



Review Article



The “Weeping Liver” and Beyond: A Perspective on Lymphatic Failure in Liver Cirrhosis

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Abstract

Ascites is the most frequent complication of cirrhosis, signaling the transition from compensated to decompensated liver disease. While traditionally linked to portal hypertension, arterial vasodilation, and renal sodium retention, previous research has broadened our understanding of its pathophysiology. The hepatic and splanchnic lymphatic systems are increasingly recognized as potential contributors to decompensation in cirrhosis. The elevated sinusoidal pressure in cirrhosis markedly increases lymph production, which is initially compensated by expanded lymphatics and lymphangiogenesis. However, progressive cirrhosis impairs lymphatic function by inducing abnormal lymphangiogenesis, vessel dilation, and poor contractility, which collectively reduce drainage. When lymph overproduction exceeds the maximum drainage capacity of the lymphatic system, the fluid leaks through the subcapsular lymphatics, leading to leakage of protein-rich lymph through the liver surface into the peritoneal cavity—a phenomenon often referred to as a “weeping liver.” The osmotic gradient of this protein-rich fluid, combined with hydrostatic pressures and lymphatic failure, may draw additional fluid from the splanchnic circulation and contribute to ascites development and progression. Simultaneously, dysfunction of the gut-splanchnic lymphatic axis may promote intestinal edema, bacterial translocation, and systemic inflammation, thereby reinforcing portal hypertension and contributing to downstream manifestations such as intestinal lymphangiectasia and refractory ascites. Yet, despite its pathophysiological relevance, the contribution of lymphatic failure to the complications of cirrhosis remains widely underappreciated. Recognizing this critical axis may help identify novel therapeutic targets in patients with cirrhosis. This review provides a detailed overview of lymphatic failure as a contributor to altered fluid dynamics and secondary complications in cirrhosis, offering a contextual evaluation of its therapeutic implications.

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Introduction

Ascites is the most prevalent complication of cirrhosis.¹ Its onset signals the transition from compensated to decompensated disease, precipitating a steep decline in median survival.^{1,2} The development of ascites has traditionally been attributed to mechanisms such as portal hypertension (PHT), splanchnic vasodilation, neurohormonal activation, and renal sodium retention.^{3,4} While these factors remain fundamental, they do not comprehensively account for several clinical observations, including the delayed onset of ascites despite long-standing PHT. Emerging pathophysiological evidence suggests that lymphatic failure may be an important contributor to the development of cirrhotic ascites.^{5–7} The liver and gut lymphatic systems form a parallel, deeply integrated network that plays an active role in fluid regulation, immune surveillance, and inflammatory signaling. As cirrhosis disrupts hepatic architecture, dysfunction of these drainage pathways may contribute to fluid overload, impaired immune homeostasis, and systemic inflammation.^{6–9}

In cirrhosis, PHT markedly increases fluid filtration into the interstitial space. The lymphatic system serves as a critical compensatory mechanism by reabsorbing this excess interstitial fluid, a process that accelerates lymph flow and drives lymphangiogenesis.^{5,6} Eventually, advancing cirrhosis overwhelms these compensatory mechanisms. This breakdown, combined with lymphatic pump failure, appears to contribute to the development of ascites.^{5–7,10} The overall process is driven by a complex interplay between PHT, systemic inflammation, endothelial permeability, and immune dysregulation, culminating in the disruption of the liver-gut-lymphatic axis.^{5,7,8,11,12} The consequences of lymphatic failure in cirrhosis extend far beyond altered fluid hemodynamics, driving a spectrum of secondary complications that worsen patient outcomes.^{5–7} Targeting this axis may help inform therapies aimed at restoring fluid balance and mitigating downstream complications of cirrhosis. This review provides a comprehensive overview of lymphatic failure in patients with cirrhosis, highlighting its potential contribution to altered fluid dynamics and secondary complications. The unique contribution of this review is the integration of hepatic capsular lymph

Keywords: Ascites; Alcohol-associated liver disease; Intestinal lymphangiectasia; Lymphatics; Portal hypertension; Liver cirrhosis.

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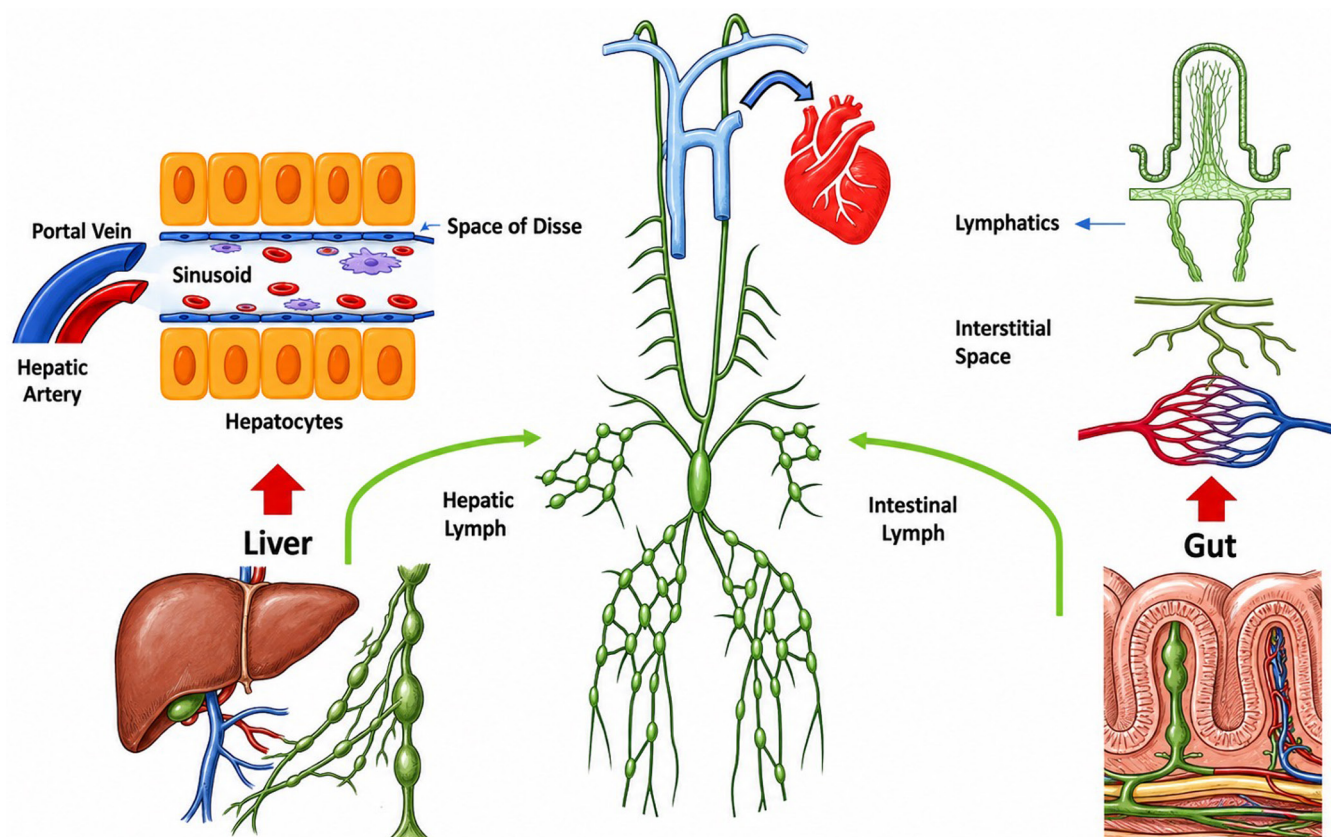


Fig. 1. The hepatic and intestinal lymphatic systems. A schematic diagram illustrates lymph flow from the liver and intestine to systemic circulation. In the liver, plasma filters through sinusoidal endothelial cells into the space of Disse to produce lymph. Lymphatic vessels from organs connect via nodes to trunks that drain into the subclavian vein through the cisterna chyli and thoracic duct. The gut's lymphatic system includes lacteals, vessels, and nodes, enabling lymph to reach the thoracic duct and enter systemic circulation, bypassing the liver.

leakage, gut-splanchnic lymphatic dysfunction, extrahepatic lymphatic outflow abnormalities, and mechanosensitive signaling into a unified model of cirrhotic decompensation, while exploring their therapeutic implications. While existing literature often uses "lymphatic dysfunction," "lymphatic failure," and "lymphatic insufficiency" interchangeably, we employ "lymphatic dysfunction" as an umbrella term, restricting "lymphatic failure" to advanced-stage functional impairment.

