narrative summaries that separately discuss risk factors, signaling pathways, or therapy, the present review is intended to integrate three levels of evidence: (1) etiology-specific inflammatory mechanisms, (2) pathway- and cell-based microenvironmental reprogramming, and (3) translational advances in biomarkers, prediction models, and mechanism-guided intervention. To improve conceptual clarity, we adopt the current consensus nomenclature MASLD (formerly NAFLD) at first mention and use MASLD/metabolic dysfunction-associated steatohepatitis (MASH), consistently throughout the manuscript^[3].

A further aim of this revision is to place recent 2025 studies into the context of landmark mechanistic and therapeutic literature that established the modern framework of HCC biology and management, including foundational work on cancer-related inflammation, sorafenib, immune checkpoint inhibition, nomogram construction, and LASSO-based modeling^[4–11].

Inflammatory microenvironment in chronic liver diseases: the soil for HCC initiation and progression

Chronic liver disease provides the ecological soil for HCC development. Across etiologies, repeated hepatocyte injury drives the release of damage-associated molecular patterns, reactive oxygen species, and inflammatory mediators that perpetuate wound-healing responses, fibrogenesis, and selection of transformed clones. However, the composition of this inflammatory soil differs by disease context, which has direct

implications for surveillance, biomarker discovery, and treatment response.

Immune-inflammatory driving mechanisms in MASLD/MASH

MASLD and its progressive inflammatory phenotype, MASH, are rapidly becoming dominant etiologies of HCC. Hepatic lipid overload induces lipotoxic stress, organelle injury, hepatocyte death, and the release of damage-associated molecular patterns that recruit and activate monocyte-derived macrophages, neutrophils, and adaptive immune cells^[3,12]. Recent work highlights substantial macrophage heterogeneity in MASH, indicating that monocyte-derived populations are not passive bystanders but active organizers of fibrogenic and pro-tumor niches^[12].

Dywicki et al. further emphasized that regulatory T cells (Tregs) in MASLD/MASH may not be uniformly protective; in some experimental contexts they acquire inflammatory features, including IL-17-associated programs, and correlate with more severe liver pathology^[13]. This observation is important because it challenges the simplistic assumption that Treg expansion is necessarily anti-inflammatory in metabolic liver disease. Liver sinusoidal endothelial cells (LSECs) also amplify MASH progression by responding to macrophage-derived IL-1 β through IL-1R1 and producing chemokines that reinforce inflammatory-cell recruitment^[14].

At the metabolic-signaling level, the ATG9A-PLA2G6 axis alters phospholipid homeostasis and links defective stress adaptation to inflammation, fibrosis, and hepatocarcinogenesis^[15]. These findings support a model in which immunometabolic dysregulation, rather than steatosis alone, drives the transition from fatty liver disease to cancer.

Persistent inflammation and carcinogenic processes associated with viral hepatitis (HBV, HCV, and HDV)

Chronic viral hepatitis remains a major global cause of HCC. In HBV infection, hepatocarcinogenesis results from both indirect inflammatory injury and direct oncogenic events, including viral DNA integration, insertional mutagenesis, and sustained transcriptional perturbation. Recent data suggest that HBV integration near the ORC1 locus may increase circulating ORC1 and improve detection of alpha-fetoprotein-negative HBV-related HCC^[16]. In parallel, preS/S single-nucleotide variants can aggravate oxidative stress, mitochondrial dysfunction, and calcium dyshomeostasis, thereby linking viral genetic evolution to inflammatory carcinogenesis^[17].

HCV-associated HCC is driven predominantly through chronic necroinflammation, oxidative stress, steatogenic signaling, and cirrhosis rather than genomic integration. High-fitness HCV variants selectively enriched in immunosuppressed hosts have been associated with more severe disease and a higher likelihood of HCC development^[18]. HDV coinfection with HBV often produces the most aggressive inflammatory phenotype, with accelerated progression to cirrhosis and HCC, although recent cohort data also underscore heterogeneity in clinical expression^[19].

Importantly, antiviral therapy alters the inflammatory field in which carcinogenesis occurs. Long-term nucleos(t)ide analogues reduce HBV-related HCC risk^[20], while sustained virologic response after direct-acting antivirals may improve liver reserve and oncologic outcomes in selected patients later treated with systemic therapy^[21]. These observations illustrate that etiologic control is itself an anti-inflammatory anticancer strategy.

Inflammation and fibrosis induced by bile acid dysregulation, alcohol, and other causes

Bile acid dysregulation is increasingly recognized as a carcinogenic inflammatory driver. In cholestatic and advanced tumor settings, glycochenodeoxycholic acid may induce hepatic progenitor-cell differentiation toward cancer-associated fibroblasts through sphingosine-1-phosphate receptor 2 (S1PR2) signaling, thereby coupling bile acid stress to fibrosis and tumor expansion^[22]. The TBA-MLR score, which combines total bile acid and monocyte-to-lymphocyte ratio, exemplifies how metabolic and inflammatory dimensions can be integrated for prognostic assessment^[23].

Alcohol-related liver disease promotes hepatocarcinogenesis through acetaldehyde toxicity, oxidative stress, gut barrier disruption, endotoxemia, and Kupffer-cell activation, with robust induction of TNF- α , IL-1 β , and IL-6^[24]. Smoking can further intensify inflammatory and angiogenic programs in cirrhosis^[25]. Autoimmune and cholestatic disorders, including autoimmune hepatitis and primary biliary cholangitis, also create chronic injury-fibrosis milieus that increase HCC risk, although absolute risk varies by fibrosis stage and disease control^[26].

Across etiologies, despite their distinct, MASLD/MASH, viral hepatitis, alcohol-related liver disease, and cholestatic/autoimmune disorders share several convergent carcinogenic features: persistent hepatocyte injury, cytokine amplification, activation of fibrogenic stromal cells, angiogenic remodeling, and progressive immune dysfunction. Their differences are equally important. MASLD/MASH is characterized by immunometabolic stress and altered lipid handling; HBV uniquely adds direct insertional oncogenesis; HCV relies more heavily on chronic inflammatory-cirrhotic remodeling; alcohol prominently involves

gut-derived endotoxin signaling; and bile acid-related disease accentuates metabolite-receptor crosstalk. Recognizing these shared and disease-specific programs helps explain why biomarkers and therapeutic response are often etiology dependent rather than universally transferable.

Key inflammatory signaling pathways and cytokine networks in HCC development

Inflammation-associated HCC is orchestrated by interconnected signaling networks rather than isolated pathways. A mechanistic framework is therefore necessary not only to explain tumor initiation but also to identify actionable nodes, biomarkers, and resistance mechanisms.

NF-κB, TLR4/MyD88, and TNF-α signaling

NF-κB is a central signaling hub linking chronic injury to carcinogenesis. Activation of TLR4/MyD88, TNF receptors, and other inflammatory inputs converges on the IKK complex, which phosphorylates IκB and allows nuclear translocation of NF-κB dimers. In hepatocytes, macrophages, and stromal cells, this program induces anti-apoptotic and proliferative mediators including BCL2, BCL-XL, MYC, cyclin D1, VEGF, matrix metalloproteinases, COX-2, and multiple chemokines, thereby supporting cell survival, angiogenesis, extracellular-matrix remodeling, and leukocyte recruitment^[1,2].

Recent experimental work suggests that colon-targeted astragalus polysaccharide nanoparticles suppress MASLD-driven hepatocarcinogenesis partly by reshaping the gut microbiota, increasing acetate, and inhibiting NF-κB through GPR43 signaling^[27]. Artemisia rup-estris similarly attenuates TLR4/MyD88/NF-κB signal-

ing and macrophage-mediated immune evasion in HCC models^[28]. TNF-α, a major upstream activator of NF-κB, also interacts with sex-hormone pathways; Groover et al. reported sex-specific relationships between estrogen receptor beta and TNF-α in HCV-related cirrhosis, suggesting that inflammatory signaling may be modulated by biological sex^[29].

COX-2/PGE2, IL-1β/IL-1R1, and IL-6/JAK/STAT3 axes

COX-2/PGE2 signaling is a canonical inflammatory amplifier in solid tumors, including HCC. PGE2 promotes proliferation, angiogenesis, and immune escape, in part through suppression of natural killer (NK) cell function and modulation of myeloid cells. After radiofrequency ablation, residual-tumor microenvironments may show increased COX-2 expression; celecoxib can reverse PGE2-mediated NK-cell suppression and enhance the efficacy of anti-PD-1 therapy in preclinical models^[30].

The IL-1β/IL-1R1 axis is especially relevant in MASH, where lipotoxic macrophages with defective autophagy overproduce IL-1β. LSECs receiving this signal activate JNK and induce chemokines such as CCL2 and CXCL10, thereby recruiting additional inflammatory cells and accelerating fibrosis^[14].

IL-6/JAK/STAT3 is another core hepatocarcinogenic circuit. Persistent IL-6 signaling activates JAK kinases and STAT3, which transactivates genes involved in proliferation and survival, including MYC, cyclin D1, survivin, BCL-XL, and VEGF, while also promoting stemness, angiogenesis, and resistance to apoptosis^[1,24]. Negative regulation by SOCS proteins, particularly SOCS3, is frequently inadequate in chronic inflammatory states, allowing sustained STAT3 activity. Mechanistically, NF-κB and STAT3 can cooperate at shared

promoters and enhancers, creating feed-forward transcriptional programs that intensify inflammatory tumor promotion^[1,2]. Following tissue ablation, cytokine panels incorporating IL-7, IL-6, IL-1α, and CXCL1 may predict radiologic response, suggesting that transient inflammatory surges can be mined for clinically useful biomarkers^[31].

Oxidative stress, endoplasmic reticulum stress, autophagy, and ferroptosis cross-talk

Oxidative stress and endoplasmic reticulum stress are integral to chronic liver injury and interact bidirectionally with inflammatory signaling. Mitochondrial dysfunction, lipid peroxidation, and reactive oxygen species formation promote DNA damage and genomic instability, while inflammatory cytokines further aggravate organelle stress^[17,24].

Autophagy normally constrains these processes by clearing damaged organelles and limiting inflammatory activation. Oroxyloside has been reported to restore autophagic flux through AMPK-ULK1 signaling, thereby reducing oxidative stress, DNA damage, IL-6 production, stellate-cell activation, and fibrosis^[32]. Conversely, inhibition of the autophagy-repressive hormone DBI/ACBP can enhance anti-tumor immunity and increase the expression of ferroptosis-related genes, sensitizing HCC cells to iron-dependent cell death^[33].

The NOTCH1-KEAP1-NRF2 axis adds another layer of complexity. NOTCH1 intracellular signaling may destabilize KEAP1-NRF2 interactions, promoting oxidative injury and ferroptosis-related vulnerability in chronic liver disease and HCC^[34]. Together, these data suggest that stress-adaptation pathways are not peripheral phenomena but central determinants of inflammation-driven malignant evolution.

Immune cell heterogeneity and functional reprogramming in the tumor microenvironment

The HCC microenvironment is a dynamic immune ecosystem in which macrophages, lymphocytes, endothelial cells, stellate cells, and progenitor populations are reprogrammed by chronic inflammation. Single-cell and spatial technologies increasingly show that functional states in HCC cannot be reduced to simple binary categories.

Tumor-associated macrophages: heterogeneity, accumulation of TREM2-positive subsets, and pro-carcinogenic functions

Tumor-associated macrophages (TAMs) are among the dominant leukocyte populations in HCC and are major mediators of tumor-promoting inflammation^[35,36]. Single-cell studies have identified a conserved FABP5-positive macrophage subset that persists across advanced fibrosis and hepatocarcinogenesis, supporting both extracellular-matrix remodeling and malignant progression^[37].

The manuscript was revised to avoid conceptual imprecision regarding TREM2. TREM2 is best understood as a marker of a distinct macrophage subset rather than a classical polarization state. Accordingly, it is more accurate to describe the accumulation or metabolic reprogramming of TREM2-expressing TAMs than the “polarization of TREM2-positive TAMs.” Metabolism-archetype HCC cells may increase oxidized low-density lipoprotein through squalene epoxidase upregulation, which in turn promotes the accumulation and reprogramming of TREM2-positive TAMs via the TREM2-SYK-CEBPα axis^[38]. These macrophages contribute to invasion, cytokine resistance, CD8-positive T-cell dysfunction, and poor

immunotherapy response.

Myeloid TGF- β signaling further shapes macrophage composition in MASH-associated HCC; loss of myeloid TGF- β signaling reduces Trem2-positive macrophages while expanding Fcrl5-positive subsets and favoring effector T-cell exhaustion^[39]. Additional mechanisms, such as RNASEH2C-driven impairment of antigen presentation, demonstrate that TAMs regulate both inflammatory tone and antigenic visibility of the tumor^[40].

T lymphocytes, Treg plasticity, and the problem of context-dependent immune suppression

CD4-positive and CD8-positive T lymphocytes are central effectors of anti-tumor immunity, yet chronic inflammatory liver disease frequently drives them into dysfunctional, exhausted, or skewed states. In MASH, increased intrahepatic CD4-positive PD-1-positive populations may help identify patients at future risk of HCC, and integration with routine clinical parameters improves predictive performance^[41].

Ajith et al. reported striking Treg enrichment in a DEN/CCl₄ mouse model of fibrosis-to-HCC progression, including approximately 125-fold and 80-fold higher infiltration in the tumor margin and surrounding non-tumor liver, respectively^[42]. Because these values appear to reflect relative cell-count enrichment in defined tissue compartments rather than a direct percentage increase in total hepatic immune cells, they should be interpreted cautiously to avoid overstatement. This revision therefore preserves the biological message—prominent Treg accumulation—while clarify the likely quantitative meaning.

The role of Tregs in MASH remains controversial rather than uniform. Dywicki et al. highlighted set-

tings in which Tregs display pro-inflammatory features and fail to protect against disease progression^[13], whereas other conceptual frameworks still support an immunosuppressive, tissue-protective role for Tregs under specific metabolic and temporal conditions. This apparent contradiction may reflect disease stage, tissue compartment, antigenic context, and phenotypic plasticity rather than true incompatibility. Such complexity is clinically relevant because it may partly explain why immunotherapy biomarkers derived from viral HCC do not always transfer to MASH-related HCC. In addition, checkpoint molecules such as PD-1 and CTLA-4 mark functionally constrained T-cell states that may be altered by locoregional therapy^[43].

Stromal and endothelial partners: hepatic stellate cells, LSECs, and hepatic progenitor cells

Inflammation-associated HCC is not created by leukocytes alone. Hepatic stellate cells, the principal fibrogenic effectors of the liver, respond to inflammatory cues and in turn regulate extracellular matrix, angiogenesis, and tumor permissiveness. Hydroxysafflor yellow A has been shown to upregulate miR-29a-3p in stellate-cell-derived exosomes and suppress extracellular matrix-receptor and PI3K/AKT signaling, thereby reducing angiogenesis in fibrosis-related HCC^[44].

LSECs function as gatekeepers of hepatic immune trafficking and become active inflammatory participants in MASH by responding to IL-1 β and generating chemotactic gradients^[14]. Hepatic progenitor cells also contribute to tumor-promoting stromal remodeling; bile-acid stress can redirect these cells toward cancer-associated fibroblast-like phenotypes via S1PR2^[22]. Endothelial circadian-regulatory programs have additionally been linked to adverse prognosis and altered immune interactions in HCC^[45].

