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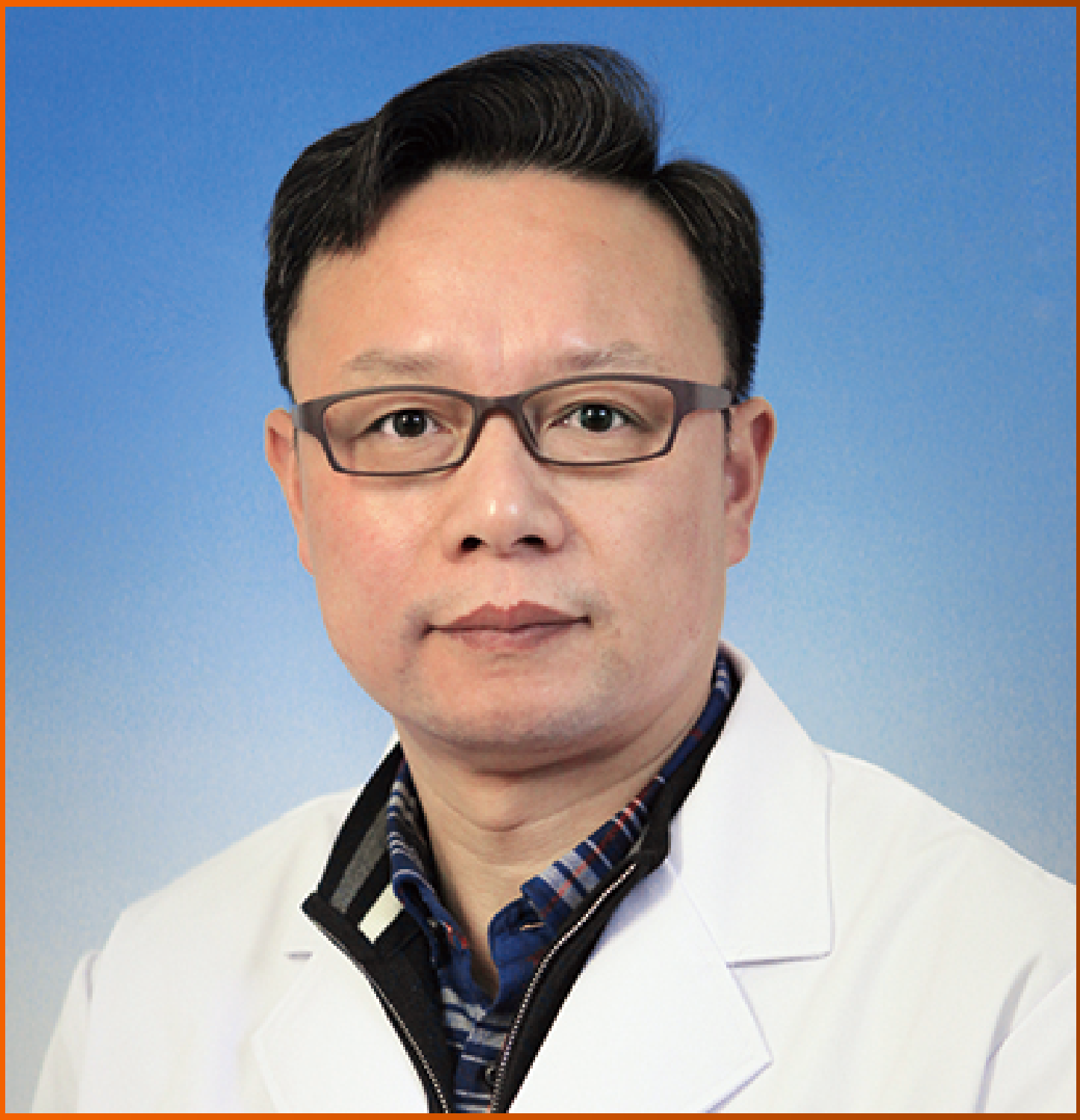

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ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Dr. Guang-Hua Luo is Director of the Clinical Medical Research Center in the Third Affiliated Hospital of Soochow University (China). He graduated from the Laboratory Medicine Department of Zhenjiang Medical College in 1996, obtained a PhD in 2013 at Soochow University, and was nominated to professorship in 2014. Currently, he is an editorial board member of Endocrine, Metabolic & Immune Disorders-Drug Targets. He has published more than 240 papers, 86 of which are included in SCI. Since 2009, four of his inventions have obtained patent authorization. His research activities mainly focus on molecular diagnostics in personalized medicine and on the regulatory role and mechanism of apolipoprotein M in liver diseases and chronic inflammatory diseases. (L-Editor: Filipodia)