Hepatic and gut lymphatics: Contextual anatomy and physiology

The liver functions as the largest lymph-producing organ, responsible for 25%–50% of the lymph entering the thoracic duct (TD).¹³ Blood plasma passes through the highly permeable, fenestrated liver sinusoidal endothelial cells (LSECs) into the space of Disse, where hepatic lymph formation is initiated. Approximately 80% of the lymph originating from the space of Disse drains into lymphatic vessels located adjacent to the portal triads. Some lymph enters the interstitium near the central vein or beneath Glisson's capsule. Most lymphatic vessels eventually merge at the hepatic hilum, flow to nearby lymph nodes, and drain into the subclavian vein through the TD or right lymphatic duct.¹⁴

The gut lymphatic vascular system consists of intestinal lacteals, collecting lymphatic vessels, and lymph nodes, through which lymph flows and drains to the TD.¹⁵ The TD begins at the cisterna chyli, which collects lymph from lum-

bar and intestinal trunks. It transports about 75% of the body's lymph into the bloodstream through the left subclavian vein.^{10,15} The lymphatic circulation operates at low pressure without a central pump, relying mainly on intrinsic forces from the lymphatic vessels to move interstitial fluid. In addition to fluid homeostasis, lymphatics are involved in fat absorption and gut immunity.^{5–7,15} Both lymphatic capillaries and collecting vessels are lined with lymphatic endothelial cells (LECs). In capillaries, LECs have open, button-like junctions that create pores, allowing particulate matter and interstitial fluid to enter and form lymph. By contrast, collecting vessels have continuous, zipper-like tight junctions that prevent lymph leakage. Additionally, these vessels have a smooth muscle cell layer that enables intrinsic contraction, propelling lymph forward.¹⁶ Figure 1 presents a schematic diagram illustrating the anatomy and physiology of hepatic and intestinal lymphatic systems.

Overview of the genesis of ascites in cirrhosis

The development of ascites in cirrhosis is driven by a complex interplay of systemic hemodynamic changes, neurohormonal activation, and lymphatic failure (Fig. 2). In cirrhosis, architectural distortion of the hepatic parenchyma elevates sinusoidal hydrostatic pressure, promoting a marked increase in plasma filtration across hepatic and splanchnic capillary beds. Concurrently, PHT drives splanchnic vascular congestion and endothelial shear stress, facilitating intestinal

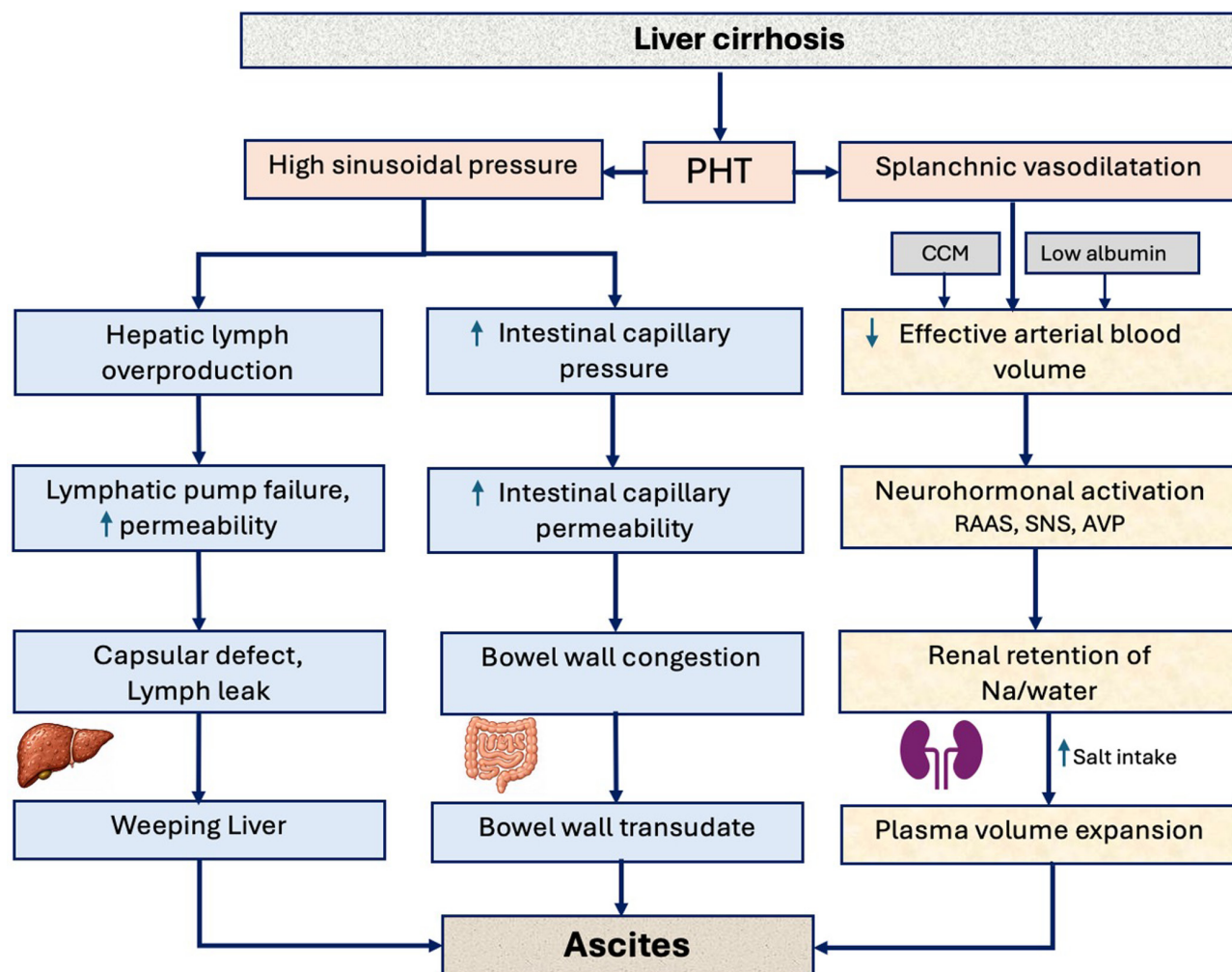


Fig. 2. An overview of the pathophysiology of ascites in patients with cirrhosis. In addition to neurohormonal activation and renal sodium retention, the failure of hepatic and intestinal lymphatic systems under conditions of increased lymph production results in fluid leakage from subcapsular hepatic lymphatics ("weeping liver") and gut or mesenteric lymphatics directly into the peritoneal cavity. These mechanisms substantially contribute to the development of ascites. AVP, arginine vasopressin; CCM, cirrhotic cardiomyopathy; PHT, portal hypertension; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system.

bacterial translocation. The resulting endotoxemia triggers systemic inflammation, in which proinflammatory cytokines promote nitric oxide (NO)-mediated arterial vasodilation.¹⁷ This induces effective arterial hypovolemia, which activates the renin-angiotensin-aldosterone system (RAAS) to promote persistent renal sodium and water retention, thereby expanding the intravascular volume.^{3,4} In a proportion of patients, this compromised axis is further aggravated by concurrent cirrhotic cardiomyopathy and excessive dietary sodium loading.^{18–20} While the regional lymphatic network initially undergoes compensatory remodeling to manage the fluid surge, lymphatic failure eventually ensues. Consequently, fluid transudation from the splanchnic vascular bed and the hepatic capsule overwhelms the system, culminating in clinical ascites as the drainage capacity of local peritoneal lymphatics is exhausted.^{5–7,17,21}

Lymphatic remodeling, compensation, and failure in cirrhosis

The lymphatic network in cirrhosis undergoes major struc-

tural and functional adaptations before eventually becoming dysfunctional and overwhelmed.^{5–10}