Gut-liver axis: microbiota dysbiosis and systemic/hepatic inflammation

The portal circulation makes the liver uniquely vulnerable to intestinal barrier failure and microbial translocation. As a result, the gut-liver axis is increasingly viewed as an upstream regulator of chronic hepatic inflammation and a potential source of biomarkers and therapeutic targets.

Gut microbiota dysbiosis, barrier disruption, and pathogen-associated molecular pattern translocation

In chronic liver disease, loss of epithelial tight-junction integrity permits bacterial products such as lipopolysaccharide to enter the portal circulation, where they activate pattern-recognition receptors including TLR4 on Kupffer cells and other myeloid populations. Microbiome studies have identified recurring compositional shifts across the spectrum of hepatitis, cirrhosis, and HCC; for example, reduced Ruminococcaceae/Lachnospiraceae and enrichment of Enterococcaceae, Enterobacteriaceae, Streptococcus, and Veillonella have been associated with HCC-related states^[46]. Pathobionts such as *Fusobacterium nucleatum*, *Helicobacter pylori*, and *Enterococcus faecalis* may contribute through barrier disruption, genotoxicity, altered bile-acid signaling, and inflammatory pathway activation^[47].

Regulatory effects of microbial metabolites

Short-chain fatty acids generally support epithelial integrity and anti-inflammatory signaling, whereas trimethylamine N-oxide and dysregulated secondary bile-acid pools have been linked to oxidative stress, insulin resistance, and carcinogenic signaling^[27,48]. These metabolites provide plausible mechanistic bridges between diet, microbiome configuration, and liver cancer risk.

Potential strategies for targeting the gut microbiota

Preclinical strategies include probiotics, prebiotics, fecal microbiota transplantation, bacterium-directed interventions, and microbiota-remodeling nanocarriers^[27,47]. Nevertheless, most approaches remain exploratory, and few have progressed to standardized clinical protocols in HCC.

Translational perspective: from association to clinically usable diagnostics

A major unresolved issue is causality versus association. Many human microbiome studies in HCC are cross-sectional and cannot easily distinguish whether dysbiosis is a driver, a consequence of cirrhosis/HCC, or simply a correlate of confounders such as proton-pump inhibitors, antibiotics, diet, or portal hypertension. For translation, candidate microbiome biomarkers must proceed through analytical validation, external cohort replication, and demonstration of incremental value over existing clinical models. Standardized sampling, prespecified classifier thresholds, and etiology-aware study design will be essential before gut microbiome signatures can become reliable diagnostic tools.

Inflammation-related biomarkers and prognostic prediction models

Inflammation-related biomarkers are clinically meaningful only when they move beyond biological plausibility to reproducible prediction, calibration, and implementation. This revised section therefore expands both the marker layer and the methodological considerations underlying model development.

Traditional and novel serum inflammatory markers

C-reactive protein, IL-6, neutrophil-related indices,

and albumin-based inflammation-nutrition markers have long been associated with HCC risk and prognosis. More recent composite indicators show stronger discrimination than single analytes alone. The CALLY index integrates C-reactive protein, albumin, and lymphocyte count, thereby jointly reflecting systemic inflammation, nutritional reserve, and host immunity^[49].

The TBA-MLR score combines total bile acid with the monocyte-to-lymphocyte ratio and may identify occult high-risk patients after curative-intent resection, including some individuals considered low risk by conventional staging or alpha-fetoprotein^[23]. Circulating hPG80, a Wnt-related peptide secreted by malignant cells, has shown promising diagnostic performance in prospective studies^[50]. Cytokine signatures after tissue ablation and serum proteomic panels linked to the TGF-beta pathway likewise suggest that inflammatory biology can be translated into blood-based risk tools^[31,51].

Nomograms and prediction models based on radiomics, clinical features, and inflammatory parameters

Nomograms are graphical prediction tools that translate multivariable regression models into individualized probability estimates. Their appropriate use requires rigorous methodology, including candidate-variable selection, handling of collinearity, transparent modeling assumptions, internal and external validation, and clinically interpretable end points^[5]. When survival is the outcome, the correct terminology is usually LASSO Cox regression rather than generic “LASSO regression”^[4,5].

Recent HCC nomograms illustrate the translational potential of inflammation-informed modeling. Hu et al. developed a large retrospective model for patients receiving PD-1/PD-L1 inhibitors by integrating tumor

burden, nutritional indicators, and inflammatory variables selected through LASSO Cox procedures; the model showed good discrimination in validation cohorts^[52]. Xu et al. constructed a recurrence-oriented nomogram for initially unresectable HCC after successful conversion therapy, outperforming conventional CNLC and BCLC staging in their dataset^[53]. In microvascular invasion-negative HCC, a model combining Ki-67, AFP-L3, and neutrophil-to-lymphocyte ratio improved postoperative recurrence stratification, thereby addressing the lack of dedicated tools for this ostensibly lower-risk subgroup^[54].

From a methodological standpoint, model reporting should include at least three domains. First, discrimination—commonly quantified by the concordance index time-dependent area under the curve, or receiver operating characteristic analysis—indicates whether the model can correctly rank patients by risk. Second, calibration curves evaluate agreement between predicted and observed outcomes across risk strata. Third, clinical utility can be explored through decision-curve analysis, risk reclassification, and comparison with existing staging systems. These components are essential because a model with statistically significant predictors may still be poorly calibrated or clinically unhelpful.

Radiomics-based models add another layer by extracting quantitative texture and shape features from ultrasound, CT, or MRI, then integrating them with inflammatory and clinical variables. For real-world deployment, however, radiomics pipelines must contend with scanner heterogeneity, segmentation reproducibility, feature stability, and external-site transportability. Therefore, future HCC nomograms should ideally combine interpretable clinicobiological variables with robust imaging features, and they should undergo prospective, multicenter validation before clinical adoption.

Finally, implementation pathways deserve emphasis. A clinically useful prediction model should define intended use (screening, recurrence surveillance, treatment selection, or toxicity prediction), specify cutoff-based action thresholds, and be deliverable through electronic calculators, radiology reporting systems, or electronic health records. Without these practical steps, even technically strong models rarely change care.

Integrated strategies for risk stratification and early diagnosis

Integrated risk stratification increasingly combines serum biomarkers, imaging, pathology, and clinical variables. The GALAD score, for example, merges sex, age, alpha-fetoprotein, AFP-L3, and PIVKA-II and continues to show utility for HCC detection in selected populations^[55]. Artificial intelligence can further support image-based phenotyping, automated lesion characterization, and multimodal fusion of radiomics with laboratory and clinical data^[56,57].

In high-risk disease contexts such as MASH, combining intrahepatic immune signatures with routine parameters may refine surveillance strategies^[41]. Yet integration should remain etiology aware: biomarkers predicting immunotherapy responsiveness or tumor emergence in viral HCC may not perform equivalently in metabolic HCC, where immune exhaustion, steatotic stress, and T-cell dysfunction can differ qualitatively. This variability should be acknowledged explicitly when proposing generalized models.

Translational perspective: mechanism-based biomarkers and development pipeline

Mechanism-based biomarker development in inflammation-associated HCC can be viewed as a staged pipeline: discovery in mechanistic or omics studies; analyti-

cal validation in blood, tissue, or imaging platforms; clinical validation in retrospective and prospective cohorts; and finally assessment of clinical utility. Serum ORC1, hPG80, TGF- β -related proteomic signatures, cytokine panels, and microbiome-derived classifiers are currently positioned at different phases of this pipeline rather than being equally mature^[16,31,50,51].

Translational gaps remain substantial. Many biomarkers are derived from single-center datasets, use non-standardized assays, or lack head-to-head comparison against established tools such as alpha-fetoprotein, GALAD, and staging systems. For therapeutic targets, the preclinical-to-clinical pipeline is similarly uneven: some pathways have clear druggable nodes and early translational readouts (for example, COX-2/PGE2, checkpoint signaling, and S1PR2), whereas others remain biologically intriguing but clinically immature (for example, DBI/ACBP or niche-specific macrophage programs). Clarifying developmental phase prevents overstatement and improves the scholarly rigor of translational discussion.

Therapeutic strategies and challenges targeting inflammation and the immune microenvironment

Immune checkpoint inhibitors and management of immune-related adverse events

The modern systemic-treatment era of HCC was established by the SHARP trial, which demonstrated survival benefit with sorafenib^[6], and subsequently broadened by immune checkpoint blockade, including nivolumab in CheckMate 040^[7] and pembrolizumab in KEYNOTE-224^[9]. More recently, immunotherapy-based combinations have reshaped first-line standards^[10,11].

Immune checkpoint inhibitors reactivate anti-tumor

T-cell responses but also expose patients to immune-related adverse events (irAEs). Predictive nomograms incorporating tumor burden, nutritional status, and inflammatory variables may improve selection of patients for PD-1/PD-L1-based therapy^[39]. However, predictive biomarkers remain inconsistent across etiologies; viral-inflammation-rich tumors may show different immune responsiveness from MASH-driven tumors, an issue that warrants continued prospective study.

Rare but clinically important irAEs have been described in HCC^[58,59]. Early identification, multidisciplinary assessment, and guideline-based immunosuppression remain central to safe immunotherapy delivery^[60].

Immune regulatory effects of local therapies and rationale for combination strategies

Locoregional therapies do more than debulk tumors; they also reshape inflammatory and immune landscapes by releasing tumor antigens, damage-associated molecular patterns, and cytokines. Radiofrequency ablation can induce COX-2/PGE2-mediated suppression of NK-cell function in residual disease, a mechanism that may be counteracted by celecoxib plus anti-PD-1 therapy^[30]. Transarterial chemoembolization induces dynamic changes in myeloid cells, NK cells, CD8-positive T cells, and CTLA-4 expression, indicating that post-treatment immune states may be exploitable for sequencing or combination design^[43].

Histotripsy and proton-beam therapy further illustrate that local therapies can serve as immunologic primers rather than purely local interventions^[31,61]. The clinical challenge is to identify the optimal timing, patient subset, and immunologic window in which local-systemic combinations are synergistic rather than merely additive.

Small-molecule inhibitors and natural products targeting inflammatory circuits

Pathway-focused small molecules remain attractive because they can modulate defined inflammatory nodes. Examples include S1PR2 inhibition to block bile-acid-driven progenitor-to-fibroblast conversion^[22], direct AMPK activation to attenuate steatosis and fibrosis^[62], and COX-2 inhibition to reverse PGE2-mediated immune suppression^[30].

Natural products are notable for multi-target effects but should be interpreted carefully because mechanistic richness does not automatically translate into clinical efficacy. Pien Tze Huang, *Artemisia rupestris*, alisol A 24-acetate, and butein all show anti-inflammatory or anti-fibrotic activity in preclinical systems^[28,63–65]. The next translational step is not additional descriptive network pharmacology alone, but rigorous pharmacokinetic characterization, target engagement, safety testing, and biomarker-linked early clinical trials.

Cell therapy, gene therapy, and nanoparticle delivery platforms

Next-generation cell therapies aim to overcome the immune paralysis of HCC. NKG2D-directed CAR-macrophages can directly phagocytose tumor cells, promote M1-like inflammatory activation, engage cGAS-STING signaling, and augment T-cell recruitment in preclinical models^[66]. Bacterial outer-membrane-vesicle-based neoantigen mRNA delivery and nucleic-acid strategies targeting genetic drivers such as PNPLA3 variants likewise illustrate the breadth of emerging liver-directed immunogenetic therapies^[67–69].

Nevertheless, these approaches remain mostly preclinical or early translational. Key barriers include liver-

specific delivery, on-target/off-tumor toxicity, manufacturing complexity, immune-related toxicity, and the need for biomarkers that identify patients most likely to benefit. Their promise is substantial, but their current developmental phase should be stated transparently.

Conclusion and outlook

Inflammation is the central biological thread linking chronic liver injury to HCC across diverse etiologies. This revised review emphasizes that the inflammatory basis of hepatocarcinogenesis is both convergent and context specific: multiple diseases activate overlapping pathways such as NF- κ B and IL-6/STAT3, yet each etiology imprints a distinct immunometabolic microenvironment with implications for surveillance, biomarker selection, and therapy.

Equally important, the field is moving from descriptive inflammation biology toward clinically actionable translation. Serum markers, cytokine panels, radiomics-clinical nomograms, and microbiome-derived signatures are expanding the toolbox for early detection and risk stratification, but only those supported by rigorous validation, calibration, and implementation pathways will influence practice. Therapeutically, progress now spans established systemic agents, checkpoint-based combinations, locoregional-immunologic synergy, pathway-specific inhibitors, and next-generation cellular and nucleic-acid interventions.

Future work should prioritize etiology-stratified biomarker validation, multicenter prospective model testing, standardized translational pipelines, and explicit integration of mechanistic insights with real-world clinical workflows. Through this precision-oriented approach, inflammation-associated HCC may increasingly become a disease that is not only treatable but also more predictable, preventable, and interceptable.

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Author contributions

Xiaoyun Chen and Shan Ji contributed to the conception, design, literature review, manuscript drafting, and critical revision of the manuscript. Both authors read and approved the final manuscript.

Conflicts of interest

All authors declare no conflicts of interest.

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Research progress on mosquito repellents and prevention of mosquito-borne diseases

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Abstract

Mosquito-borne diseases remain a critical focus in global public health, with conditions such as malaria, dengue fever, and chikungunya fever causing millions of infections and deaths worldwide annually, posing a persistent threat to human health. Nearly half of the global population is at risk of mosquito-borne infections. Concurrently, environmental factors including climate change and accelerated urbanization are expanding the geographic distribution of these diseases, further complicating prevention and control efforts. This study systematically examines two core strategies: insect repellent development and vector control. It details the current applications of chemical repellents, natural plant-based repellents, and spatial repellents, while systematically analyzing implementation priorities for integrated vector control, comprehensive vector management, disease diagnosis and vaccine development, and public health education. The research identifies key challenges in vector control, including pesticide resistance, climate change, and emerging pathogens. Based on existing findings, it outlines future directions for innovative repellent development, biological control technologies, epidemic monitoring systems, and interdisciplinary collaboration. The study concludes that effective vector control requires a dynamic, multi-strategy integrated system adaptable to evolving mosquito behaviors, environmental conditions, and pathogen characteristics.

Keywords: mosquito-borne diseases, insect repellents, vector control, public health, insecticide resistance, integrated pest management

Mosquito control and prevention of mosquito-borne diseases are critical components of global public health, as vector-borne diseases such as malaria, dengue fever, chikungunya, yellow fever, and Zika virus infection cause millions of cases and deaths annually ^[1–3]. The continuous rise in these diseases has progressively become a major threat to global public health ^[2, 4]. Effective management of mosquito populations and preven-

tion of bites require a combination of multiple strategies, which is of paramount importance ^[4, 5].