Overproduction of lymph and adaptive lymphatic expansion

Experimental studies have shown that hepatic lymph production can rise up to 30-fold in cirrhosis.^{22–25} A substantial increase in TD flow has been observed before the onset of clinically detectable ascites.²⁴ Witte *et al.* reported that the high-protein lymph from the TD in patients with cirrhosis originates predominantly from the liver.²⁵ Increased demand for fluid drainage triggers lymphatic expansion via enhanced lymphangiogenesis. This adaptive lymphatic expansion may delay the development of ascites despite significant PHT. Dumont and Mulholland first characterized hepatic lymphatic remodeling in cirrhosis, showing the TD dilation.²¹ Subsequent studies demonstrated lymphatic expansion through computed tomography and direct laparoscopic observation.^{26,27} Quantifying this structural evolution using immunohistochemical analysis, Yokomori *et al.* demonstrated that lymphatic vessel density increases linearly with hepatic ar-

chitectural changes, peaking at the most advanced stages of cirrhosis.²⁸ Recent studies by Arya *et al.* and Juneja *et al.* have demonstrated a significant expansion of duodenal lymphatic vessels in patients with decompensated cirrhosis.^{29,30}

Exhaustion of lymphatic drainage

Progressive cirrhosis eventually exhausts compensatory lymphatic mechanisms, which may signal a critical transition from compensated to decompensated disease.^{1,5} This functional collapse is driven by both structural and mechanical failure. At the microstructural level, advanced cirrhosis triggers disorganized lymphangiogenesis, producing tortuous, hyperpermeable, and ectatic vessels with defective intraluminal valves and disrupted endothelial junctions.^{5,6,31} Concurrently, the intrinsic pumping mechanism, driven by lymphatic smooth muscle contraction, is severely blunted. Ultimately, chronic PHT imposes a massive, unsustainable hydrostatic load that completely overwhelms lymphatic transport capacity.^{5,6,22,29,32} Recent evidence also indicates that the cisterna chyli and TD, which initially dilate in response to elevated portal pressure, progressively narrow as cirrhosis advances.³³ In patients with decompensated cirrhosis and a constricted cisterna chyli (<4 mm), lymphatic drainage into the systemic circulation becomes impaired.³⁴ Additionally, studies have reported a pressure gradient between the TD and left subclavian vein, with ascites resolution following TD stenting.³⁵ These findings highlight the additional complexity of lymphatic dysfunction in advanced cirrhosis.

"Weeping liver" and splanchnic transudation

When hepatic lymph production exceeds the drainage capacity of the expanded lymphatic system and is compounded by lymphatic pump dysfunction, protein-rich lymph seeps through Glisson's capsule into the peritoneal cavity as droplets. This phenomenon is known as the "weeping liver." This was first documented by Hyatt and colleagues in 1955 during an experimental study on PHT.³⁶ Dumont and Mulholland also observed that when the hepatic venous outflow is obstructed, the liver capsule becomes covered with continuous beads of transuding lymph fluid.²¹ During abdominal surgery or liver transplantation in patients with advanced cirrhosis, surgeons frequently observe that the surface of the cirrhotic liver releases clear, straw-colored fluid. Microscopic analysis of Glisson's capsule further supports the weeping-liver phenomenon.^{37–39} In cirrhosis, the capsule transforms from a thin, tightly sealed membrane into a thicker, more permeable mesh. This transformation results from matrix remodeling, characterized by dense collagen fiber accumulation and altered alignment, which makes the membrane softer and more stretchable.^{37,38} In addition, persistent hydrostatic pressure and excessive stretching of the capsule result in loss of mesothelial cells from the outermost layer of the liver capsule.³⁹ Overall, these changes appear to facilitate the escape of hepatic lymph through the overloaded lymphatics.

In parallel with hepatic changes, PHT elevates hydrostatic pressure throughout the splanchnic circulation. This elevation increases mesenteric capillary filtration, intestinal edema, and vascular permeability.⁴⁰ While mesenteric lymphatics initially compensate by increasing lymph flow, progressive PHT and chronic inflammation eventually induce lymphatic failure. Consequently, fluid may transudate directly across the mesenteric serosa into the peritoneal cavity, manifesting as ascites. It also appears that the protein-rich fluid leaking from the liver creates a transient osmotic gradient, causing transudation of fluid from the mesenteric circulation, which is already under high hydrostatic pressure.⁴¹ As the fluid from the mesenteric circulation is low in protein, mix-

ing and dilution may ultimately produce low-protein ascites typically observed in advanced cirrhosis.^{25,42} With advancing disease, ascitic fluid protein levels decline further, driven by progressive hepatic synthetic failure and impaired lymphatic transport.²⁹ Nevertheless, this mechanism remains largely hypothesis-generating, based on extrapolated data that require clinical validation. Moreover, the quantitative contribution of "weeping liver" and splanchnic transudation to ascites formation in humans remains incompletely defined.

Role of the peritoneum and its lymphatics

The peritoneum is a highly specialized, semipermeable membrane rather than a passive anatomical lining.⁴³ Under physiological conditions, it maintains a minimal volume of fluid to lubricate abdominal organs, but in cirrhosis the accumulation of ascites is determined by the balance between fluid formation and peritoneal clearance. The diaphragmatic parietal peritoneum and its submesothelial lymphatic network serve as the primary site for this clearance. Fluid exits the abdominal cavity via microscopic intercellular openings called lymphatic stomata to enter subdiaphragmatic lacunae, where respiratory motion acts as a mechanical pump to drive forward flow.^{44,45} To accommodate the massive fluid overload leaking from the liver and splanchnic vasculature in cirrhosis, these lymphatics undergo adaptive structural remodeling, resulting in significantly dilated lacunae and enlarged stomata.⁴⁶ Concurrently, chronic exposure to circulating pro-inflammatory cytokines triggers structural alterations within the peritoneum. These modifications, characterized by fibroblastic proliferation, reactive mesothelial hyperplasia, and heightened microvascular permeability, disrupt baseline membrane physiology.⁴⁷ In tandem with PHT and hypoalbuminemia, this altered state accelerates fluid transudation directly into the peritoneal cavity. As fluid accumulates and ascites becomes tense, the resulting elevation in intra-abdominal pressure paradoxically compresses the subdiaphragmatic lymphatics, obstructing the primary resorption pathways.⁴⁸

Secondary intestinal lymphangiectasia

An increased lymph load from PHT, coupled with systemic inflammation and lymphatic pump failure, exerts retrograde pressure on the intestinal lymphatic system to cause secondary intestinal lymphangiectasia.^{29,30} In a recent study, the proportion of patients with intestinal lymphangiectasia was significantly greater among those with decompensated cirrhosis than among those with compensated cirrhosis, and the density of intestinal lymphangiectasia on duodenal biopsy correlated with systemic inflammation.³⁰ Arya *et al.* reported intestinal lymphangiectasia in 27% of patients with cirrhosis and refractory ascites.²⁹ Once dilated intestinal lymphatics are excessively stretched, they may rupture into the gastrointestinal tract. Because intestinal lymph is rich in lymphocytes, proteins, and lipoproteins, its enteric loss induces lymphocytopenia, hypogammaglobulinemia, and hypoalbuminemia.^{5,29} The resulting depletion of serum albumin alters the oncotic gradient, further compounding systemic fluid overload.⁴⁹ Furthermore, intestinal lymphatic function may also be compromised by gut dysmotility and dysbiosis, both of which are frequently observed in advanced stages of cirrhosis.^{50,51}

Cellular and molecular drivers of lymphatic dysfunction

PHT and systemic inflammation serve as primary contributors to the pathophysiological changes observed in cirrhosis,

Table 1. Molecular and cellular drivers of lymphatic dysfunction

Mediator/cell type	Pathological effects on lymphatics	Molecular basis and signaling
PAMPs/DAMPs	Systemic inflammation; increased lymphatic permeability	LPS and cell-death signals bind to TLR4 and TLR9 on LECs and macrophages
Proinflammatory cytokines (TNF- α , IL-1 β , IL-6)	Lymph leakage; impaired intrinsic lymphatic pumping	NF- κ B signaling; downregulation of cadherin, claudin-5
Chemokines (CCL2, CX3CL1)	Aggravation of perilymphatic inflammation	Recruitment and activation of macrophages, with release of ROS and proteases
VEGF family (VEGF-C, VEGF-D)	Stimulation of pathological lymphangiogenesis	Binding to VEGF receptors on LECs; activation of PI3K/Akt and MAPK/ERK pathways
ROS	Endothelial cytotoxicity; disruption of lymphatic valve and vessel integrity	Overproduction via cellular NADPH oxidases; oxidative injury
Nitric oxide (NO)	Lymphatic vessel dilation and leakage; lymphatic pump failure	iNOS up-regulation via cytokines produces excessive NO; eNOS dysregulation impairs normal pulsatile NO release
TGF- β	Stiffens lymphatic vessel walls and deforms intraluminal valves, causing lymph backflow	Activates Smad2/3-dependent transcription and p38 MAPK signaling in perilymphatic fibroblasts
RAAS	Lymphatic fluid overload and lymphatic pump failure	Elevated angiotensin II increases aldosterone, promoting Na retention
Angiopoietins	Increased lymphatic permeability and impaired intrinsic lymphatic pumping	Disruption of LEC stability; high Ang-2 levels competitively inhibit Ang-1 binding to the Tie-2 receptor
Endothelin-1	Uncoordinated lymphatic spasms that impair rhythmic pumping	Binding to endothelin receptors on LSMCs, triggering calcium influx
Hepatic stellate cells	Intrahepatic fibrosis and upstream lymphatic load	Activation by TGF- β and PDGF; transformation into contractile myofibroblasts depositing type I/III collagen
LSECs	Structural breakdown, hyperproliferation, and increased permeability	Downregulation of VEGFR-3 signaling; loss of VE-cadherin; eNOS dysfunction
Peritoneal macrophages	Transdifferentiation into LECs and formation of abnormal lymphatic vessels; secretion of pro-lymphangiogenic factors and cytokines	Overproduction of VEGF-C and VEGF-D, Ang-2, TNF- α , IL-1 β , and IL-6; RAAS activation; macrophage recruitment
Kupffer cells	Hepatic stellate cell activation; sinusoidal hypertension; increased intrahepatic lymph production	Activation of TLR4 by LPS, upregulating TGF- β , TNF- α , and thromboxane A2

Akt, protein kinase B; Ang-1, angiopoietin-1; Ang-2, angiopoietin-2; CCL2, chemokine ligand 2; CX3CL1, C-X3-C motif chemokine ligand 1; DAMPs, damage-associated molecular patterns; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-regulated kinase; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LECs, lymphatic endothelial cells; LPS, lipopolysaccharide; LSECs, liver sinusoidal endothelial cells; LSMCs, lymphatic smooth muscle cells; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; Na, sodium; NF- κ B, nuclear factor kappa B; PAMPs, pathogen-associated molecular patterns; PDGF, platelet-derived growth factor; PI3K, phosphoinositide 3-kinase; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; TGF- β , transforming growth factor-beta; Tie-2, tyrosine kinase with immunoglobulin-like and EGF-like domains 2; TLR4, Toll-like receptor 4; TLR9, Toll-like receptor 9; TNF- α , tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

including lymphatic failure. These mechanisms are not mutually exclusive but typically coexist in the majority of patients with cirrhosis. Various cellular and molecular factors initiate and exacerbate PHT and systemic inflammation during cirrhosis (Table 1).

Onset of PHT

The pathological crosstalk between LSECs and hepatic stellate cells (HSCs) is the primary driver of increased intrahepatic vascular resistance in cirrhosis. In a healthy liver, LSECs maintain HSC quiescence primarily through the continuous release of NO.⁵² However, chronic liver injury triggers LSECs to undergo capillarization, a process characterized by the loss of endothelial fenestrae and the development of an organized basement membrane.⁵³ Furthermore, dysfunctional LSECs underproduce NO, a key vasodilator, while

overproducing endothelin-1 (ET-1), a potent vasoconstrictor. Deprived of LSEC-derived NO, HSCs transform into myofibroblasts, depositing excessive extracellular matrix into the space of Disse. This dense matrix physically constricts sinusoids, forming a structural barrier to blood flow. Concurrently, the NO deficit and ET-1 overabundance induce localized vascular spasms and continuous HSC contraction, driving dynamic intrahepatic resistance.^{54,55}

Liver-gut-lymphatic axis

Chronic PHT structurally disrupts the intestinal mucosal barrier, facilitating the pathological translocation of gut-derived pathogen-associated molecular patterns, including lipopolysaccharide (LPS), and damage-associated molecular patterns into the portal circulation.^{7,56,57} Mechanistically, translocated LPS binds to Toll-like receptor 4 (TLR4) on hepatic

and mesenteric immune cells. This binding recruits the adaptor protein MyD88, initiating a phosphorylation cascade that activates the I κ B kinase complex. Once active, this complex degrades the inhibitory protein I κ B α , liberating the transcription factor nuclear factor kappa B (NF- κ B) for direct nuclear translocation. Inside the nucleus, NF- κ B orchestrates the up-regulation of proinflammatory cytokines, most notably tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , and IL-6.^{56,58,59}

These inflammatory signals upregulate endothelial NO synthase (eNOS) and induce inducible NO synthase (iNOS) within the splanchnic bed, leading to splanchnic arterial vasodilation.^{60,61} In parallel, mesenteric arterial vasoconstriction is impaired via angiotensin II receptor desensitization and angiotensin-converting enzyme 2-MAS receptor axis activation.^{62,63} The resulting splanchnic arterial vasodilation triggers a state of "effective" arterial hypovolemia, which activates the RAAS, the sympathetic nervous system, and antidiuretic hormone to promote renal sodium and water retention.⁶⁴ Excessive NO also suppresses cardiac contraction.⁶⁵ Combined with sympathetic overstimulation, splanchnic vasodilation, and endotoxemia, these factors may contribute to cirrhotic cardiomyopathy, which subsequently effective arterial hypovolemia, compounding RAAS activation in patients with cirrhosis.^{20,65}

Proinflammatory signaling and lymphangiogenesis

Inflammation triggers macrophages to secrete prolymphangiogenic morphogens, specifically vascular endothelial growth factor (VEGF)-C and VEGF-D.^{66,67} These macrophage-derived VEGFs bind directly to VEGF receptor-3 (VEGFR-3) expressed on the surface of local LECs, driving proliferation, migration, sprouting, and vessel-tube formation. Moreover, inflammatory signaling may promote transdifferentiation of CD11b+ myeloid macrophages into lymphatic progenitor cells, accelerating structural lymphatic remodeling.^{68,69} Concurrently, circulating cytokines and reactive oxygen species (ROS) phosphorylate and disassemble tight and adherens junctions (e.g., VE-cadherin).^{70,71} This junctional disruption can significantly compromise microvascular integrity across hepatic, splanchnic, and peritoneal beds, leading to accelerated capillary filtration and elevated interstitial lymph production. Recent evidence indicates that sympathetic nerves within the portal tract also contribute to lymphangiogenesis by inducing VEGF-C production in Schwann cells.⁷²⁻⁷⁴ Interestingly, halting this lymphangiogenic process via sympathetic denervation or a VEGF-C-neutralizing antibody worsened portal tract fibrosis in rat models.⁷³ Moreover, studies have found increased sympathetic nerve density in cirrhotic liver tissue.⁷⁴ Given the bidirectional crosstalk between proinflammatory signaling and the sympathetic nervous system, the intricate neurolymphatic axis may provide avenues for therapeutic research in hepatology.⁷⁴

Lymphatic pump failure and leakage

The mechanisms driving lymphatic pump failure in cirrhosis remain unclear. Experimental evidence suggests a complex role of various mediators and signaling molecules. During chronic inflammation, the overproduction of NO derived from iNOS can suppress the spontaneous, rhythmic contractions of the lymphatic pump by impairing smooth muscle cell function.^{75,76} This mechanical failure is compounded by structural instability. Driven by elevated portal shear stress and local TNF- α expression, endothelial cells upregulate Angiopoietin-2 (Ang-2). High levels of Ang-2 competitively displace Angiopoietin-1 from the Tie-2 receptor on LECs.⁷⁷ This molecular switch destabilizes the endothelium, compro-