Global overview and impact of Mosquito-borne diseases

Mosquitoes, as vectors of numerous pathogens, are among the most lethal animals on Earth ^[3, 6]. They

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rank among the most dangerous organisms due to their capacity to transmit various pathogenic microorganisms. These insects transmit diseases including malaria, dengue fever, yellow fever, chikungunya, Zika virus, West Nile virus, and lymphatic filariasis ^[1, 2, 7, 8]. Approximately 4 billion people worldwide, accounting for about 50% of the global population, are at risk of infection from mosquito-borne diseases ^[5]. For instance, dengue fever is prevalent in over 100 countries, particularly in Africa, the Americas, Southeast Asia, and the Western Pacific region ^[9]. Mosquito-borne diseases cause approximately 700,000 to 1 million deaths annually, with malaria being the most lethal among them. According to the Global Burden of Disease Study 2021, malaria resulted in approximately 608,000 deaths worldwide in 2021, of which about 76% were children under 5 years of age. Although dengue fever has a relatively low case fatality rate, its epidemiological impact is substantial, with an estimated 100 to 400 million symptomatic cases annually. In 2023 alone, over 5 million cases were reported globally, leading to more than 3,000 deaths. Yellow fever can cause tens of thousands of annual deaths in unvaccinated regions. While Zika virus rarely causes direct fatalities, congenital Zika syndrome (e.g., microcephaly) has been reported in over 2,000 confirmed cases during the 2015-2017 Brazilian outbreak. The geographical spread of mosquito-borne diseases is expanding, closely linked to environmental factors such as climate change, urbanization, deforestation, and inadequate drainage systems ^[2, 6, 7]. For example, climate change can alter the geographic distribution of mosquitoes and the exogenous incubation period of pathogens within their bodies, thereby reshaping the global risk profile of mosquito-borne diseases ^[6].

Mosquito repellent strategies

Mosquito repellent is one of the key methods of personal protection, which reduces the risk of infection

by preventing mosquitoes from approaching or biting human hosts ^[10-12]. Repellents work by interfering with the host-seeking behavior of mosquitoes ^[10].

Chemical repellents

Using high-efficiency chemical repellents is the key method to protect oneself.

DEET: DEET (N, N-diethyl-3-methylbenzamide) is considered the gold standard for mosquito repellents and has been used for decades ^[13]. However, the emergence of mosquito resistance to DEET has prompted the development of novel repellents ^[13].

Picaridin and IR3535: In addition to DEET, picaridin and IR3535 are also widely recommended synthetic repellents.

Other synthetic repellents: Recent studies have focused on developing novel silicone-based mosquito repellents to address the limitations of existing repellents and prolong protection duration ^[13]. For instance, one study synthesized and evaluated a series of novel silicone compounds as potential mosquito repellents, aiming to enhance protective efficacy ^[13].

Sustained-release formulations: To prolong the effective duration of repellents, researchers are developing sustained-release formulations, such as encapsulating repellents in microcapsules to achieve more prolonged protection ^[14, 15]. The use of poly(ε-caprolactone) microcapsules encapsulating citronella oil has been demonstrated for mosquito repellent efficacy ^[15].

Natural plant-based repellents

With the increasing concern about the resistance to synthetic pesticides and the potential harm to the environment and human health, plant-based repellents

have attracted more and more attention ^[1, 16–21].

Essential oils: Essential oils such as lemongrass, eucalyptus, clove, and marigold have been evaluated for their mosquito repellent efficacy and can be applied to textiles to provide protection ^[22]. Lemongrass oil is a common natural plant product that has been used in repellent formulations ^[12].

Plant Extracts: Extracts from plants such as *Azadirachta indica* and *Vitex negundo* are used to prepare herbal mosquito repellents due to their repellent effects against vectors of various mosquito-borne diseases (e.g., dengue fever, malaria, Zika virus infection) ^[20, 21]. Studies have demonstrated that plant monomeric compounds exhibit significant potential as mosquito repellents in combating mosquito-borne diseases, as they generally possess superior biodegradability and are less prone to resistance development ^[19].

Blended formulations: Studies have demonstrated that the combination of β -caryophyllene oxide and vetiver oil exhibits synergistic repellent and stimulant effects against multiple mosquito species, including *Aedes aegypti*, *Aedes albopictus*, *Aedes microcephalus*, and *Culex tritaeniorhynchus* ^[23].

Formulation: Natural repellents can be formulated into various forms such as sprays, emulsions, roll-ons, and scents ^[12, 17, 18]. A study developed and evaluated a herbal roll-on mosquito repellent formulation aimed at providing safe and effective personal protection ^[18].

Mosquito-repellent textiles: The application of mosquito-repellent ingredients (including synthetic chemicals and natural extracts) to textiles can be used to produce mosquito nets, clothing, and uniforms, providing sustained protection for individuals ^[22, 24].

Spatial repellents

Spatial repellents repel mosquitoes by releasing volatile compounds into the environment ^[25]. Deltamethrin, a volatile pyrethroid insecticide, achieves both pest control and repelling effects through widespread application. Studies have demonstrated that low concentrations of deltamethrin can effectively repel *Aedes aegypti* by enhancing the response of olfactory receptors ^[25].

Prevention and control strategies for Mosquito-borne diseases

The prevention and control of mosquito-borne diseases require a multifaceted and comprehensive approach, including vector control, disease surveillance, public education, and personal protection ^[26–28].

Vector Control

Vector control is a key strategy to reduce the transmission of mosquito-borne diseases, aiming to decrease mosquito population density or their ability to transmit pathogens ^[4, 26, 29].

Environmental management and fecundity site removal: The elimination of mosquito breeding sites is one of the most direct and effective methods for controlling mosquito populations ^[26, 30]. This involves measures such as removing standing water from tires, flower pots, and discarded containers ^[30]. Emerging technologies, such as drones or automated patrol vehicles, are being developed for the detection and removal of mosquito breeding sites ^[31].

Chemical control:

Larvicides: Used to kill mosquito larvae and can be applied in waterlogged areas ^[11, 30]. Mosquito control agents: including indoor residual spraying and ultra-low volume spraying, which can rapidly reduce the

density of adult mosquitoes ^[32]. Pesticide resistance: However, long-term use of synthetic insecticides has led to widespread resistance in mosquitoes, severely threatening the effectiveness of traditional vector control strategies ^[1, 3, 5, 29, 32–35]. For example, the increase in dengue fever cases in India is consistent with the rising trend of resistance to insecticides in *Aedes aegypti* ^[35].

Biological control:

Mosquito-eating fish: Capturing mosquito larvae through fish schools ^[36]. The Israeli subspecies of *Bacillus thuringiensis* is a bacterial insecticide specifically effective against mosquito larvae ^[36]. Wolbachia: By infecting mosquitoes, Wolbachia bacteria can inhibit viral replication within mosquitoes and affect mosquito reproduction, thereby reducing the transmission of mosquito-borne diseases ^[29].

As alternatives to chemical pesticides, entomopathogenic fungi such as *Beauveria* spp. and *Metarhizium* spp. are being investigated for mosquito control ^[33].

Sterile Insect Technique is a method that releases radiation-treated or genetically edited sterile male mosquitoes to mate with wild female mosquitoes, thereby reducing mosquito populations ^[3].

Synthetic Biology and Gene Drive: Gene drive technology utilizes gene-editing tools such as CRISPR to rapidly propagate specific genes (e.g., those causing sterility or reduced viral transmission capacity) within mosquito populations, thereby achieving suppression or modification of mosquito populations to block disease transmission ^[3].

Surfactants: Studies have demonstrated that surfactants can alter the flight capacity and physiological status of mosquitoes, potentially serving as a novel vector control strategy ^[37].

Integrated Vector Management

The Integrated Vector Management (IVM) strategy recommended by the World Health Organization emphasizes multisectoral collaboration and evidence-based decision-making, integrating environmental, biological, and chemical control methods to achieve effective control of mosquito-borne diseases ^[27]. IVM aims to optimize the combination of various interventions based on local conditions to achieve synergistic effects ^[27].

Disease treatment and vaccines

Treatment methods: Currently, there are no specific antiviral drugs or long-lasting vaccines widely used for the treatment of diseases such as dengue fever ^[9]. Studies have explored the potential of drugs such as loratadine in reducing the incidence of dengue hemorrhagic fever, as it can decrease endothelial dysfunction in vitro and reduce vascular leakage in mouse models ^[38].

Vaccine development: Although vaccines are available for diseases such as malaria and yellow fever, the development of effective vaccines for many mosquito-borne diseases, including dengue fever, remains challenging ^[19].

Public health and education

Public awareness: It is crucial to enhance public understanding of the risks of mosquito-borne diseases and personal protective measures ^[11, 27].

Early diagnosis and surveillance: Rapid and accurate diagnosis, along with an effective disease surveillance system, contributes to controlling the outbreak ^[24].

Challenges and Future Directions

Prevention and control of Mosquito-borne diseases face multiple challenges:

Pesticide resistance: The development of insect resistance to multiple pesticides represents one of the most significant challenges in contemporary pest control ^[1, 3, 5, 29, 32–35].

Climate change: Global warming leads to the expansion of mosquito activity ranges, thereby increasing the likelihood of disease transmission ^[2, 6].

Emerging pathogens: The emergence of new mosquito-borne viruses (e.g., Zika virus) and mutations in existing viruses have increased the complexity of prevention and control efforts ^[2].

Future research directions include:

Development of novel repellents and insecticides: The objective is to identify environmentally safer alternatives that are less prone to resistance development and exhibit prolonged efficacy ^[12, 13, 19].

Innovations in biological control methods: Continued development and refinement of biological control technologies based on Wolbachia, gene drive, and insect pathogenic fungi ^[3, 33].

Integrated monitoring and prediction: Utilizing mathematical models and data analysis to predict disease outbreak risks and guide the deployment of interventions ^[4, 11, 29]. A study proposed a mathematical model for dengue transmission incorporating the use of mosquito repellents, and analyzed its stability and optimal control strategies ^[4].

Multidisciplinary collaboration: Strengthen coopera-

tion in fields such as medicine, ecology, entomology, engineering, and social sciences to jointly address the challenges of mosquito-borne diseases ^[28].

The prevention of mosquito-borne diseases requires a continuously evolving, multi-strategy integrated approach to adapt to the ever-changing mosquito behaviors, environmental conditions, and pathogen characteristics ^[5].

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dai Shi, Taotao Wei, Shengli Yue, Min Lin, Lei Zhou, and Jiakang Yu. The first draft of the manuscript was written by Dai Shi and all authors commented on previous versions of the manuscript. All authors read, revised and approved the final manuscript.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Meta-analysis and systematic review of the incidence and influencing factors of acute skin failure in ICU patients

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Abstract

Objective To systematically evaluate the incidence of acute skin failure (ASF) and influencing factors among patients in the intensive care unit (ICU).

Methods Cohort studies investigating the incidence and determinants of ASF in ICU patients were systematically searched in PubMed, Cochrane Library, Web of Science, Embase, China National Knowledge Infrastructure, Wanfang Database, CQVIP, and China Biology Medicine from database inception to August 31, 2025. A meta-analysis was performed using R software.

Results Ten studies involving 2,870 participants were included in the meta-analysis. The pooled incidence of ASF among ICU patients was 38.4% (95% *CI*: 0.246–0.545). Subgroup analysis indicated significant regional differences in ASF incidence ($P < 0.001$). Meta-regression analysis demonstrated that sample size ($\beta = -0.001$), study design ($\beta = 1.353$), and publication year ($\beta = -1.114$) were significantly associated with the effect size. Furthermore, pooled analyses identified sepsis ($OR = 2.72$), renal failure ($OR = 2.88$), use of vasoactive agents ($OR = 3.31$), and use of sedative and analgesic medications ($OR = 5.15$) as significant factors associated with ASF occurrence.

Conclusion ASF is common among ICU patients. Sepsis, renal failure, and the use of vasoactive agents and sedative-analgesic medications may be associated with an increased risk of ASF, providing a basis for early identification and targeted interventions in clinical practice. However, given the substantial heterogeneity among the included studies, these findings require further validation.

Keywords: intensive care unit, acute skin failure, meta-analysis, systematic review, nursing

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Introduction

Acute skin failure (ASF) is defined as a cutaneous and subcutaneous tissue death event caused by inadequate perfusion due to hemodynamic instability and reduced tissue tolerance^[1]. Patients in the intensive care unit (ICU) are particularly susceptible to ASF due to complex medical conditions, frequent complications, and common comorbidities, such as low tissue perfusion status, malnutrition, infection, and prolonged bed rest^[2]. At present, there is no universally accepted diagnostic standard for ASF. Considerable variation among studies regarding diagnostic criteria and assessment procedures has led to substantial discrepancies in the reported incidence of ASF among ICU patients, ranging from 14.46% to 83.7%, with limited consistency and comparability^[3,4]. ASF can result in a significantly prolonged hospital stay, increased mortality risk, and worsened prognosis^[5]. In addition, because the clinical manifestations of ASF are highly similar to those of pressure injuries (PI), ASF is easily misdiagnosed as a nursing-related adverse event in clinical practice, thereby imposing considerable psychological burden and occupational stress on nursing staff^[6,7]. Despite increasing studies of the incidence and risk factors for ASF in recent years, the inconsistencies in diagnostic standards, heterogeneity in study populations, and variations in study design and methodology have made it difficult to draw conclusions and establish strong clinical guidelines. Therefore, in this study, a systematic review was conducted to synthesize the current evidence and clarify the incidence and key determinants of ASF in ICU patients, with the aim of providing scientific evidence for the early identification of high-risk populations, development of targeted preventive strategies, and promotion of standardized ASF assessment and risk management in clinical practice.

Materials and Methods

Materials

Literature Search: A computerized literature search was conducted using the English-language databases PubMed, Cochrane Library, Web of Science, and Embase as well as the Chinese-language databases CNKI, Wanfang Database, CQVIP, and CBM. Studies reporting the incidence of and risk factors for ASF were collected. The search period covered the inception of each database up to August 31, 2025 and the search was limited to publications in Chinese or English. To avoid missing potentially relevant studies that did not explicitly mention “ICU” in their titles or abstracts, “ICU” was not used as a search restriction term. English search terms included “acute skin failure,” “skin failure,” and “terminal skin failure.” Chinese search terms included “急性皮肤衰竭” (acute skin failure) and “皮肤衰竭” (skin failure). Manual searches were performed as a supplement. Because ASF-related MeSH terms or Emtree terms are currently unavailable, free-text terms were used for the search. Using PubMed as an example, the search strategy was as follows: (acute skin failure[Title/Abstract]) OR (skin failure[Title/Abstract]) OR (terminal skin failure[Title/Abstract]). The detailed search strategy is presented in Table S1.

This study followed the PRISMA 2020 reporting guideline for systematic reviews and has been preregistered with PROSPERO (registration number: CRD420251038549). Further registration details can be accessed at <https://www.crd.york.ac.uk/prospero/>.

Inclusion and Exclusion Criteria: The inclusion criteria were as follows. (1) The study population consisted of ICU patients aged ≥18 years. (2) The study reported the incidence of ASF. If influencing factors were investigated, multivariate analysis results (e.g.,

the odds ratio [OR] and 95% confidence interval [95% CI]) or raw data allowing for the calculation/conversion of effect sizes were required. (3) A cohort study design was used. (4) Clearly defined ASF diagnostic criteria (including clinical definitions, characteristics of skin lesions, and relevant hemodynamic indicators) were included to facilitate the assessment of inter-study heterogeneity. The exclusion criteria were as follows: (1) duplicate publications or studies with data originating from the same patient population, (2) data that could not be extracted, and (3) articles not published in Chinese or English. The literature screening flow diagram is shown in Figure 1.

Methods

Literature Screening: Two researchers independently used NoteExpress software to deduplicate and preliminarily screen the retrieved literature. They then independently extracted data from the included studies, followed by cross-verification. In the event of disagree-

ments, a third researcher was consulted to participate in the discussion and make the final judgment.

Quality Assessment and Data Extraction: The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies. The NOS contains eight items covering three domains: selection of study groups, comparability of the groups, and ascertainment of the outcome. The maximum total score is 9 points, and scores of 0–3 indicate low quality, 4–6 indicate moderate quality, and ≥ 7 indicate high quality. Two researchers independently performed the quality assessment and cross-verification. Disagreements were resolved through discussion and consensus, with the involvement of a third researcher as needed. The extracted items included the first author, publication year, study population, country where the study was conducted, study design, sample size, ASF diagnostic method, ASF incidence, and reported influencing factors.

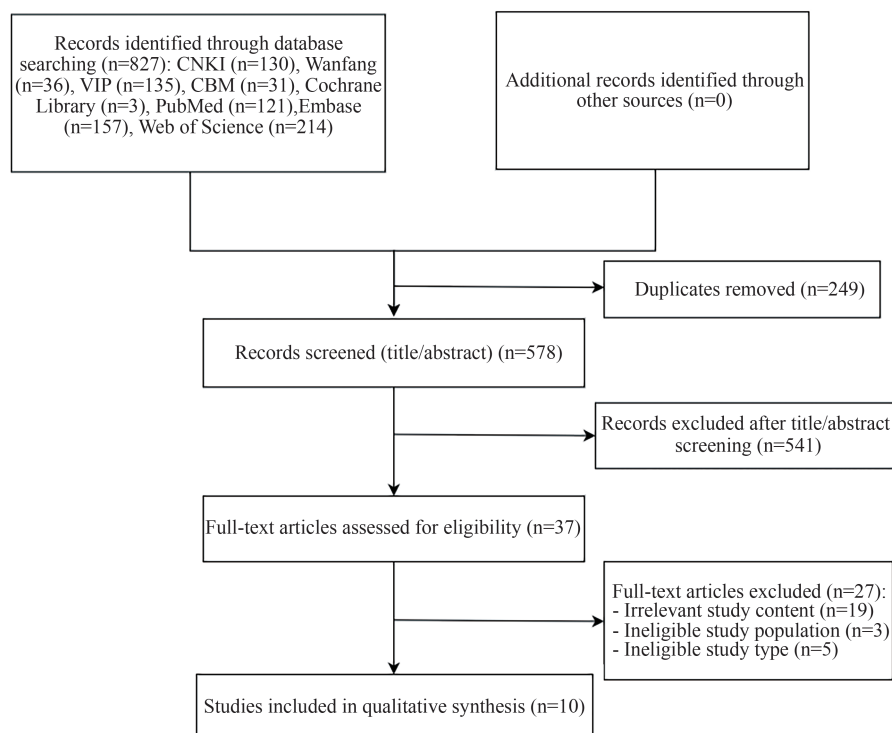


Figure 1. Flow diagram of the literature screening process.

Statistical Methods

Statistical analyses were performed using R software (version 4.2.2). For the pooled incidence of ASF, a generalized linear mixed model (GLMM) with a logit link function was applied using a one-step approach. To identify influencing factors, risk factors reported in at least two studies were included in the meta-analysis. *ORs* and corresponding 95% *CI*s reported in individual studies were extracted. Standard errors were calculated after logarithmic transformation, and pooled effect sizes were estimated using the inverse variance method under a random-effects model, with between-study variance (τ^2) estimated using the restricted maximum likelihood (REML) method.

Considering the potential differences in study populations, diagnostic criteria, and methodologies among studies, random-effects models were applied throughout the analyses. Heterogeneity across studies was assessed using Cochran's *Q* test ($\alpha=0.10$) and the I^2 statistic. I^2 values of <25%, 25%–50%, 50%–75%, and >75% were considered to indicate low, moderate, high, and considerable heterogeneity, respectively. When substantial heterogeneity was observed ($I^2>50\%$), subgroup analyses and meta-regression analyses were conducted to explore potential sources of heterogeneity. A sensitivity analysis was performed using a leave-one-out approach to assess the robustness of the results. When at least 10 studies were included, publication bias was initially assessed using funnel plots and further quantified using Egger's regression test. All statistical tests were two-sided, and a value of $P<0.05$ was considered statistically significant.

Results

General Characteristics

In total, 827 records were identified through the data-

base search. After removing duplicates, 578 records remained. Following the initial screening of titles and abstracts, 37 articles were selected for full-text assessment. Ultimately, 10 studies [3,4,8–15] met the inclusion criteria, including 7 identified as high quality [3,4,8–11,14] and 3 identified as moderate quality [12,13,15]. The studies involved 2,870 patients, of whom 847 developed ASF. All 10 studies [3,4,8–15] reported the incidence of ASF in ICU patients, and 5 studies [3,9,10,12,13] provided multivariate-adjusted *ORs* with 95% *CI*s for factors influencing ASF in ICU patients. The basic characteristics of the included studies are detailed in Table 1, and methodological quality assessment results are shown in Table S2.

Meta-analysis Results

Overall incidence of acute skin failure in ICU patients: A meta-analysis of the 10 studies meeting the inclusion criteria showed that the pooled incidence of ASF among ICU patients was 38.4% (95% *CI*: 0.246–0.545). Considerable heterogeneity was observed across studies ($I^2=96.5\%$, $P<0.001$). The results are presented in Figure 2.

Influencing factors for ASF in ICU patients

Concurrent sepsis and renal failure

Three studies [9,12,13] reported the effect of concurrent sepsis on ASF. The pooled analysis showed that concurrent sepsis was significantly associated with the occurrence of ASF [*OR*=2.72, (95% *CI* 1.69–4.36), $P<0.001$], with no significant heterogeneity among studies ($I^2=0\%$, $P=0.736$). Two studies [9,13] reported the effect of concurrent renal failure on ASF. The pooled analysis indicated that concurrent renal failure was significantly associated with ASF occurrence [*OR*=2.88, (95% *CI* 1.59–5.22), $P<0.001$], and no significant heterogeneity was detected across studies ($I^2=0\%$, $P=0.996$).

Table 1. Basic characteristics and quality assessment of included studies.

Author (Year)	Country	Study design	Sample size	Study population	ASF diagnostic criteria	ASF incidence (%)	Influencing factors
Liu ^[11] (2025)	China	A	150	ICU patients with septic shock	①, ②, ③	23.30%	-
Xu ^[9] (2025)	China	A	80	ICU patients aged ≥ 80 years	④	41.00%	BMI, renal failure, sepsis, sedative/analgesic drugs, NRS2002 score, Braden score
Tang ^[10] (2025)	China	A	254	ICU patients with sepsis	At least one of ④, ⑤ > 2s, ⑥, ⑦ plus concurrent ① and ②	35.00%	Peripheral artery disease, mechanical ventilation, vasoactive agents, APACHE-II score, mean arterial pressure, lactate level
Zhang ^[8] (2025)	China	B	217	General ICU patients	Any one of ④, ⑤ > 3s, ⑧ plus concurrent ②	23.04%	-
Zhu ^[12] (2024)	China	B	204	General ICU patients	①, ②	28.43%	Age, sepsis, vasoactive agents, peripheral perfusion index, serum albumin level
Zhang ^[14] (2024)	China	B	1036	General ICU patients	Any one of ③, ④, ⑤ > 3s, ⑧	24.32%	-
Xu ^[13] (2024)	China	B	251	ICU patients aged ≥ 65 years	At least one of ④, ⑤ > 2s, ⑧ plus concurrent ① and ②	41.83%	Braden score, renal failure, heart failure, sepsis, lactate level, sedative/analgesic drugs
Wang ^[3] (2024)	China	A	491	ICU patients with septic shock	Any one of ④, ⑤ > 2s, ⑥, ⑦, ⑧	14.46%	Body surface area, NEWS score, SOFA score, lactate level, peripheral perfusion index, capillary refill time
Wang ^[4] (2022)	China	A	123	ICU patients with septic shock	Any one of ④, ⑤ > 2s, ⑥, ⑦, ⑧	83.70%	-
Greenway ^[15] (2021)	USA	A	64	ICU patients with COVID-19-positive status	-	79.70%	-

Notes: A: Retrospective cohort study; B: Prospective cohort study. ① Ischemia due to poor blood perfusion (e.g., cyanosis, gangrene of fingers or toes, or skin blister formation, typically purple, yellow, or black in color); ② Relatively rapid disease progression. Most lesions are not associated with bony prominences and often appear pear-shaped, butterfly-shaped, or horseshoe-shaped; ③ Skin perfusion pressure ≤ 25 mmHg; ④ Skin mottling score > 0; ⑤ Capillary refill time; ⑥ After excluding non-circulatory factors, severe anemia, and other blood disorders, the patient's fingertip transcutaneous oxygen saturation decreases by >5%; ⑦ Decreased skin sensation; ⑧ Cold and clammy skin: ambient temperature 18–22 °C, humidity 55%–65%, body surface temperature measured using an infrared thermometer of <33.5 °C in the absence of physical cooling, accompanied by moist skin. ASF: acute skin failure; NRS2002 score: Nutritional Risk Screening 2002 score; Braden score: Braden Scale for Predicting Pressure Sore Risk score; NEWS: National Early Warning Score; SOFA: Sequential Organ Failure Assessment score; APACHE II score: Acute Physiology and Chronic Health Evaluation II score.

Use of vasoactive agents and sedative/analgesic drugs

Two studies ^[10,12] reported the effect of vasoactive agent use on ASF. The pooled results demonstrated that the use of vasoactive agents was significantly associated with the occurrence of ASF [$OR=3.31$, 95% CI (1.64–6.68), $P=0.001$], with moderate heterogeneity observed across studies ($I^2=36.9\%$, $P=0.208$). Two

studies ^[9,13] reported the effect of sedative/analgesic drug use on ASF. The pooled analysis showed that the use of sedative/analgesic drugs was significantly associated with ASF occurrence [$OR=5.15$, 95% CI (1.35–19.64), $P=0.016$], with substantial heterogeneity detected among studies ($I^2=58.7\%$, $P=0.120$).

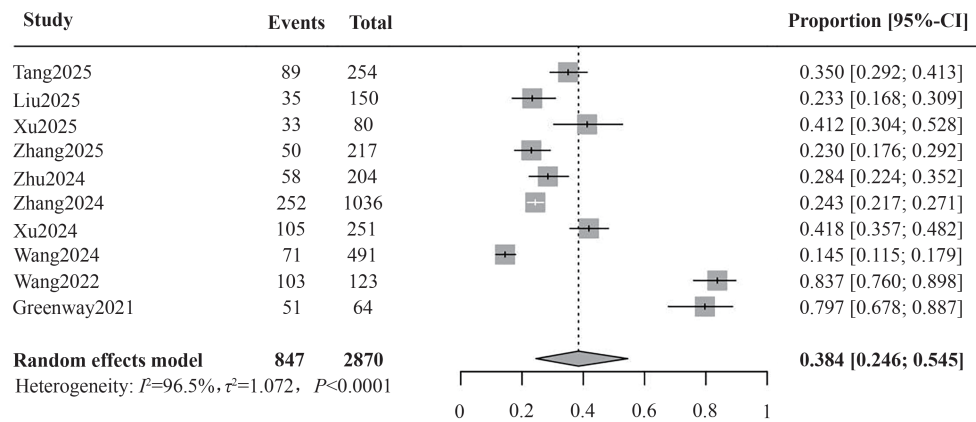


Figure 2. Forest plot of the incidence of ASF in ICU patients.

Lactate level and peripheral perfusion index

Three studies ^[3,10,13] reported the effect of lactate level on ASF. In a meta-analysis, lactate levels were not significantly associated with the risk of ASF occurrence [$OR=2.16$, 95% CI (0.70–6.70), $P=0.183$], and there was considerable heterogeneity among studies ($I^2=93.3\%$, $P<0.001$). Two studies ^[3,12] reported the effect of the peripheral perfusion index on ASF. The pooled results indicated that the peripheral perfusion index was not significantly associated with the risk of ASF occurrence [$OR=0.04$, (95% CI : <0.01–4.80), $P=0.189$], with considerable heterogeneity observed across studies ($I^2=91.8\%$, $P<0.001$).

Subgroup analysis and meta-regression analysis

Subgroup analyses of ASF incidence were conducted according to study design, sepsis status, age group, and geographic region. The pooled incidences of ASF in retrospective cohort studies and prospective cohort studies were 41.2% (95% CI : 0.195–0.670) and 34.9% (95% CI : 0.280–0.427), respectively, with no significant between-group heterogeneity ($Q=0.22$, $P=0.642$). The pooled incidences of ASF among patients with and without sepsis were 38.7% (95% CI : 0.243–0.554) and 37.8% (95% CI : 0.146–0.684), respectively, with no significant between-group heterogeneity ($Q=0.00$, $P=0.959$). The pooled incidences of ASF

among patients aged ≥ 60 years and <60 years were 41.7% (95% CI : 0.365–0.471) and 37.8% (95% CI : 0.212–0.579), respectively, with no significant between-group heterogeneity ($Q=0.14$, $P=0.706$). The pooled incidences of ASF in studies conducted in China and the United States were 33.9% (95% CI : 0.221–0.481) and 79.7% (95% CI : 0.681–0.878), respectively, with significant between-group heterogeneity observed ($Q=22.7$, $P<0.001$).

Meta-regression analysis was performed by including publication year, sample size, study design, sepsis status, age group, and geographic region as covariates. Sample size ($\beta=-0.001$, $P=0.024$), study design ($\beta=1.353$, $P=0.013$), and publication year ($\beta=-1.114$, $P<0.001$) were significantly associated with the effect size. Residual heterogeneity remained substantial after meta-regression ($I^2=79.2\%$).

Sensitivity analysis and publication bias

The results of a sensitivity analysis showed that after sequentially excluding each study, the pooled incidence of ASF ranged from 0.329 to 0.420, with highly overlapping confidence intervals, indicating that the overall results were stable and reliable. Visual inspection of the funnel plot showed that most studies were distributed on both sides of the central axis, although some

asymmetry in the distribution of study estimates was observed (Figure 3). Egger's regression test yielded a *P*-value of 0.066, suggesting a lack of significant publication bias.

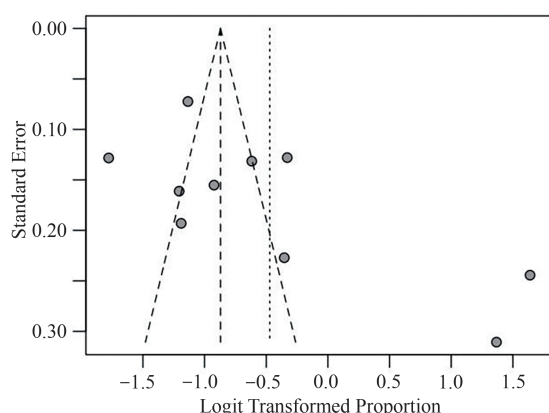


Figure 3. Funnel plot of the incidence of ASF in ICU patients.

Discussion

The present study demonstrated that ASF may represent a relatively common skin complication in critically ill patients, with a pooled incidence of 38.4% among ICU patients. However, considerable heterogeneity was observed across studies ($I^2=96.5\%$); therefore, these findings should be interpreted cautiously within the context of study characteristics and clinical settings.

Meta-regression analysis indicated that sample size, study design, and publication year were significantly associated with effect size. The negative association between sample size and effect size suggests that smaller studies are more likely to report higher incidence estimates. With respect to study design, it is possible that prospective studies allow continuous and dynamic patient monitoring, potentially improving ASF detection rates, whereas retrospective studies rely primarily on medical records and may therefore be more susceptible to information bias. In addition, the negative association between publication year and effect size may be related to the increasing awareness of

ASF and ongoing improvements in critical care management strategies. Notably, a subgroup analysis demonstrated significant regional differences in ASF incidence; however, these findings should be interpreted with caution. International data included in this study were derived from a single study involving patients with COVID-19 conducted during the pandemic period^[15]. Critically ill patients with COVID-19 frequently present with systemic inflammatory responses, microcirculatory dysfunction, and coagulation abnormalities, all of which may increase the risk of impaired skin perfusion^[16]. Therefore, regional differences observed in this study may have been influenced by specific disease characteristics.