mises pericyte coverage, and elevates vascular permeability. Ultimately, these combined signals disrupt normal structural maturation, shifting the system away from organized, contractile drainage pathways and toward disorganized, pathological lymphangiogenesis.^{5,6,77-79} This structural vulnerability is compounded by ongoing inflammation, oxidative stress, and persistent PHT, all of which halt the proper maturation and stabilization of newly formed lymphatics. The resulting vessels are malformed, pathologically dilated, leaky, and have diminished drainage capacity.^{78,79} With no viable drainage pathway, the excess interstitial fluid physically weeps through the liver surface and the mesenteric serosa, accumulating directly within the peritoneal cavity as ascites. Moreover, evidence suggests that under the influence of chronic mechanical stretch from interstitial fluid overload, mesothelial cells on the liver surface undergo epithelial-to-mesenchymal transition.^{39,80} This phenotypic shift causes a downregulation of cell-adhesion molecules, loosening the outermost cell layer of the liver. This, along with extracellular matrix remodeling, may enhance the permeability of Glisson's capsule. This increase in permeability could facilitate the transcapsular leakage of hepatic lymph into the peritoneal cavity.^{37,39} Recent research suggests that activation of Piezo1, a mechanosensitive ion channel highly expressed on LSECs and peritoneal endothelial cells, contributes to portal hypertensive ascites via the NF- κ B-aquaporin 1 pathway.^{81,82} In cirrhotic mice, structural studies show that animals with ascites have reduced lymphatic smooth muscle cell coverage compared with those without ascites.⁸² Strikingly, endothelial deletion of Piezo1 restores and even increases this smooth muscle cell coverage in cirrhotic murine models, suggesting that Piezo1 signaling may contribute to lymphatic failure with subsequent ascites formation.⁸² The profibrotic cytokine transforming growth factor-beta (TGF- β), which is chronically elevated in patients with cirrhosis, may serve as an important driver of lymphatic failure. TGF- β 1 is a potent inhibitor of LEC proliferation and migration.⁸³ Concurrently, TGF- β -mediated extracellular matrix deposition around the lymphatic vessels compromises their mechanical pumping capacity.⁸⁴

Thus, the interplay between persistent PHT and systemic inflammation appears to drive maladaptive lymphatic remodeling in cirrhosis. Sustained activation of NO, VEGF, Ang-2, TGF- β , Piezo1, and oxidative stress pathways may underlie the development of a dysfunctional lymphatic phenotype characterized by hyperpermeability and impaired pumping. The contrasting effects of NO inside the liver versus the mesenteric circulation reflect a compartment-specific action. On the one hand, excessive NO production within the splanchnic circulation drives systemic vasodilation and impairs lymphatic pumping.^{60,61,75,76} On the other hand, deficient NO signaling within the hepatic microcirculation elevates intrahepatic vascular resistance and accelerates lymph production.^{54,55}

Factors affecting lymphatic function

In addition to gut dysbiosis, bacterial translocation, and systemic inflammation, several endogenous and exogenous factors are known to influence lymphatic function and may be relevant to patients with cirrhosis (Table 2).

Demographic factors

Advanced age, obesity, and diabetes are known to negatively influence lymphatic function. The aging process results in structural modifications of lymphatic vessels, including extracellular matrix degradation, diminished expression of contractile proteins, and alterations in eNOS expression, all of

Table 2. Factors that may affect lymphatic function in patients with cirrhosis

Factor	Pathophysiological mechanism
Advanced age	Extracellular matrix degradation; reduced contractile proteins and eNOS expression
Obesity	Junctional protein degradation; induction of perilymphatic adipose inflammation and fibrosis
Diabetes mellitus	LEC nitric oxide overproduction; vessel dilation and valvular failure
Etiology of cirrhosis	Etiology-specific variations in metabolic inflammation, gut-barrier dysfunction, and immune trafficking
Excess dietary salt	Saturates non-osmotic GAG storage; promotes macrophage VEGF-C production
Systemic inflammation	Driven by bacterial translocation; upregulates TNF- α , IL-6, and TGF- β
Vasoactive substances (noradrenaline, histamine, substance P, and prostaglandins)	Alter endothelial junctions and lymphatic smooth muscle-cell contraction
Multikinase inhibitors (sorafenib, lenvatinib)	VEGFR-3 blockade; inhibition of endothelial cell signaling and sprouting pathways
Calcium channel blockers	L-type calcium-channel blockade; suppression of rhythmic smooth muscle contractions
mTOR inhibitors (e.g., sirolimus, everolimus)	Anti-lymphangiogenic effects; downregulation of VEGF-C-mediated sprouting
NSAIDs	Reduces vasodilatory PGE2 and PGI2 synthesis; induces renal vasoconstriction
Nonselective beta-blockers	Blunting of sympathetic input; decreased beta-adrenergic drive required for pumping
Thiazolidinediones	Increased renal sodium and water reabsorption, causing plasma volume expansion
Corticosteroids	Downregulation of tissue VEGF-C; inhibition of endothelial proliferation and survival

eNOS, endothelial nitric oxide synthase; GAG, glycosaminoglycan; IL-6, interleukin-6; LEC, lymphatic endothelial cell; mTOR, mechanistic target of rapamycin; NSAIDs, non-steroidal anti-inflammatory drugs; PGE2, prostaglandin E2; PGI2, prostaglandin I2 (prostacyclin); TGF- β , transforming growth factor-beta; TNF- α , tumor necrosis factor-alpha; VEGF-C, vascular endothelial growth factor C; VEGFR-3, vascular endothelial growth factor receptor 3

which contribute to reduced lymphatic drainage.^{85,86} Obesity induces structural degradation of junctional proteins within collecting lymphatics, significantly increasing vessel permeability. Additionally, excessive adipose accumulation surrounding lymphatic structures damages lymphatic smooth muscle cells, which impairs their spontaneous contraction and pumping efficiency. Furthermore, obese adipose tissue recruits inflammatory cells that aggregate along lymphatic pathways, triggering localized fibrosis that physically hinders fluid drainage.^{87,88} Hyperglycemia in diabetes alters cellular gradients, triggering the overproduction of NO by LECs. This excess induces pathological dilation, fluid stagnation, and mechanical dysfunction within lymph vessels. Concurrently, elevated blood glucose degrades the extracellular matrix supporting lymphatic walls, accelerating structural stiffening and valvular failure.^{89–91} The underlying etiology of cirrhosis may also influence lymphatic function; however, direct comparative studies on this remain scarce. The metabolic inflammation in metabolic dysfunction-associated steatohepatitis (MASH)-related cirrhosis, prominent gut barrier dysfunction and endotoxemia in alcohol-associated cirrhosis, and localized patterns of portal inflammation and fibrosis in primary biliary cholangitis (PBC) or primary sclerosing cholangitis (PSC) may all differentially impact lymphatic remodeling. Tamburini *et al.* demonstrated significant differences in the LEC transcriptional profiles and signaling pathways between MASH- and hepatitis C virus-associated liver diseases.⁹² Specifically, IL-13, a potent profibrogenic factor, was uniquely upregulated in LECs from patients with end-stage MASH. This up-regulation of IL-13, in tandem with oxidized low-density lipoprotein, reduces the transcription of prolymphangiogenic factor PROX1, thereby compromising lymphatic stability.⁹² Etiology-specific variation in immune trafficking

through lymphatics may also occur. Grant *et al.* found that hepatic expression of the lymphoid chemokine CCL21 was significantly higher in PBC and PSC than in alcohol-associated liver disease.⁹³

Dietary salt intake

Salt consumption increases ascites in cirrhosis because of excess sodium and water retention. Growing evidence shows that the link between salt intake and ascites in cirrhosis is not linear, but depends on individual salt sensitivity, counter-regulatory mechanisms, and non-osmotic sodium storage managed by immune cells and the lymphatic system.¹⁹ When humans consume excess dietary salt, a significant portion of this surplus sodium is shunted into a non-osmotic reservoir located primarily in the skin, skeletal muscle, and cartilage. Within the interstitium of these tissues, sodium binds to negatively charged glycosaminoglycans (GAGs), which renders it osmotically inactive.⁹⁴ This allows interstitial sodium concentrations to attain hypertonic levels without drawing in water. However, the hypertonic sodium environment recruits macrophages into the subcutaneous and interstitial tissues.⁹⁵ The osmotic stress activates osmosensitive transcription factors in these macrophages, promoting VEGF-C synthesis and secretion.⁹⁶ In turn, VEGF-C induces lymphatic expansion, facilitating the return of excess sodium to the systemic circulation for regulated renal excretion. When lymphatic function fails, the non-osmotic GAG storage capacity becomes fully saturated, and extra sodium becomes osmotically active. Furthermore, in advanced cirrhosis, marked RAAS activation and alteration of GAGs due to chronic inflammation and protein malnutrition might overwhelm the interstitial buffer, causing excess sodium to remain osmotically active and contribute to systemic fluid overload.