Substantial residual heterogeneity remained after meta-regression ($I^2=79.2\%$), indicating that additional unexplained sources of heterogeneity may exist. This may be attributable in part to the lack of a standardized diagnostic framework for ASF. As an emerging concept introduced in recent years, universally accepted diagnostic criteria for ASF are lacking, resulting in inconsistencies in case identification across studies^[17]. Most studies have relied on a combination of skin manifestations, tissue perfusion indicators, and relevant clinical features for diagnosis. Variation in the criteria used to identify ASF may influence incidence estimates and reduce comparability across studies. Therefore, establishing standardized diagnostic criteria and risk assessment tools for ASF may be necessary to improve consistency across studies and facilitate early clinical identification and targeted interventions.

In a pooled analysis, concurrent sepsis and renal failure were significantly associated with ASF occurrence. These findings are generally consistent with those reported by Savage et al.^[18], who observed that 80.8% of patients with ASF had sepsis and 76.9% experienced acute kidney injury. Similarly, Curry et al.^[19] reported

that all patients with ASF had at least two organ dysfunctions or a single organ failure combined with sepsis at the time of diagnosis. One possible explanation is that infection-induced systemic inflammatory responses substantially impair microcirculatory function, leading to inadequate tissue perfusion, imbalance between oxygen supply and demand, and ultimately tissue injury and organ dysfunction^[20]. In addition, under severe physiological stress, compensatory mechanisms generally prioritize blood flow to vital organs, such as the brain, heart, and kidneys, while perfusion to peripheral tissues including the skin may be further reduced, thereby increasing susceptibility to ASF.

The use of vasoactive agents and sedative/analgesic drugs was significantly associated with ASF occurrence. Mileski et al.^[21] identified several medications associated with ASF development, including norepinephrine, fentanyl, morphine, and propofol. There is evidence that vasoactive agents may reduce tissue perfusion and restrict capillary blood flow through vasoconstriction. Moreover, certain sedative and analgesic agents may impair vasomotor regulation and attenuate compensatory microcirculatory responses to ischemic conditions. These mechanisms may collectively contribute to the development and progression of ASF^[22].

Distinguishing ASF from PI remains a major challenge in clinical practice. Previous studies have described ASF as an “unavoidable PI” or “critical illness-related PI”^[23,24]. However, increasing evidence suggests that ASF and PI differ fundamentally in both pathological mechanisms and clinical characteristics. PI is primarily caused by external factors, including prolonged pressure, shear forces, and friction, and commonly occurs over bony prominences, such as the sacrum and heels. In contrast, ASF typically occurs in the context of critical illness and results from hemodynamic instability and tissue hypoperfusion, represent-

ing a cutaneous manifestation of systemic pathological processes^[7]. Because of overlapping clinical presentations, ASF may be misdiagnosed as PI and consequently regarded as a preventable nursing adverse event, thereby increasing management burden and potentially affecting accurate skin injury management. Therefore, focusing on ASF incidence and associated factors among ICU patients may contribute to improving differential diagnosis between ASF and PI and facilitating early identification and targeted interventions for high-risk critically ill populations.

This study had several limitations. First, there was substantial differences among included studies in terms of diagnostic criteria, study populations, and regional characteristics. Although meta-regression was conducted to explore potential sources of heterogeneity, subgroup analyses based on diagnostic criteria could not be performed owing to the limited number of studies; therefore, heterogeneity may not have been fully explained. Second, most included studies were single-center studies with relatively small sample sizes. The lack of large multicenter prospective studies may limit the representativeness and generalizability of the pooled incidence estimate. Third, the number of included studies was limited, and evidence regarding several associated factors remained insufficient; therefore, the stability of these findings requires further confirmation.

Conclusion

ASF appears to be relatively common among ICU patients. Sepsis, renal failure, and the use of vasoactive agents and sedative-analgesic medications may be associated with ASF occurrence. Future studies should focus on establishing standardized diagnostic criteria and developing early warning tools to improve the identification of high-risk populations.

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Author contributions

Yulin Zheng and Guojing Sui contributed equally to this work. Lili Zhang and Yanmei Gu served as corresponding authors. Yulin Zheng, Guojing Sui, Huimin Guo, Shuangmei Xi, Xin Li, Chaoqun Wang, Lili Zhang, and Yanmei Gu contributed to the study conception, design, data collection, analysis, and manuscript preparation. All authors reviewed and approved the final manuscript.

Conflict of interest

All authors declare no conflicts of interest.

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Etiology of community-acquired pneumonia among adults in the Chinese mainland: a systematic review and meta-analysis

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Abstract

Background: This meta-analysis aimed to determine the etiology, comorbidities, and clinical features of community-acquired pneumonia (CAP) among adults in mainland China.

Methods: A systematic literature search was conducted in PubMed, Embase, and Cochrane Library to identify relevant studies that reported the etiology, pathogen distribution, and clinical characteristics of CAP in Chinese adults (aged >18 years) from 2004 to December 2024. Overall evidence from the included studies was quantitatively synthesized, and pooled estimates were expressed as weighted values with corresponding 95% confidence intervals (CIs).

Results: Of 5770 studies, 49 studies were eligible for inclusion. Among these, 44 studies (89%) reported bacterial agents; 21 studies (43%) and 33 studies (67%) reported viral and fungal pathogens, respectively. Furthermore, atypical pathogens were reported in 30 studies (61.2%). The predominant bacterial agents among patients diagnosed with CAP were Methicillin-resistant *Staphylococcus aureus* (13%), and *Streptococcus pneumoniae* (9%). Similarly, among viral and fungal pathogens, *influenza virus* (18%) and *Candida albicans* (17%) were most frequently identified in patients with CAP. Moreover, *Mycoplasma pneumoniae* (9%) was identified as a predominant other pathogen in patients with CAP, whereas overall other pathogens accounted for 23% of CAP cases.

Conclusion: CAP has become a serious public health issue in the Chinese Mainland. This systematic review represents a comprehensive evaluation currently available on the factors leading to CAP within the Chinese adult population. Among various etiological agents, bacteria continue to predominate and are the leading cause of CAP

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in this population.

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Keywords: community-acquired pneumonia, comorbidities, clinical symptoms, etiology, pooled proportions, pathogens

Introduction

Pneumonia is the most common respiratory infection experienced in the emergency department, which has caused significant morbidity and mortality in patients ^[1]. Community-acquired pneumonia (CAP) is a serious infectious inflammation of the lower respiratory tract involving the alveoli acquired from non-hospital pathogens ^[2–4]. In adults, CAP is a leading cause of morbidity and mortality in China and in the rest of the world ^[2,5]. In China, the annual incidence of CAP is approximately 7.13 cases per 1000 persons/year ^[6]. However, in the United States, adults experienced a high incidence of CAP, ranging from 1.76 to 7.03 per 1000 persons/year, whereas a few countries in Europe reported a CAP hospitalization rate of 20.6 cases per 10,000 adults/year and 4.7 per 1000 persons annually ^[7]. Furthermore, the mortality rate is reported to be closely associated with increasing age, with 5% among CAP patients aged ≥65 years, 8% in those patients aged from 65 to 79 years, and 14% in patients aged ≥80 years ^[8].

In addition, CAP represents a heterogeneous condition with diverse clinical manifestations and a wide range of causative pathogens, which can vary depending upon various factors, such as age, geography, and recent exposures ^[2]. Several respiratory pathogens are known to cause CAP, including bacteria, fungi, and viruses, by invading the lung as a single pathogen or in co-infection ^[9,10]. Despite advancement in diagnosis

and treatment modalities, CAP is still a common and potentially lethal infectious disease where *Spneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* remain the leading causes of CAP ^[11], whereas *Influenza* virus, *human parainfluenza viruses*, respiratory syncytial virus (RSV), human rhinovirus (HRV)/ *human enterovirus*/, human adenovirus (HAdV), human coronavirus (HCoV), and human metapneumovirus are reported to be the major viruses causing CAP ^[12]. However, the causative pathogen remains unknown in 30% to 60% of cases despite vigorous clinical investigation ^[11]. Furthermore, the growing number of causative agents associated with CAP, along with the growing number of the at-risk population, continues to pose challenges to existing diagnostic and therapeutic approaches ^[11]. *Streptococcus pneumoniae* (*S pneumoniae*) is among the primary infectious causes that lead to illness and death from CAP globally among young children, persons with underlying chronic systemic conditions, and the elderly ^[11]. According to the global burden of disease study published in 2017, *S pneumoniae* was the most commonly identified lower respiratory tract infection (LRTI) among all age groups, responsible for causing more than 1.5 million LRTI-related deaths. Moreover, there were 0.7 million deaths in patients >70 years and 0.4 million deaths among children <5 years of age ^[13].

There have been several comprehensive meta-analyses on the etiology of CAP in adult patients ^[2,11,14]. Existing meta-analyses have focused on different

perspectives of CAP, such as diagnostic strategies and drug-resistant pathogens. There is a lack of integrated analyses, which demonstrates the etiology of the disease across all major pathogens. This meta-analysis will offer a combination of the bacterial, viral, fungal, and other pathogenic causes of CAP while investigating the comorbidities by incorporating data till December 2024, which will guide clinicians in disease management and selecting an appropriate treatment strategy.

Methodology

The methodology of the present systematic review and meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines^[15] (Figure 1). Protocol for this systematic review was prospectively registered with the Prospective Register

of Systematic Reviews (PROSPERO; CRD42022323132) website.

Data source

A comprehensive literature search was conducted using the PubMed, Embase, Cochrane Library databases, and ClinicalTrials.gov for the published literature from 2004 to December 2024, using a predetermined search strategy developed previously. The search strategy involved the use of predefined keywords along with database indexing terms, which are listed as below: “Community-acquired pneumonia,” “CAP,” “etiologic agent,” “pathogen,” “Chinese,” “China.” A manual search was conducted to identify studies that met the selection criteria from additional sources not covered in the above database, including dissertations and conference papers. The full search strategy is provided in Supplementary: Appendix I.

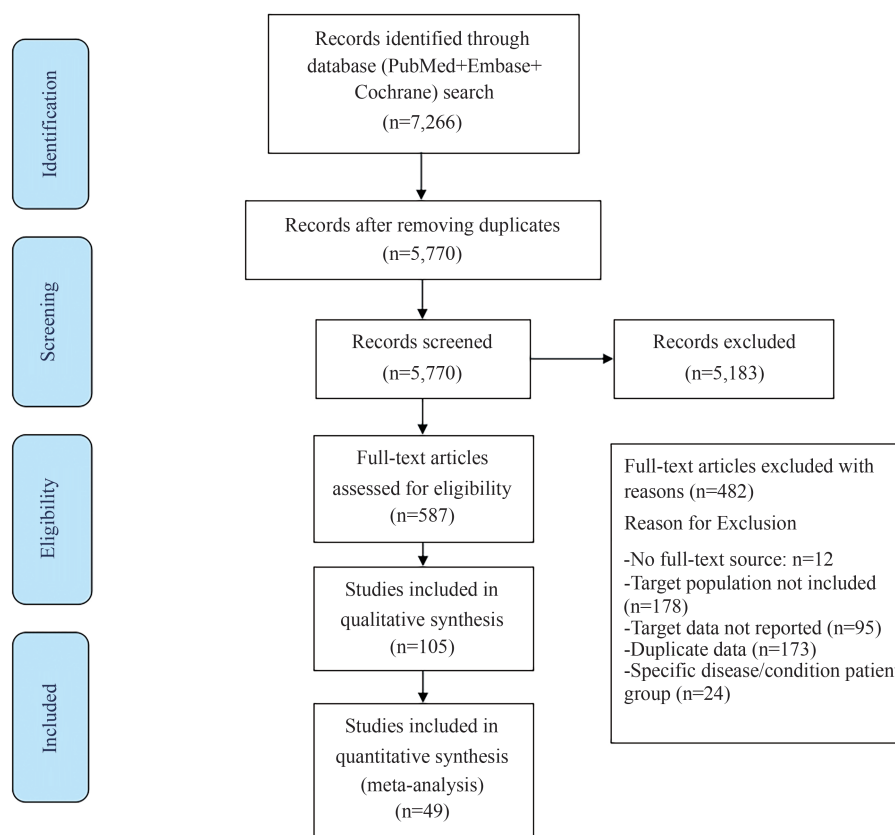


Figure 1. PRISMA Flow Diagram.

Abbreviations: n: number; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Criteria for study selection

All eligible peer-reviewed full-text studies available in English were included in the review. Studies were considered for inclusion in this review when they fulfilled all of the following inclusion criteria if they were: prospective observational, cross-sectional and retrospective; adult patient population in China (aged >18 years) diagnosed with CAP; including both immunocompetent and immunocompromised individuals (e.g., those with HIV infection or organ transplant recipients), as well as patients with comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, cardiovascular diseases, and others; published between 2004 and 2024; outcomes related to pathogen distribution, including viral, bacterial, and fungal pathogens in CAP, etiology and clinical features of CAP in Chinese adults and outcomes are stratified based on comorbidities and source of pathogen identification. The articles were excluded if they were: randomized controlled trials and focused on therapies, diagnostic methods, single pathogens, or complications of pneumonia; (2) reviews, meta-analyses, case reports, and duplicate publications (Supplementary: Appendix II).

Study selection

The titles and abstracts of publications retrieved by the initial search were reviewed by two independent reviewers to identify potentially eligible articles. Discrepancies were resolved by the third reviewer. All potentially relevant citations were inspected in detail by using the full-text version. Studies meeting the pre-defined eligibility criteria were included in the review and used for the subsequent analysis.

Data extraction

Data extraction protocol was developed, and the rel-

evant information was extracted from each of the included study including: (1) Study characteristics, such as study design, title, first author, publication year, and trial phase; (2) patient characteristics, including total study population, age, and patient stratification; and (3) outcomes: etiology of CAP, total number of cases and the numbers with confirmed causative agents, comorbid conditions, and clinical symptoms. Furthermore, there is no threshold for a fixed number of studies. We did the qualitative assessment but did not limit the studies based on the quality to improve statistical power.

Assessment of study quality and risk of bias

The Newcastle-Ottawa Scale (NOS) assessment scale was used to evaluate the quality of included observational studies based on 3 domains with a maximum possible score of 9 points ^[16]. The quality of each study was categorized using the following scoring algorithms: scores ≥ 7 were considered “good,” scores of 2 to 6 were considered “fair,” and scores ≤ 1 was considered “poor” quality. Furthermore, the risk of bias scale ^[17] was applied to evaluate the included RCTs based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias.

Statistical analyses

Statistical analysis was performed using MetaProp, a package for meta-analysis of binomial data (R version 4.1.1) ^[18]. Heterogeneity among the studies was explored by calculation of I^2 statistics proposed by Higgins et al. ^[19,20] Random-effect analysis was performed when I^2 value was >50%; otherwise, a fixed-effect model was used to quantify the effect size. For each outcome, the individual effect size for each study and the

summarized effect size with 95% confidence intervals (CI) were calculated and represented as forest plots. The pooled effect size is given as the “point estimate” with lower and upper limits in the forest plot, and the values were rounded off and represented with 2 decimals. The study weighting was performed using the DerSimonian-Laird method ^[21]. Sensitivity analysis was conducted using the Egger method. Two-sided $P \leq 0.05$ was considered indicative of statistical significance.

Results

Study selection

The literature search resulted in the retrieval of 7,266 articles from different databases. After removing duplicates, a total of 5,770 articles underwent for screening. Furthermore, based on title and abstract screening, 49 eligible studies were included for final analysis (Figure 1).

Characteristics of included studies

Total of 48,918 patients were included across the eligible studies. The studies were stratified into 5 different groups based on etiologic agents of the CAP (bacteria, virus, fungi, other agents, and overall other). Among these, bacterial agents were reported in 44 studies and viral and fungal agents were reported in 33 and 21 studies, respectively. The total number of studies reported from overall other and other agents was 30 and 11, respectively. The PRISMA flow diagram illustrating the study selection process is presented in Figure 1. The baseline characteristics of the included studies are provided in Table S1.

Spectrum of various pathogens

Spectrum of bacterial agents causing CAP

Across the 49 studies included in the analysis, the pooled

prevalence of major causative agents responsible for CAP was classified into bacterial, fungal, viral, other, and overall other pathogens. Among bacterial etiologies, the most frequently identified etiologic agent in patients with CAP was *gram-negative bacilli*. The pooled proportion of patients with *gram-negative bacilli* was 51% of patients (95% CI, 11–90; $I^2=92\%$; $P<.01$; Table s2) from a cohort of 237 patients ^[22–24], including *K. pneumoniae* (7%; 95% CI, 5–10), *Haemophilus influenzae* (6%; 95% CI, 4–9), *Acinetobacter baumannii* (6%; 95% CI, 3–13), *Pseudomonas aeruginosa* (4%; 95% CI, 2–7), and *Escherichia coli* (2%; 95% CI, 1–4). *Gram-positive cocci* were another common etiologic agent of CAP, which were identified in a pooled proportion of 23% of patients (95% CI: 18.0–29.0; $I^2=0\%$; $P=0.48$; Table s2) from a cohort of 237 patients involving 3 studies ^[22–24]. Among gram-positive cocci, methicillin-resistant staphylococcus aureus (MRSA) and *S pneumoniae* were identified in a pooled proportions of 13% (95% CI: 0–99.0; $I^2=94\%$; $P<.01$) ^[24–26] and 9% (95% CI: 6–13; $I^2=98\%$; $P<.01$) (Table S1) ^[22,24,26–48].

Spectrum of fungal agents

A total of 21 studies were reviewed for the CAP episodes caused by different fungal agents. The pooled proportion of patients infected with *Candida albicans* (*C. albicans*) was 17% of patients (95% CI: 4.0–49.0; $I^2=54\%$; $P=0.11$; Table s2) from a cohort of 158 patients ^[22,28,49]. Fungal infection and *Aspergillus* had a pooled prevalence of 9% (95% CI: 4.0–19.0; $I^2=97\%$; $P<.01$) and 7% (95% CI: 0.0–70.0; $I^2=91\%$; $P<.01$) from a cohort of 10, 933 and 452 patients, respectively ^[22,23,28,29,42,50–56].

Spectrum of other pathogens

Among other pathogens, *Mycoplasma pneumoniae* (*M. pneumoniae*) demonstrated the highest pooled prevalence of 9% (95% CI: 5.0–17.0; $I^2=98\%$; $P<.01$) ^[22,22,26,27,29,32–40,42–44,47,56–59] followed by atypical pathogens at 4% (95% CI: 2.0–9.0; $I^2=86\%$; $P<.01$)

from a cohort of 16,268 and 2578 patients, respectively (Table S2).

Spectrum of Overall Other Pathogens

Among overall other pathogens, a pooled prevalence of 23% (95% CI: 11.0–42.0; $I^2=98\%$; $P<.01$) was demonstrated in a cohort of 3280 patients [28,31,39,41,44,45,48,52,55,60–63] (Table S2).

Spectrum of viral agents

A total of 33 studies were reviewed for the CAP episodes caused by different viral agents. The most commonly identified etiologic viral agent was *influenza* virus, which was detected in a pooled proportion of 18% of the patients (95% CI: 7.0–37.0; $I^2=99$; $P<.01$; Table S2) from a cohort of 10,658 patients involving 9 studies [24,26,29,32–34,47,58,44] followed by viral infection where the pooled proportion was 15% of the patients (95% CI: 8.0–25.0; $I^2=98$; $P<.01$) from a cohort of 18,431 patients involving 19 studies [28,30,32–34,41,44,50–57,62–65].

Comorbidities and clinical characteristics associated with various pathogens

Comorbidities and clinical characteristics associated with bacterial agents

Major comorbidities associated with patients with *H influenzae*-positive CAP were hypertension (26%; 95% CI: 16.0–40.0; $I^2=60\%$; $P=.08$) [22,48,65], chest pain (15%; 95% CI: 10.0–22.0; $I^2=83\%$; $P<.01$) [22,38,42,43,66] and COPD (13%; 95% CI: 7.0–22.0; $I^2=96\%$; $P<.01$) [22,36,39,41,42,65,43]. The associated common clinical signs and symptoms are also discussed in Table S3).

In the case of patients with “(*K pneumoniae*)” positive CAP, hypertension (40%; 95% CI: 27.0–55.0; $I^2=94\%$; $P<.01$) [22–24,28,30,44], cerebrovascular disease (15%; 95% CI: 8.0–24.0; $I^2=98\%$; $P<.01$) [24,30,32,36,42,45,44,66] and diabetes mellitus (15%; 95% CI: 10.0–22.0; $I^2=95\%$;

$P<.01$) [22–24,28,30,32,35,36,39,41,42,45,60,44,43,26] were observed as the major comorbidities. The most common clinical signs and symptoms are also discussed in Table S3.

In the case of patients with *S aureus*-positive CAP, hypertension (38%; 95% CI: 23.0–55.0; $I^2=98\%$; $P<.01$) [22–24,30,48,44], diabetes mellitus (15%; 95% CI: 10.0–22.0; $I^2=96\%$; $P<.01$) [22–24,30,35,36,39,41,42,48,60,44,43,26] and cerebrovascular disease (14%; 95% CI: 8.0–26.0; $I^2=98\%$; $P<.01$) [24,30,36,41,42,48,44] were observed as the major comorbidities. The most common clinical signs and symptoms are also discussed here in Table S3.

In the case of patients with *S pneumoniae*-positive CAP, hypertension (32%; 95% CI: 21.0–47.0; $I^2=98\%$; $P<.01$) [22,24,28,30,47,48,44], diabetes mellitus (15%; 95% CI: 10.0–21.0; $I^2=95\%$; $P<.01$) [22,24,28,30,32,35,36,39,41,42,45,47,48,44,43,26] and cerebrovascular disease (14%; 95% CI: 9.0–22.0; $I^2=98\%$; $P<.01$) [24,30,32,36,41,42,45,48,44] were observed as the major comorbidities (Table s3). The most common clinical signs and symptoms included are discussed here in Table S3.

In the case of patients with *Escherichia coli*-positive CAP, hypertension (38%; 95% CI: 18.0–63.0; $I^2=96\%$; $P<.01$) [22,23,30,44], diabetes mellitus (16%; 95% CI: 11.0–22.0; $I^2=95\%$; $P<.01$) [22,23,30,35,36,41,42,45,60,44,43,26] and chest pain (15%; 95% CI: 10.0–22.0; $I^2=83\%$; $P<.01$) [22,38,41,42,43] were observed as the major comorbidities. The most common clinical signs and symptoms included are discussed here in Table S3.

In the case of patients with *Pseudomonas*-positive CAP, hypertension (41%; 95% CI: 24.0–60.0; $I^2=95\%$; $P<.01$) [22–24,30,44], cerebrovascular disease (16%; 95% CI: 7.0–31.0; $I^2=98\%$; $P<.01$) [24,30,41,42,45,44] and diabetes mellitus (14%; 95% CI: 9.0–23.0; $I^2=96\%$; $P<.01$) [22–24,30,35,39,41,42,45,44,43,26]. were observed as the major comorbidities. The most common clinical signs and symptoms included are discussed here in Table S3.

Comorbidities and clinical symptoms associated with viral agents

The major comorbidities associated with patients with influenza A-positive CAP were diabetes mellitus (11%; 95% CI: 7.0–19.0; $I^2=92\%$; $P<.01$)^[35,42,60,61,64,67]. The most common clinical symptoms included are discussed in Table S3.

Comorbidities and clinical symptoms associated with other pathogens

The major comorbidities associated with patients with *M pneumoniae*-positive CAP were hypertension (37%; 95% CI: 14.0–69.0; $I^2=96\%$; $P<.01$)^[22,47,56,44,67], chest pain (12%; 95% CI: 8.0–18.0; $I^2=90\%$; $P<.01$)^[22,32,38,41,42,47,59,43,67] and diabetes mellitus (11%; 95% CI: 7.0–18.0; $I^2=94\%$; $P<.01$)^[22,32,35,36,39,41,42,47,56,59,44,43,26,67]. The most common clinical symptoms included are discussed in Table S3.

Overview of studies reporting etiology of CAP

Overview of studies reporting bacterial etiology of CAP

A total of 19 studies reported bacterial agents associated with CAP, with study populations ranging from 19 to 1420 patients. In a study with a larger cohort (n=253), 1 case of *Streptococcus pyogenes*, 2 cases of *Chryseobacterium indole* (n=488), 1 case of *Citrobacter* spp, *Flavobacterium* and *Klebsiella acidogens*, respectively, and 13 cases of another *Streptococcus* spp. A separate study with a larger cohort (n=1420) reported 2 cases of *Aspergillus* spp, 8 cases of *K acidogens*, and 23 cases of another *Streptococcus* spp. In another study with n=909, 40 and 78 cases of *Enterobacter aerogenes* and *Legionella* spp, respectively, were reported. Another study with a large cohort (n=593) reported 23 cases of other bacterial species (Table S4).

Overview of studies reporting fungal etiology of CAP

A total of 6 studies (n=593) reported fungal agents as-

sociated with CAP with only 1 case reported *Candida parapsilosis* from a study (n=52), whereas 24 cases reported *Candida spp* (n=72). Another investigation (n=19) reported only 2 cases of *Candida tropicalis*, whereas 11 cases reported non-*Pneumocystis jirovecii* from a different study (n=81). (Table S5).

Overview of Studies Reporting Viral Etiology of CAP

Overall, 7 studies (n=871) reported viral agents associated with CAP, with n=43 to n=321. Cytomegalovirus was reported in 2 studies, with 53 and 2 cases reported in a population size of n=288 and n=43, respectively. In addition, 72 cases of CAP reported no influenza virus (n=288). However, another study (n=124) reported 8 and 7 cases of CAP caused by H1N1 and H3N2 viruses, respectively. (Table S6).

Overview of studies reporting the etiology of CAP of other organisms

A total of 9 studies (n=2341) reported cases of CAP caused by different organisms. The highest number of cases reported was 142, followed by 112, 109, 83, and 76 cases. In addition to this, 30 cases were undetermined (Table S7).

Discussion

This systemic review demonstrated the etiologies of several pathogens in the adult population with CAP (> 18 years) from different Chinese provinces. Previous studies on adult patients with CAP in China reported that bacterial etiology was significantly higher than viral causes, with rates ranging from 30.3% to 53.1% compared with 10.6% to 19.0%^[35,68,69]. Several epidemiological studies on the adult population in China with CAP have reported *S pneumoniae* and *M. pneumoniae* as important causative pathogens^[39,70–72]. Furthermore, a prospective surveillance study conducted by Cao et al. (2010) reported *M. pneumoniae* as the most common pathogen responsible for causing CAP

among adult Chinese patients ^[71]. Moreover, Tao et al. (2012) conducted a prospective surveillance study on the etiology of CAP involving adult patients across 36 centers in 22 cities in China and identified *S pneumoniae*, *H influenzae*, and *K pneumoniae* as the three most common bacterial agents responsible for CAP in the Chinese adult population ^[39]. In consistent with the previous studies, the current study revealed that *gram-negative bacilli* were the predominant bacterial pathogens, followed by bacterial infection, *gram-positive cocci*, MRSA, *S pneumoniae*, and other bacterial infections among patients with CAP in China. In the present study, it was demonstrated that the pooled proportion of *S pneumoniae* among patients with CAP was reported at 9%, based on the results from multiple studies. In the present analysis MRSA demonstrated a pooled proportion of 13% however, the estimate showed a very wide CI (95% CI: 0–99%) with substantial heterogeneity ($I^2=94\%$; $P<.01$), due to the small number of included studies and low event rates, thereby indicating limited stability and interpretability. In contrast, *S pneumoniae* continues to be the classical and predominant cause of CAP.

In recent years, viral pathogens have been demonstrated to cause CAP in both children and adults. In a study, Zhou et al. (2019) conducted a national, prospective, multicenter study in China and reported that among immunocompetent patients with pneumonia, the most commonly found virus was *influenza virus* (28.4%), followed by *RSV* (3.6%), *HAdV* (3.3%), and *HCoV* (3.0%) ^[73]. In addition to that, a recent meta-analysis incorporating 31 observational studies excluding regional differences in study populations, reported *influenza A* and *B* as the most frequently identified viruses in patients with CAP, followed by *HRV*, *RSV*, and *HCoV* ^[74]. These findings are in line with the results of the present findings, where the most commonly identified etiologic viral agent was the *influenza virus* (18%), followed by other viral infections (15%).

In recent years, fungal pathogens have demonstrated an upsurge in etiologies of CAP in both children and adults, although they are less commonly reported pathogens as compared with bacteria and viruses ^[75]. Among the studies, *Candida* species, that is, *C. albicans* (8%), was identified as the most common fungal pathogen causing CAP in adult Chinese patients. In consistent with the previous studies, the present study also demonstrated *C. albicans* (17%) as the most common fungal pathogen causing CAP in the Chinese adult population. Several studies indicated the possibility of causing pneumonia by fungal pathogens in combination with bacterial pathogens ^[76,77]. Airway fungal colonization has been reported to compromise the host immune system, thereby allowing the development of bacterial pneumonia ^[76,78]. In addition, fungal pathogens such as *Candida* species have been implicated in CAP infections among patients with underlying conditions, including chronic aspiration and immunodeficiency disorders ^[79,80]. The diagnosis of *Candida* pneumonia should be made with considerable caution. In addition to this, confirmation also requires histopathological evidence from a lung biopsy, which will remain as the diagnostic gold standard. Apart from this, clinical symptoms, microbiological results, and radiographic reports should not be the only diagnostic parameters for a reliable diagnosis ^[80]. Similarly, *Aspergillus* species detected in respiratory specimens may also represent colonization rather than true CAP pathogens, and their clinical relevance should be interpreted with caution in the absence of supporting clinical and histopathological evidence.

Among other pathogens, *M pneumoniae* (9%) was identified as the most common agent causing CAP in Chinese adults, followed by atypical pathogens. Moreover, for a comprehensive understanding of the overall prevalence of CAP in the Chinese Mainland, we have also considered the studies that reported atypical pathogens (4%) as causative agents of CAP. This

might be a reason for the inclusion of *Candida* species, as it is the most common fungal pathogen among adults with CAP in this study.

Furthermore, the results of the current study revealed that the most common comorbidities associated, among patients with bacterial, viral, and other forms of CAP, were hypertension and diabetes mellitus. Similarly, a previous study by Mai et al. conducted a retrospective cohort study to investigate associations between comorbidities and in-hospital mortality caused by CAP. The results from this study reported that comorbid burden, such as congestive heart failure, renal disease, diabetes with complications, and dementia, was associated with an increased risk of in-hospital mortality^[81]. Therefore, these findings indicated the importance of clinical management of CAP patients with such comorbid conditions.