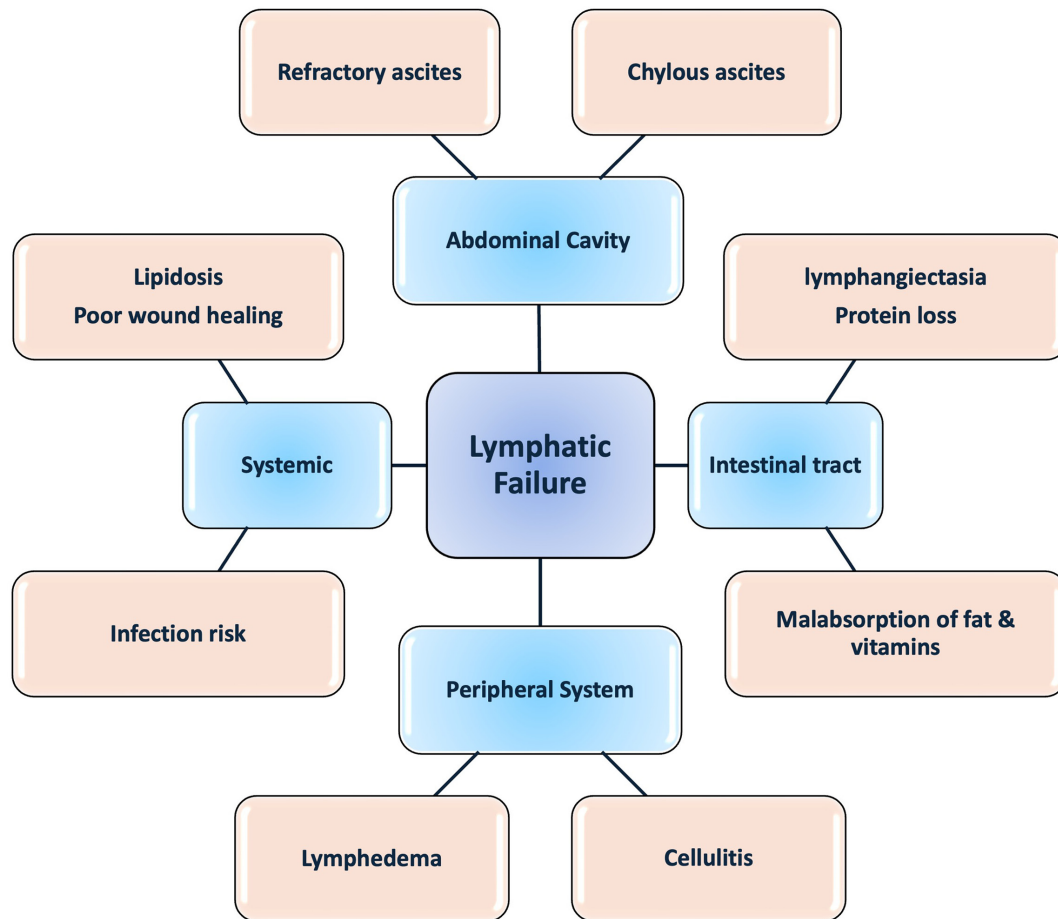


Fig. 3. Clinical consequences and manifestations of lymphatic dysfunction in cirrhosis.

Medications

Several drug classes may impair lymphatic function in cirrhosis, but the current evidence is largely extrapolated from experimental studies and non-cirrhotic subjects. Multikinase inhibitors such as sorafenib and lenvatinib are potent inhibitors of VEGFR-3. While clinically indicated to target tumor angiogenesis in hepatocellular carcinoma, their systemic activity may impair compensatory lymphangiogenesis and could contribute to peripheral edema and ascites.⁹⁷ Similarly, calcium channel blockers may impair lymphatic function by blocking L-type calcium channels, thereby suppressing the rhythmic smooth muscle contractions of peripheral and mesenteric lymphatic vessels.⁹⁸ Furthermore, mTOR inhibitors (e.g., sirolimus, everolimus), used in oncology and post-transplant immunosuppression, exert robust anti-lymphangiogenic effects by downregulating VEGF-C-mediated endothelial sprouting. Consequently, their administration may contribute to edema or lymphatic complications in patients with advanced cirrhosis.⁹⁹ By reducing the synthesis of prostaglandin E2 and I2, and also by causing renal vasoconstriction, non-steroidal anti-inflammatory drugs can worsen systemic fluid overload in patients with cirrhosis. As sympathetic nervous system activation is required to maintain lymphatic pumping frequencies, nonselective beta-blockers (NSBBs) may alter lymphatic contractility and fluid handling.¹⁰⁰ Thiazolidinediones (e.g., pioglitazone), by increasing sodium and water reabsorption in the renal collecting ducts, can cause

plasma volume expansion, further increasing the burden on lymphatic drainage capacity.¹⁰¹ Corticosteroids have been shown to suppress corneal lymphangiogenesis by inhibiting LEC proliferation,¹⁰² suggesting a mechanism by which they could theoretically worsen fluid balance in cirrhotic patients. However, despite strong mechanistic plausibility, the exact frequency and clinical extent of drug-induced lymphatic dysfunction in cirrhotic patients remain speculative, as there are no clinical studies specifically evaluating these mechanisms in this population.

Clinical implications of lymphatic failure

Lymphatic adaptation during the early stages of cirrhosis may represent a protective mechanism with several physiological benefits. Improved lymphatic drainage mitigates fluid accumulation, attenuates hepatic inflammation and fibrosis, and facilitates tissue repair.^{66,103} However, as cirrhosis progresses and lymphatic failure develops, a range of clinical manifestations may occur, including refractory ascites, depletion of intestinal lymph and nutrients, persistent edema, lymphedema, and an increased susceptibility to infection (Fig. 3). Nevertheless, the role of lymphatics in these complications remains under-recognized and insufficiently investigated in patients with cirrhosis.^{5,29,104}

Impaired lymphatic drainage, combined with increased renal retention of sodium and water, may increase the risk of refractory ascites in cirrhosis.⁵ Lymphatic failure may further

worsen hypoalbuminemia by hindering albumin recirculation and causing protein loss through ruptured intestinal lymphangiectasia. This, in turn, alters transcapillary oncotic pressure, aggravates fluid imbalance, and promotes refractory ascites and edema.⁴⁹ Impaired lymphatic drainage, together with lymph leakage resulting from elevated backpressure and compromised structural integrity, may lead to the accumulation of protein- and lipid-rich lymphatic fluid within tissues, ultimately causing lymphedema. This condition is frequently under-recognized in patients with cirrhosis, but may be identified by a *peau d'orange* appearance and a positive Stemmer sign.^{5,29} In an observational study involving patients with cirrhosis and refractory ascites, nearly one-third demonstrated peripheral edema indicative of lymphedema.²⁹ Lymphedema increases the risk of skin infections such as cellulitis due to thickened skin, deep cracks, stagnant lymph fluid, and weakened immunity. One study found that 13% of patients with lymphedema experienced lower limb cellulitis, while none of those without lymphedema did.²⁹ Indeed, lymphedema is regarded as a major risk factor for cellulitis.

Rupture of intestinal lymphangiectasia leads to a clinical state known as protein-losing enteropathy. Furthermore, interference with lymphatic flow can disrupt the absorption of fats and fat-soluble vitamins, which may lead to steatorrhea, vision difficulties, muscle weakness, osteopenia, and coagulopathy in patients with cirrhosis.⁵ Chylous ascites is an uncommon complication that occurs when subserosal lymphatic vessels rupture due to persistently high portal pressure.^{5,29,105} Although chylous ascites is uncommon, cirrhosis is believed to be its most common atraumatic cause.¹⁰⁵ Since the intestinal lymph contains chylomicrons, which are rich in triglycerides, chylous ascites appears milky in color. Importantly, ruptures of hepatic lymphatic vessels do not lead to chylous ascites because these vessels lack chylomicrons. Data regarding the independent prognostic implications of lymphatic failure in cirrhosis remain sparse. In a prospective cohort study, Juneja *et al.* showed that dilated duodenal lymphatic vessels in cirrhosis were independently associated with three-month mortality.³⁰ While direct prognostic studies are sparse, the poor outcomes associated with complications of cirrhosis involving lymphatic failure, such as refractory or chylous ascites, are well documented.^{106,107}

Finally, lymphatic dysfunction in cirrhosis may be considered in the context of the emerging clinical concept of recompensation. Baveno VII defines recompensation of cirrhosis as a clinical state in which a patient with previously decompensated disease returns to a stable compensated phase after the primary cause of liver injury is removed or controlled.¹⁰⁸ For a patient to achieve recompensation, ascites must resolve without diuretics; adequate fluid handling, potentially including recovery of lymphatic drainage capacity, may therefore be relevant.