Despite the strengths, the present review also has certain limitations. First, comparing the etiologies of CAP across published studies is challenging because of the use of diverse laboratory tests to identify pathogens. In addition, diagnostic testing in many patients with CAP reveals >2 pathogens, including combinations of viral and bacterial pathogens, which complicate the determination of the clinical significance of any individual pathogen^[82,83]. Second, some studies reported the frequency of detected etiologic agents using different sample types without reporting potential overlaps between the results. In addition, certain studies reported the data based on the numbers of microbial isolates rather than the numbers of individual patients, inflating the prevalence of a specific etiologic agent. Third, this review is limited by significant heterogeneity among included studies, for which the possible reasons remain unknown. Furthermore, it is important to note that heterogeneity cannot be avoided in a meta-analysis, particularly in etiologic-based data. Previous studies demonstrating the etiology of CAP reported significant het-

erogeneity^[68,74]. This heterogeneity was largely due to clinical diversity across the included studies, which comprised immunocompetent and immunocompromised patients as well as those with comorbidities. In view of this clinical and methodological heterogeneity, formal subgroup analyses based on immune status or other clinical characteristics were not feasible. Therefore, subtyping or serotyping of identified pathogens was not performed or reviewed, which limits the level of detail regarding the specific causes of CAP among patients. Furthermore, for less frequently reported pathogens such as MRSA, small sample size resulted in low statistical power and wide CI, so the pooled estimates should be interpreted cautiously and may reflect potential detection and reporting bias rather than true epidemiological differences.

Conclusions

In China, bacterial infections were reported to be the primary cause of CAP the adult population, with *S pneumoniae* being among the most identified bacterial agents. Although viral and fungal pathogens also contributed significantly across a range of severities in patients with CAP. The findings of the present review will be helpful to estimate the disease burden associated with these pathogens among the adult population with CAP and may support the development of more effective and targeted therapeutic approaches.

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Author contribution

JX contributed to the literature search, study selection, data extraction, and assessment of study quality; interpreted the results, provided substantive suggestions for revision. YS contributed to the literature search, study selection, data extraction, and assessment of study quality; wrote the initial and final drafts of the manuscript. MG interpreted the results, provided substantive suggestions for revision. All authors reviewed the initial and final version of the manuscript, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Conflict of interest

Yongyu Su is an employee of MSD China. No other disclosures were reported.

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Clinical observations of integrated traditional Chinese medicine rehabilitation interventions after the treatment of severe organophosphorus pesticide poisoning

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Abstract

Background Acute organophosphorus pesticide poisoning (AOPP) is one of the most common critical conditions encountered in clinical practice, with an estimated annual incidence exceeding 3 million cases worldwide. Most cases of AOPP result from accidental ingestion or deliberate self-poisoning. Owing to its high toxicity, AOPP can lead to multi-organ dysfunction affecting the lungs, liver, and kidneys, and may be fatal in severe cases. Although conventional emergency treatments have markedly improved survival rates, many patients experience long-term complications such as neuromuscular deficits, respiratory dysfunction, and impaired ability to perform activities of daily living. Therefore, it is essential to develop effective post-acute rehabilitation strategies.

Objective To describe the clinical course and review the effectiveness of traditional Chinese medicine (TCM) rehabilitation strategies after severe AOPP.

Methods This paper presents the clinical course of a patient with severe AOPP who underwent comprehensive rehabilitation using TCM comprising acupuncture, electrotherapy, pulmonary and swallowing function training, and herbal adjuvant therapy.

Results Following the integration of TCM rehabilitation with conventional supportive care, the patient demonstrated substantial improvements in muscle strength, respiratory function, swallowing ability, and overall functional independence.

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Conclusion TCM-based comprehensive rehabilitation may serve as a valuable adjunct to standard care in patients recovering from AOPP. Early implementation of TCM-based rehabilitation may facilitate functional recovery and improve long-term outcomes. Further clinical studies are warranted to confirm the broader applicability of TCM-based rehabilitation.

Keywords: organophosphorus pesticide poisoning, integrated traditional Chinese medicine rehabilitation, acupuncture, dysphagia

Introduction

Acute organophosphorus pesticide poisoning (AOPP) is one of the leading causes of poisoning-related mortality worldwide, particularly in developing countries. According to epidemiological data, AOPP accounts for approximately 20%–50% of all poisoning cases, with a mortality rate ranging from 3%–40%^[1]. AOPP is mainly associated with accidental ingestion of pesticides, occupational exposure, and deliberate self-poisoning. After entering the body through the skin, gastrointestinal tract, or respiratory tract, organophosphorus compounds rapidly inhibit cholinesterase activity, resulting in dysfunction of the cholinergic system. This subsequently leads to a series of toxic manifestations, including muscarinic symptoms (such as salivation, wheezing, nausea, and vomiting), nicotinic symptoms (such as muscle fasciculations, convulsions, and respiratory distress), and central nervous system symptoms (such as anxiety, coma, and seizures)^[2]. In severe cases, AOPP may result in acute pulmonary edema, respiratory failure, cardiogenic shock, hepatic and renal dysfunction, and multiple organ failure, which may ultimately lead to death.

Although the acute mortality rate of AOPP has decreased with advances in modern emergency medical care, current treatment strategies mainly focus on life support and detoxification during the acute phase via gastric lavage, administration of cholinesterase reactivators,

atropine administration, hemoperfusion, and plasma exchange^[3]. These therapeutic approaches play a crucial role in saving lives. However, after successful rescue in the acute stage, a considerable proportion of patients experience long-term functional impairments. Some patients develop complications during the recovery period, such as acute respiratory distress syndrome, pulmonary injury, delayed neuropathy, and gastrointestinal dysfunction, which prevent them from returning to normal daily activities and markedly impair their quality of life^[4]. Particularly during the rehabilitation stage following emergency treatment, the effective evaluation and management of these sequelae present major challenges in clinical practice^[5]. At present, systematic and effective interventions for these long-term functional impairments remain limited and are often overlooked in clinical treatment, leading to delayed functional recovery and even loss of independence in performing activities of daily living^[6].

Traditional Chinese medicine (TCM) provides a theoretical framework for AOPP rehabilitation. In TCM theory, the severe neuromuscular deficits and delayed neuropathy caused by AOPP are primarily categorized as “Wei syndrome” (flaccidity syndrome) or “Bi syndrome” (impediment syndrome). By applying targeted treatments based on this syndrome differentiation, TCM has gradually opened a new avenue for patient recovery^[7]. TCM-based rehabilitation integrates

multiple therapeutic approaches, including acupuncture, electroacupuncture, tuina (therapeutic massage), herbal medicine, and functional training. These interventions can enhance the body's self-regulatory capacity, improve nervous system function, promote blood circulation, and alleviate muscle atrophy. Notably, TCM rehabilitation has demonstrated unique therapeutic advantages in the recovery of neurological disorders, respiratory diseases, and post-poisoning rehabilitation. In recent years, an increasing number of clinical studies have supported the beneficial role of TCM rehabilitation in functional recovery among patients with AOPP. In particular, acupuncture and electroacupuncture have been shown to effectively improve neuromuscular function, swallowing function, and respiratory function in affected patients^[8].

This study aimed to retrospectively review the comprehensive TCM rehabilitation performed in the successful management of a patient with severe AOPP, and to explore the potential mechanisms and clinical efficacy of TCM rehabilitation in improving the sequelae of AOPP. Through this case report, we seek to provide useful evidence for clinical practice and offer new insights and strategies for the rehabilitation management of patients with AOPP.

Materials and Methods

A 37-year-old woman ingested approximately 270 mL of dichlorvos at home on 10 September 2024. Shortly thereafter, she developed coma, was unresponsive to verbal stimuli, and presented with frothing at the mouth. No limb tremors or urinary and fecal incontinence were observed. She was immediately transferred to the emergency intensive care unit of our hospital. Upon admission, emergency treatments were promptly initiated, including gastric lavage, cathartic enema, endotracheal intubation with mechanical venti-

lation, gastric mucosal protection, detoxification therapy, plasma transfusion, and supportive treatments to maintain the acid-base balance, fluid and electrolyte balance, and nutritional support. Repeated hemoperfusion and plasma exchange were also performed. The patient experienced repeated failed attempts at weaning from mechanical ventilation and extubation. Therefore, a tracheostomy was performed on 1 October 2024. After clinical improvement, the patient was discharged on 15 October 2024 and transferred to a local hospital for continued treatment. However, on 16 October 2024, the patient suddenly developed dyspnea accompanied by cyanosis of the lips and tachycardia, and was again transferred to the emergency department of our hospital for treatment. After her condition stabilized, she was transferred to our department for further management. Before the poisoning event, the patient had no history of cardiovascular or cerebrovascular diseases, pulmonary diseases, renal diseases, or endocrine disorders. She denied any history of drug or food allergies and had no history of surgery or trauma.

Physical examination on admission revealed a body temperature of 36.7 °C, pulse rate of 121 beats/minute, respiratory rate of 23 breaths/minute, blood pressure of 112/91 mmHg, and oxygen saturation (SpO₂) of 93%. The borderline hypoxemia (SpO₂ 93%) on admission was considered multifactorial, primarily resulting from a pulmonary infection with copious sputum retention, and exacerbated by compromised airway clearance owing to AOPP-induced respiratory muscle weakness. The patient appeared lethargic and weak, with a pale complexion. She had intermittent coughing with the expectoration of large amounts of white viscous sputum and had no control of urination or defecation. A nasogastric tube and tracheostomy tube were in place. The patient was in a passive position. She could cooperate with the physical examination but was unable to speak. Assessments of orientation,

memory, judgment, comprehension, calculation ability, and cognitive function could not be completed owing to poor cooperation. The convergence reflex could not be assessed. The patient was unable to perform facial movements, including closing the eyes, frowning, wrinkling the forehead, puffing the cheeks, or whistling. She exhibited dysarthria and severe dysphagia (grade 5). Her muscle tone was slightly decreased. The muscle strength was grade 3 in the proximal and distal muscles of both upper limbs and grade 1 in the proximal and distal muscles of both lower limbs. Both superficial and deep sensations in the four limbs were reduced to varying degrees. The abdominal reflex was symmetrical. Tendon reflexes were present bilaterally, including the biceps reflex, triceps reflex, radial periosteal reflex, knee reflex, and Achilles tendon reflex. Coordination tests, including rapid alternating move-

ments of the upper limbs, the finger-to-nose test, and the heel-knee-shin test, could not be performed owing to poor cooperation. No pathological reflexes were elicited. The total Barthel Index score was 0, indicating complete dependence in performing activities of daily living. Electrocardiography showed sinus tachycardia with T-wave changes.

Western medical diagnoses comprised limb motor dysfunction, speech disorder, dysphagia, severe dependence in performing activities of daily living, tracheostomy placement, organophosphate-induced delayed neuropathy, moderate anemia, hypoproteinemia, severe malnutrition, and electrolyte metabolism disorder. The TCM diagnosis was pesticide poisoning resulting in deficiency of both Qi and Yin. On the day of admission, the patient received symptomatic and

Table 1. Laboratory examination findings.

Category	Test item	Result	Reference Range
Complete Blood Count	Red blood cell count ($\times 10^{12}/L$)	2.21	3.5–5.5
	Hematocrit (%)	22.9	36.0–50.0
	Hemoglobin (g/L)	66	110–160
Liver and Renal Function, Electrolytes	Alkaline phosphatase (U/L)	135	35–100
	Total protein (g/L)	50.8	60.0–85.0
	Albumin (g/L)	22.6	35.0–55.0
	Cholinesterase (U/L)	2516	3930–10800
	Glucose (mmol/L)	3.74	3.89–6.11
	Urea (mmol/L)	1.79	2.86–8.20
	Creatinine ($\mu\text{mol/L}$)	21	44–106
	Potassium (mmol/L)	3.24	3.50–5.30
	Sodium (mmol/L)	135	137–147
	Chloride (mmol/L)	93.8	99.0–110.0
	Calcium (mmol/L)	1.77	2.11–2.52
	C-reactive protein (mg/L)	32	0–8
	ESR (mm/h)	49.0	2.0–25.7
Cardiac Enzymes	Creatine kinase-MB (U/L)	28	0–24
Serum Myoglobin	Myoglobin (ng/mL)	141.86	0–80.00
Coagulation Tests	Prothrombin time (s)	12.7	10.0–14.0
	Activated partial thromboplastin time (s)	29.6	22.0–38.0
	Fibrinogen (g/L)	3.78	2.00–4.00
Urinalysis	Urinary leukocytes ($/\mu\text{L}$)	3+ (500/ μL)	(–)
	Urinary leukocytes (HPF)	3–6	0–3
	Occult blood ($/\mu\text{L}$)	2+ (80/ μL)	(–)



Figure 1. Chest CT scan showing bilateral scattered patchy opacities in the lungs, suggesting infection in the left lower lobe.

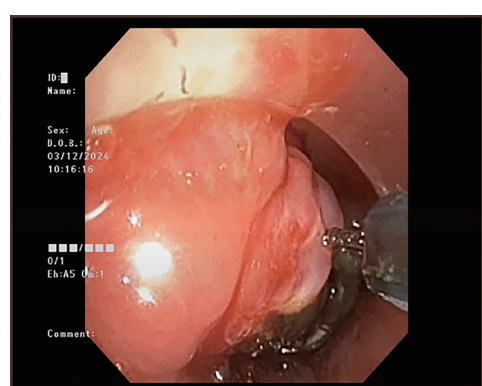


Figure 2. Fiberoptic bronchoscopy image showing granulation tissue hyperplasia at the upper edge of the tracheostomy tube.

supportive treatments, including citicoline for neurotrophic support, correction of electrolyte imbalances, albumin supplementation, nebulized acetylcysteine solution, oxygen therapy, sputum suction, tracheostomy care, and enteral nutritional support via nasogastric feeding.

Physical examination on 17 October 2024 revealed that the patient was conscious but appeared fatigued, with copious sputum that was difficult to expectorate. The limb motor dysfunction, speech disorder, and dysphagia persisted (Kubota water swallowing test: grade 5).

An individualized, multidimensional rehabilitation program was implemented. Scalp acupuncture was performed at Sishencong (EX-HN1) with a needle retention time of 30 minutes. Electroacupuncture was

applied to Ding Sanzhen, Quchi (LI11), and Zusanli (ST36) using a disperse-dense wave at a frequency of 2/100 Hz, with the intensity adjusted in accordance with the patient's tolerance for 30 minutes. For the dysphagia, microneedle acupuncture at Jinjin (EX-HN12) and Yuye (EX-HN13) was performed with the swift pricking technique to induce minor bleeding. Neuromuscular & functional training comprised comprehensive limb training including passive range-of-motion exercises (30 minutes/session) and progressive resistance training. Electric-assisted standing training was conducted for 20 minutes daily to improve orthostatic tolerance. Swallowing training consisted of ice stimulation to the posterior pharyngeal wall (3 sets/day), lingual resistance exercises, and the Mendelsohn maneuver. Pulmonary interventions focused on diaphragmatic breathing exercises and manual chest wall percussion for secretion clearance.

On 18 October 2024, the patient's hemoglobin concentration was <60 g/L and the hematocrit was 20.6%. A hematology consultation was requested, and 2 units of suspended red blood cells were transfused.