Biomarkers and diagnostic approach

Although formal guidelines for evaluating lymphatic failure in cirrhosis do not yet exist, several clinical and laboratory markers, endoscopic findings, and imaging modalities can signal its presence. Clinically, lymphatic failure is suspected in patients with cirrhosis who present with a characteristic *“peau d'orange”* appearance of peripheral edema, intestinal lymphangiectasia on endoscopy, or elevated triglyceride levels in the ascitic fluid.^{5,29} On laboratory evaluation, disproportionate hypoproteinemia, combined with lymphocytopenia (<15% of total leukocyte count), may suggest lymphatic dysfunction associated with lymph leakage.^{5,29} Several molecules serve as biomarkers of lymphatic struc-

ture and function.¹⁰⁹ Key circulatory markers include VEGF-C, VEGF-D, soluble VEGFR-3, Ang-2, and platelet factor 4 (PF4). While elevated levels of VEGF-C, VEGF-D, VEGFR-3, and Ang-2 are commonly noted during lymphatic dysfunction, they are not specific to lymphatic failure. They can be significantly elevated in a wide range of nonlymphatic conditions, including solid tumors, cardiovascular diseases, sepsis, and chronic inflammatory disorders.¹¹⁰ Conversely, PF4 is a promising biomarker for broader lymphatic disorders but remains unevaluated in cirrhosis.¹¹¹ Essential histopathological markers include lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1), PROX-1, and podoplanin (D2-40).^{29,76,112} While LYVE-1, podoplanin, PROX-1, and VEGFR-3 serve as valuable histopathological biomarkers, they lack absolute specificity for lymphatic cells. For instance, LYVE-1 is also expressed on hepatic Kupffer cells.¹¹³ Consequently, a panel combining multiple lymphatic markers is necessary to ensure accurate identification. Intestinal lymphangiectasia serves as an endoscopic manifestation of lymphatic failure in cirrhosis, classically characterized by swollen mucosa with scattered white spots. However, even in the absence of these gross endoscopic findings, intestinal lymphangiectasia can be identified histopathologically by the presence of dilated intestinal lacteals within the lamina propria.²⁹ Finally, the presence of chylous ascites, evidenced by a milky appearance of the ascitic fluid and triglyceride levels exceeding 200 mg/dL,¹¹⁴ may indicate a cirrhosis-related lymphatic abnormality, provided alternative causes have been excluded.

Radiologic evaluation of lymphatics remains an evolving field and includes dynamic contrast-enhanced magnetic resonance lymphangiography, technetium-99m lymphoscintigraphy, and duplex ultrasonography.^{5,115,116} However, the utility of these imaging modalities in patients with advanced cirrhosis is frequently limited by suboptimal resolution, interference from ascites, a lack of standardization, risks associated with radiation or contrast exposure, and limited availability.^{116,117} Dynamic contrast-enhanced magnetic resonance lymphangiography is an established method for mapping the central lymphatic system. It involves injecting a gadolinium-based contrast agent directly into the inguinal lymph nodes, followed by high-resolution, time-resolved T1-weighted sequences to track cranial migration of the contrast.¹¹⁶ This technique can reveal abnormal lymphatic channels, collateralization, flow stasis, lymphangiectasia, and active leaks. Cross-sectional imaging modalities such as computed tomography or MRI can be used to measure the diameter of the cisterna chyli and TD. Both structures undergo initial luminal dilatation from elevated portal pressure, followed by paradoxical narrowing as cirrhosis advances.^{33,34} Near-infrared indocyanine green lymphatic imaging is a valuable method for assessing lymphatic drainage.¹¹⁸ However, in cirrhotic patients, the diagnostic utility of this technique is limited by optical attenuation from ascites, delayed hepatic clearance of the tracer, and tracer extravasation from the leaky lymphatic vessels.

Therapeutic considerations

To date, the lymphatic system remains largely overlooked in cirrhosis therapeutics. There are no formal guidelines regarding the optimal treatment of lymphatic failure in patients with cirrhosis. While direct lymphatic therapies are still in preclinical stages, several standard-of-care therapies for cirrhosis indirectly modulate the structure and function of the lymphatic system (Table 3). Existing clinical evidence for targeted therapies, mainly regarding intestinal lymphangiectasia and chylous ascites, is limited to case reports and series.

Table 3. Current and future treatment options for lymphatic dysfunction in cirrhosis

Options	Mechanism	Effects	Evidence/clinical applicability
Diuretics (spironolactone and furosemide)	Inhibit renal sodium reabsorption; reduce total plasma volume	Decreases lymph formation by lowering interstitial fluid filtration	Indirect evidence, standard of care
Nonselective beta-blockers (carvedilol/ propranolol)	Splanchnic vasoconstriction; reduce portal hypertension	Decompresses the lymphatic system by lowering the upstream fluid burden and reducing plasma filtration	Indirect evidence, standard of care
Weight reduction/ antidiabetic therapy	Metabolic control	Reduce systemic inflammation and tissue mechanical stress and restore lymphatic contractility	Mechanistic plausibility, standard of care
Dietary salt restriction (~5 g/d)	Decreases renal retention of sodium/water	Reduced hepatic and splanchnic lymph production	Indirect evidence, standard of care
Medium-chain triglycerides	Reduce long-chain fat absorption through lacteals	Reduces intestinal lymphatic congestion; may improve hypoalbuminemia	Clinical experience, standard of care
Luminal antibiotics (rifaximin)	Reduction of bacterial translocation and inflammation; restoration of intestinal barrier integrity	May indirectly reduce lymphatic fluid load and support lymphatic integrity and function	Mechanistic plausibility, standard of care
Octreotide	Splanchnic vasoconstriction to reduce portal venous inflow	Reduced lymph load; prevention of postprandial engorgement of intestinal lacteals	Clinical experience (case reports/series)
Recombinant VEGF-C (Cys156Ser)	Promotes organized functional lymphangiogenesis	Restores lymphatic drainage networks	Preclinical evidence
eNOS inhibitor (L-NMMA)	Inhibits local eNOS overactivation	Restores lymphatic pump activity	Preclinical evidence
TGF- β synthesis downregulator (Pirfenidone)	Inhibits TGF- β production and disrupts SMAD pathways	Reduces lymphatic fibrosis and may improve function	Preclinical evidence
Noradrenaline infusion	Activates α -adrenergic receptors on LSMCs	Enhances lymphatic vessel contractility and improves drainage	Preclinical evidence
Statins	May modulate lymphangiogenesis via VEGFR-3 and improve LEC function	May promote functional lymphangiogenesis and lymphatic function	Hypothesis-generating
Leukotriene inhibitor (bestatin)	Inhibition of leukotriene B4 signaling	Restoration of lymphatic architecture and drainage capacity	Preclinical evidence
Transjugular intrahepatic portosystemic shunt	Reduces portal pressure	Decompresses the central lymphatic system by reducing fluid filtration into the space of Disse	Clinical experience (case reports/series)
Endovascular intervention: thoracic duct stenting	Resolves pressure gradient between thoracic duct and venous system	Improves overall lymphatic drainage capacity	Clinical experience (case reports)

eNOS, endothelial nitric oxide synthase; g/d, grams per day; LECs, lymphatic endothelial cells; L-NMMA, N^G-monomethyl-L-arginine; LSMCs, lymphatic smooth muscle cells; SMAD, mothers against decapentaplegic homolog; TGF- β , transforming growth factor-beta; VEGF-C, vascular endothelial growth factor C; VEGFR-3, vascular endothelial growth factor receptor 3

Therapies indirectly supporting lymphatic function

These are standard-of-care therapies for patients with cirrhosis that target PHT, fluid overload, metabolic dysfunction, and gut dysbiosis. These include diuretic therapy, dietary salt restriction, NSBBs, luminal antibiotics, and control of obesity and diabetes mellitus. Although direct evidence of their beneficial effects on lymphatic function is scarce, the association of PHT, metabolic comorbidities, systemic inflammation, and fluid overload with lymphatic failure provides a plausible basis for their use. General recommendations to enhance lymphatic function include management of obesity and diabetes, if present. Caloric restriction and weight reduction have been

shown to improve the pumping efficiency of collecting lymphatics.¹¹⁹ Effective diabetes control reduces cellular oxidative stress, decreases lymphatic permeability, and lowers microvascular fluid load, thereby supporting overall lymphatic function.¹²⁰ Moderate physical activity may improve muscle activity and facilitate lymphatic drainage. Dietary salt restriction and diuretic therapy are standard-of-care treatments for fluid mobilization in patients with cirrhosis.¹⁹ These can be beneficial in the initial stages of lymphatic edema; however, as the condition progresses and lymphatic pump failure becomes significant, the effectiveness of these interventions diminishes.⁵ NSBBs are recommended in patients with cir-

rhosis to control PHT.¹ By reducing portal pressure, NSBBs can indirectly reduce the burden on the overloaded lymphatic system.⁵ However, given that NSBBs may also alter lymphatic contractility, their net impact on lymphatic function remains unclear.¹⁰⁰ To date, no clinical or preclinical studies have directly evaluated changes in lymph flow in response to NSBB therapy. Luminal therapies like rifaximin can help reduce bacterial translocation and endotoxemia, thereby potentially improving systemic hemodynamics and lymphatic function.¹²¹ Similarly, prompt and effective treatment of infection may help reduce systemic inflammation and its adverse impact on lymphatic function.⁵

Therapies supported by clinical experience

Several therapeutic options exist with direct evidence regarding their role in lymphatic function, including medium-chain triglycerides, octreotide, thoracic duct stenting, and lymphatic embolization. However, this evidence primarily consists of case reports, case series, and nonrandomized clinical trials, which are insufficient to support strong clinical recommendations.

Treatment of intestinal lymphangiectasia and chylous ascites mainly involves dietary adjustments, medication, and sometimes radiological intervention.^{49,122–125} A low-fat, high-protein diet with medium-chain triglycerides helps reduce lymphatic pressure by reducing long-chain fat absorption through intestinal lymphatics.^{122,123,126} Octreotide has shown promise in intestinal lymphangiectasia cases by decreasing lymphatic flow.¹²⁷ There are multiple case reports showing successful treatment of cirrhosis-related chylous ascites with octreotide.^{124,128} Transjugular intrahepatic portosystemic shunt (TIPS) has been used to treat intestinal lymphangiectasia-induced protein-losing enteropathy and chylous ascites.^{125,129} TIPS reduces TD congestion, as shown by a decrease in the average TD diameter from 6.4 mm to 5.1 mm after the procedure.¹³⁰ Recently, endovascular lymphatic decompression using TD stent placement has been reported in patients with cirrhosis and refractory ascites when TIPS is contraindicated.^{35,131} While the technical success rate for this procedure was 100%, only about one-third of patients experienced clinical improvement.

Preclinical and experimental therapies

Recent preclinical studies indicate that VEGF-C may benefit chronic liver disease by promoting lymphatic drainage.^{31,132} Recombinant VEGF-C (Cys156Ser) nanoparticles, which enhance mesenteric lymphatic drainage, have been shown to lower portal pressure and ascites in cirrhotic rats.³¹ An experimental study also revealed that liver-targeted VEGF-C overexpression decreased liver fibrosis and injury and mitigated PHT without altering systemic hemodynamics.¹⁰³ Administration of adeno-associated viral VEGF-C (AAV8-VEGF-C) into the cisterna magna has been demonstrated to enhance meningeal lymphatic drainage, thereby reducing neuroinflammation in rat models of hepatic encephalopathy.¹³³ It remains unclear why bioengineered VEGF-C nanoparticles improve lymphatic drainage even though endogenous VEGF-C can be overproduced in cirrhosis and contribute to pathological lymphangiogenesis remains unclear. However, this apparent paradox may be explained by several key findings from the experimental study by Juneja *et al*.³¹ First, while endogenous VEGF-C is inherently unstable, targeted nanocarriers protect the protein from degradation, ensuring high-concentration delivery directly to the mesenteric and intestinal lymphatic systems. Second, recombinant VEGF-C treatment directly reinforces the endothelial barrier by upregulating vascular endothelial cadherin. Third, it exerts systemic benefits

by lowering portal pressure, mitigating bacterial translocation, and dampening endotoxemia, all of which may interrupt the vicious cycle of lymphatic failure.³¹ However, limited data render these mechanisms preliminary, necessitating further translational studies to define the therapeutic utility of VEGF-C. Recently, a preclinical study demonstrated that platelet-rich plasma enhanced lymphatic drainage, reduced portal pressure, and alleviated liver fibrosis.¹³⁴ The beneficial effects of platelets are likely mediated by the VEGF-C/VEGFR-3 pathway in LECs.¹³⁵ However, no clinical studies have yet evaluated platelet intervention as a viable therapeutic strategy for cirrhosis and lymphatic failure. Given the role of NO in lymphatic failure, the effect of NO inhibition was evaluated in a preclinical study. In a rat cirrhosis model, Ribera *et al*. found that the eNOS inhibitor N^G-monomethyl-L-arginine (L-NMMA) improved lymphatic drainage and reduced ascites by increasing smooth muscle cell coverage on LECs.¹³⁶ However, translation of such results to human cirrhosis remains uncertain. Moreover, indiscriminate NO inhibition within the hepatic microcirculation could raise intrahepatic vascular resistance and increase lymph production, potentially offsetting therapeutic benefits.⁶⁰ Consequently, effective clinical translation requires tissue-specific delivery systems designed to exclusively target extrahepatic lymphatic eNOS.

Intravenous infusion of adrenaline has been found to increase both the frequency of lymphatic contractions and lymph flow in efferent lymphatic vessels in an animal study.¹³⁷ However, no such evidence is available in humans. Clinical trials are currently evaluating pharmacologic inhibitors of leukotriene B₄ (LTB₄) signaling to treat abnormal lymphatic structure and function. Preclinical validation in a mouse model of experimental lymphedema demonstrated that targeted inhibition of LTB₄ using bestatin achieved significant therapeutic outcomes, including restored lymphatic architecture and drainage capacity.¹³⁸ However, no study has yet evaluated the impact of LTB₄ inhibition on lymphatic failure in the context of cirrhosis. In mouse models, pirfenidone, which has anti-TGF- β effects, was found to improve lymphedema.¹³⁹ However, blocking TGF- β in cirrhosis faces major translational barriers, including the risk of systemic toxicity and malignancy. Statins hold the potential to enhance lymphatic function; however, their general effects remain inconsistent, and their impact on cirrhotic models of lymphatic failure is largely unknown.^{140,141} A recent animal study demonstrated that the cholesterol-depleting agent cyclodextrin restored lymphatic drainage through the regeneration of lymphatic vessels. The findings elucidate the impact of impaired cholesterol clearance on the development of lymphedema and suggest tissue cholesterol as a potential therapeutic target.¹⁴²

In summary, although numerous agents show potential for enhancing lymphatic function, evidence remains preliminary and mostly restricted to non-cirrhotic preclinical models. These therapies must progress through rigorous clinical trials before definitive conclusions can be established.

Conclusions

The hepatic and mesenteric lymphatic systems are important yet under-recognized contributors to cirrhosis progression. While initial lymphatic remodeling appears to be a protective and compensatory response that may delay decompensation, persistent PHT, chronic inflammation, and hydrostatic overload may eventually contribute to lymphatic failure and ascites. Although several pathophysiological changes in cirrhosis appear to adversely impact the structural and functional integrity of the liver-gut-lymphatic axis, the precise molecular pathogenesis remains incompletely understood.

Identifying individual phenotypes of lymphatic dysfunction is essential for developing targeted therapies. Managing this dysfunction may require multimodal therapy. A combination of luminal therapies to lower endotoxin loads, systemic anti-inflammatory approaches, and prolymphangiogenic strategies warrants investigation as potential components of lymphatic-directed therapy. Future research should focus on decoding and refining the molecular mechanisms behind this lymphatic dysfunction, establishing highly specific biomarkers of lymphatic failure, and developing targeted therapies.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conceptualization (RK, S), data curation (RK, S, RN, SK), writing original draft (RK, S), review and editing (RN, SK). All authors made significant contributions to this work and approved the final manuscript.

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