On 27 October 2024, the anemia had improved. Laboratory tests showed that the serum albumin concentration was 34.2 g/L and serum potassium concentration was 2.60 mmol/L. The patient had an intermittent cough with copious sputum and recurrent abdominal distension with marked bloating. Emergency whole-abdomen CT showed no abnormalities in the liver, spleen, bilateral kidneys, or bladder; however, there was a small amount of fluid in the rectouterine pouch, and infection in the left lower lung lobe. The abdominal distension was considered to be related to gastrointestinal injury caused by pesticide poisoning, resulting in decreased gastrointestinal function and poor absorption. To address the persistent abdominal distension, targeted TCM gastrointestinal interventions were

implemented on 27 October 2024. Approximately 500 g of crushed fennel seeds (*Foeniculum vulgare*) were stir-fried until they were fragrant and warm (approximately 40–50 °C), wrapped in a cotton bag, and applied to the umbilical region (Shenque, RN8) for 20 minutes twice daily. Abdominal massage comprising manual clockwise circular rubbing and kneading (Mo-fa and Rou-fa techniques) was performed for 15 minutes daily. The massage focused on the specific acupoints Zhongwan (RN12), bilateral Tianshu (ST25), and Qihai (RN6) to promote intestinal peristalsis.

Following 9 days of integrated treatment, the abdominal distension had substantially improved and normal defecation and flatus had resumed by 5 November 2024. The muscle strength of both upper limbs had substantially increased, with proximal and distal muscle strengths of grade 5 in both upper limbs and grade 1+ in both the proximal and distal muscles of the lower limbs. The superficial and deep sensations of the limbs remained reduced to varying degrees. Physical therapy for the upper limbs was suspended, and rehabilitation focused on the lower limbs, swallowing function training, and rectal control training.

On 11 November 2024, the patient still had dysphagia (Kubota water swallowing test: grade 4). The muscle bulk of the limbs was symmetrical, muscle tone was slightly decreased, and muscle strength was grade 5 in the proximal and distal muscles of both upper limbs, grade 1 in the proximal and distal muscles of the left lower limb, and grade 2 in the proximal and distal muscles of the right lower limb. The limb function and swallowing function had improved substantially, and symptomatic treatment was continued.

On 22 November 2024, an overflow of intermittent light-red blood from the tracheostomy site after sputum expectoration led to the suspicion of airway mucosal in-

jury. A respiratory medicine consultation was requested, and pulmonary angiography showed scattered patchy blurred opacities in both lungs, predominantly in the left lower lobe (Figure 1). There were no abnormalities in the major vessels, no pleural effusion bilaterally, and the pulmonary arteries appeared normal. Hemostatic treatment was initiated with hemocoagulase (1 ku daily) and tranexamic acid injection (0.5 g daily).

On 26 November 2024, the patient still had an intermittent cough with copious, thick sputum that was difficult to expectorate, and a small amount of light-red blood continued to overflow from the tracheostomy site. After multidisciplinary discussion, fiberoptic bronchoscopy was performed and revealed granulation tissue hyperplasia at the upper margin of the tracheostomy tube (Figure 2), resulting in approximately 50% luminal stenosis. Mild mucosal erosion with bleeding was observed in the lower trachea. Mucosal swelling was noted in bronchi at various levels in both lungs, and purulent secretions were observed in the left lower lung lobe. Sputum suction combined with bronchoalveolar lavage of the left lower lobe was performed, and anti-infective therapy with ceftazidime (2 g every 12 hours) was initiated.

On 2 December 2024, the sputum production decreased and became easier to expectorate and there was no longer any blood overflow from the trachea. Sputum culture showed *Pseudomonas aeruginosa* that was not multidrug-resistant. The dysphagia persisted but had improved (Kubota water swallowing test: grade 3). The muscle strength was grade 5 in the proximal and distal muscles of both upper limbs and grade 4 in the proximal and distal muscles of both lower limbs. The infection was effectively controlled, and muscle strength had improved. Physical therapy for the upper limbs was discontinued, while the remaining treatment regimen remained unchanged.

On 3 December 2024, the patient continued to produce a large amount of sputum. Hyperplastic granulation tissue remained at the upper margin of the tracheostomy tube, with approximately 50% luminal stenosis leading to poor sputum drainage and preventing decannulation, which resulted in dyspnea. The granulation tissue was successfully removed via electrocautery performed under general anesthesia with fiberoptic bronchoscopy. The airway mucosa showed mild hyperemia and edema. Nebulized dexamethasone (10 mg) was administered to reduce the mucosal edema. Physical therapy, swallowing rehabilitation training, and pharmacological treatment were continued.

On 9 December 2024, the patient showed marked dyspnea during intermittent tracheostomy tube occlusion trials, with the SpO₂ fluctuating between 92% and 98%. No obvious cough was observed, and a small amount of white viscous sputum was expectorated. Electroacupuncture and exercise training were discontinued, and treatment was mainly focused on pulmonary rehabilitation and swallowing therapy to facilitate the patient's adaptation to the occlusion of the tracheostomy tube.

On 11 December 2024, the patient developed a cough with copious sputum, expectorating yellow, thick sputum that was difficult to clear, and a small amount of blood at the tracheostomy site. This was considered to be related to airway mucosal injury or the recent removal of airway polyps. Ambroxol (15 mg every 12 hours) was injected to promote sputum expectoration, and tranexamic acid injection (0.5 g daily) was administered for hemostatic therapy. Pulmonary rehabilitation, swallowing training, and aerobic training were continued.

On 17 December 2024, the patient was producing less sputum that was easily expectorated. The SpO₂ was 97%. The muscle strength was grade 5 in the proximal

and distal muscles of both upper limbs and grade 5 in the proximal and distal muscles of both lower limbs. There was mild dysphagia (Kubota water swallowing test: grade 2). An otorhinolaryngology consultation was requested, and the tracheostomy tube was replaced with a metal tracheostomy tube. Physical therapy was discontinued, while nebulization therapy, expectorant treatment, intermittent tracheostomy tube occlusion, swallowing rehabilitation training, and speech training were continued.

On 23 December 2024, the SpO₂ was 98%. Sputum production was minimal and could be spontaneously expectorated. No blood overflow was observed from the tracheostomy site, and the patient reported no discomfort such as chest tightness or dyspnea. The patient was able to phonate. Removal of the tracheostomy tube did not result in dyspnea. The tracheostomy site healed well without redness, swelling, or exudation. The patient was able to walk independently, with normal swallowing and speech function, and was discharged from the hospital. At the 6-month follow-up after discharge, the pulmonary function had returned to normal, and the patient was able to perform routine physical activities.

Discussion

AOPP is a common and highly lethal form of poisoning characterized by sudden onset and rapid progression. Clinically, most cases of AOPP result from accidental ingestion or deliberate self-poisoning. The toxic compounds rapidly inhibit cholinesterase activity, inducing severe muscarinic, nicotinic, and central nervous system manifestations ^[3,4]. While advances in emergency medical treatments (*e. g.*, gastric lavage, antidotes, blood purification) have markedly decreased acute-phase mortality, a considerable proportion of survivors develop long-term complications such as delayed neuropathy, speech and swallowing disorders, and

profound motor dysfunction^[5,6]. It is essential to address these sequelae early and systematically to restore bodily functions and improve long-term quality of life.

In the present paper, we retrospectively analyzed the rescue and rehabilitation process of a patient with severe AOPP. After the acute toxic progression was effectively controlled by conventional Western medicine, the patient remained completely dependent (Barthel Index: 0) with deep coma, tracheostomy placement, and severe limb weakness. From the perspective of TCM, the severe neuromuscular deficits caused by AOPP are considered a systemic depletion of Qi and Yin induced by profound toxic heat. Furthermore, the prominent clinical manifestation-profound muscle weakness and motor dysfunction is categorized as Wei syndrome (flaccidity syndrome). According to the foundational TCM text Huangdi Neijing (Yellow Emperor's Inner Canon), the paramount guiding principle for treating this condition is "treating flaccidity by uniquely selecting the Yangming meridian"^[7]. The Yangming meridian is regarded as the "sea of water and grain" and the primary source of Qi and blood; when its flow is abundant, the muscles and tendons are properly nourished.

This classic TCM theory guided our highly targeted integrated TCM rehabilitation strategy. For motor dysfunction, the acupuncture protocol featured Yangming acupoints, such as Quchi (LI11) and Zusanli (ST36). Combined with electroacupuncture, this treatment forcefully stimulated Qi circulation in the meridians to nourish the malnourished muscles and promote neuromuscular junction recovery^[8]. To address the central nervous system impairment and prolonged coma status, scalp acupuncture at Sishencong (EX-HN1) was selected to regulate the Shen (spirit) and stimulate the Du meridian, thereby promoting neuroplasticity and cognitive awakening. For the severe dysphagia, we

performed microneedle quick-pricking at the sublingual points Jinjin (EX-HN12) and Yuye (EX-HN13). TCM theory suggests that this technique clears local heat, resolves blood stasis, and opens the sensory orifices. From an integrated medical perspective, this local pricking, combined with low-frequency electrical stimulation and ice stimulation therapy, provides direct physical excitation to the glossopharyngeal and hypoglossal nerves to restore swallowing reflexes^[9,10].

Closely tied to the recovery of the motor and bulbar functions was the improvement of the patient's respiratory status. Notably, the initial hypoxemia was not solely driven by the localized pulmonary infection, but was exacerbated by AOPP-induced respiratory muscle weakness. The subsequent integrated rehabilitation training specifically addressed this neuromuscular deficit. By progressively restoring overall and respiratory muscle strength, the interventions effectively enhanced the airway clearance and cough efficacy, ultimately resolving the underlying cause of the hypoxemia.

During the rehabilitation process, the patient also experienced marked gastrointestinal dysfunction presenting as severe abdominal distension. In TCM theory, this symptom is attributed to "Qi stagnation in the Middle Jiao" following toxic insult. To address this, we implemented fennel warm compresses on the umbilical region (Shenque, RN8) to warm the meridians and dispel cold, as the volatile oils in fennel effectively relieve intestinal vasospasm. This was synergistically combined with abdominal massage targeting the Ren and Yangming meridians (Zhongwan RN12, Tianshu ST25) to restore the descending function of the gastrointestinal tract^[11]. These targeted TCM external therapies rapidly alleviated the abdominal distension within days, accelerating the overall functional recovery and nutritional absorption.

This case suggests that for patients with AOPP, early

initiation of systematic TCM rehabilitation training after successful emergency treatment may substantially shorten the time required for functional recovery and reduce the disability rate ^[12]. TCM rehabilitation emphasizes a holistic perspective combined with precise syndrome differentiation. By leveraging classical theories (such as treating Wei syndrome via the Yangming meridian) and integrating them with modern physical rehabilitation techniques, TCM effectively addresses the limitations of conventional medicine in functional reconstruction ^[13,14]. However, this study represents a single-case experience. Prospective, multicenter studies with large sample sizes are required to verify these therapeutic mechanisms and provide robust evidence-based support for AOPP rehabilitation based on TCM.

Conclusion

Integrated TCM rehabilitation training plays a positive role in the functional recovery of patients after AOPP ^[14,15]. Systematic and individualized TCM rehabilitation interventions may achieve marked improvements in neurological, respiratory, swallowing, and motor functions, thereby enhancing the patient's ability to perform activities of daily living and promoting overall recovery ^[16]. TCM rehabilitation emphasizes syndrome differentiation and holistic regulation, which forms an effective complement to modern Western medical treatment strategies ^[17]. Particularly in the rehabilitation of functional impairments resulting from AOPP sequelae, TCM demonstrates favorable clinical outcomes and considerable potential for broader clinical application. Early implementation of TCM rehabilitation after successful emergency treatment may improve the long-term quality of life and reduce disability rates. Future multicenter studies with large sample sizes are needed to further validate the therapeutic efficacy and underlying mechanisms of TCM rehabilitation after AOPP.

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Author contributions

Hao Wu, Xueying Du, and Hao Su contributed to the investigation, data collection, analysis, and interpretation of the study. Li Wang participated in methodology

development, validation, and manuscript revision. Xiaobing Li conceived and designed the study, supervised the project, and critically revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest

All authors declare no conflicts of interest.

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Vaccinate Children on Time

Healthy Children, Fewer Worries

National Immunization Program — Childhood Immunization Schedule (2026 Edition)

Disease Prevented	Vaccine	Route	Dose	Abbreviation	Age at Vaccination														
					At Birth	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	8 mo	9 mo	18 mo	2 yr	3 yr	4 yr	6 yr	13 yr
Hepatitis B	Hepatitis B Vaccine	IM	10 or 20 µg	HepB	1	2					3								
Tuberculosis ¹	BCG Vaccine	ID	0.1 mL	BCG	1														
Poliomyelitis	Inactivated Polio Vaccine	IM	0.5 mL	IPV			1	2											
Poliomyelitis	Bivalent Oral Polio Vaccine	Oral	1 tablet or 2 drops	bOPV					3								4		
Diphtheria, Pertussis, Tetanus ²	DTaP Vaccine	IM	0.5 mL	DTaP			1		2		3			4				5	
Measles, Rubella, Mumps	MMR Vaccine	SC	0.5 mL	MMR							1		2						
Japanese Encephalitis B ³	Live Attenuated JE Vaccine	SC	0.5 mL	JE–L							1		2						
Japanese Encephalitis B ³	Inactivated JE Vaccine	IM	0.5 mL	JE–I							1,2			3				4	
Epidemic Cerebrospinal Meningitis	Group A Meningococcal Polysaccharide Vaccine	SC	0.5 mL	MPSV–A							1		2						
Epidemic Cerebrospinal Meningitis	Groups A & C Meningococcal Polysaccharide Vaccine	SC	0.5 mL	MPSV–AC												3		4	
Hepatitis A ⁴	Live Attenuated Hepatitis A Vaccine	SC	0.5 or 1.0 mL	HepA–L										1					
Hepatitis A ⁴	Inactivated Hepatitis A Vaccine	IM	0.5 mL	HepA–I										1	2				
Human Papillomavirus Infection ⁵	Bivalent HPV Vaccine	IM	0.5 mL	2vHPV															1,2

Notes:

1. Mainly prevents tuberculous meningitis and miliary tuberculosis.
2. The diphtheria-tetanus vaccine (DT) is for children aged 7–11 years.
3. For live attenuated JE vaccine, use a 2-dose schedule. For inactivated JE vaccine, use a 4-dose schedule; the interval between doses 1 and 2 is 7–10 days.
4. For live attenuated hepatitis A vaccine, use a 1-dose schedule. For inactivated hepatitis A vaccine, use a 2-dose schedule.
5. The bivalent HPV vaccine uses a 2-dose schedule, with a 6-month interval between doses 1 and 2.

Abbreviations: IM, intramuscular; ID, intradermal; SC, subcutaneous; HepB, hepatitis B vaccine; BCG, Bacillus Calmette–Guérin vaccine; IPV, inactivated poliovirus vaccine; bOPV, bivalent oral poliovirus vaccine; DTaP, diphtheria–tetanus–acellular pertussis vaccine; MMR, measles–mumps–rubella vaccine; JE-L, live attenuated Japanese encephalitis vaccine; JE-I, inactivated Japanese encephalitis vaccine; MPSV-A, group A meningococcal polysaccharide vaccine; MPSV-AC, groups A and C meningococcal polysaccharide vaccine; HepA-L, live attenuated hepatitis A vaccine; HepA-I, inactivated hepatitis A vaccine; 2vHPV, bivalent human papillomavirus vaccine.