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MINIREVIEWS

Lymphatic dysfunction in advanced cirrhosis: Contextual perspective and clinical implications

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Abstract

The lymphatic system plays a very important role in body fluid homeostasis, adaptive immunity, and the transportation of lipid and waste products. In patients with liver cirrhosis, capillary filtration markedly increases, primarily due to a rise in hydrostatic pressure, leading to enhanced production of lymph. Initially, lymphatic vasculature expansion helps to prevent fluid from accumulating by returning it back to the systemic circulation. However, the lymphatic functions become compromised with the progression of cirrhosis and, consequently, the lymphatic compensatory mechanism gets overwhelmed, contributing to the development and eventual worsening of ascites and edema. Neurohormonal changes, low-grade chronic inflammation, and compounding effects of predisposing factors such as old age, obesity, and metabolic syndrome appear to play a significant role in the lymphatic dysfunction of cirrhosis. Sustained portal hypertension can contribute to the development of intestinal lymphangiectasia, which may rupture into the intestinal lumen, resulting in the loss of protein, chylomicrons, and lymphocyte, with many clinical consequences. Rarely, due to high pressure, the rupture of the subserosal lymphatics into the abdomen results in the formation of chylous ascites. Despite being highly significant, lymphatic dysfunctions in cirrhosis have largely been ignored; its mechanistic pathogenesis and clinical implications have not been studied in depth. No recommendation exists for the diagnostic evaluation and therapeutic strategies, with respect to lymphatic dysfunction in patients with cirrhosis. This article discusses the perspectives and clinical implications, and provides insights into the management strategies for lymphatic dysfunction in patients with cirrhosis.

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Core Tip: Lymphatic dysfunction appears to play a significant role in the pathophysiology of advanced cirrhosis. Sustained portal hypertension, neurohormonal changes, and low-grade chronic inflammation have been implicated in causing lymphatic dysfunction in advanced cirrhosis, leading to worsening of ascites, lymphedema, and abnormal lipid transport; it also results in increased susceptibility to infections. Chylous ascites and intestinal lymphangiectasia are the rare manifestations of lymphatic dysfunction in cirrhosis, leading to loss of protein, fat, lymphocytes, and immunoglobins, with several clinical consequences. Lymphatic dysfunctions in cirrhosis have been ignored to date; hence, new exploratory research must be undertaken to gain insight into this important subject.

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INTRODUCTION

The lymphatic system consists of capillaries located inside the tissue that are highly permeable and are needed to transport lymph containing cellular proteins, lymphocytes, and lipoproteins[1-4]. It is essential for maintaining homeostasis of tissue *via* interstitial fluid reabsorption, immune cell trafficking, and the transport of lipids[3-5]. The lymphatic system removes interstitial fluid from tissues and returns it to the bloodstream. When this interstitial fluid gets into lymphatic capillaries, it is called lymph. The liver is the largest organ generating lymph, and liver lymphatics are believed to play a vital role in maintaining normal hepatic function by helping to eliminate protein, cholesterol, and immune infiltrates[5]. In the absence of normal lymphatic function, interstitial fluid accumulation may contribute to clinical manifestations such as lymphedema and ascites[6]. In patients with early cirrhosis, the lymphatic system helps to prevent development of ascites by reabsorbing excess fluid in the hepatic and splanchnic areas. As a result, lymph flow is enhanced, which promotes hepatic lymphangiogenesis[7,8]. However, in advanced cirrhosis patients, this compensatory mechanism is not adequate to prevent the development of ascites. Moreover, there appears to be an impaired lymphatic pump function in patients with an advanced liver disease[9]. Despite its significant clinical value, the literature on lymphatic dysfunction in cirrhosis is very limited, and the area remains open for new investigations. This article summarizes the current knowledge regarding dysfunctions of lymphatic system in patients diagnosed with liver cirrhosis, with special attention to pathophysiology, clinical implications, and insights into management strategies.

LYMPHATIC VASCULAR SYSTEM

The lymphatic system consists of a large network of lymphatic vessels, with lymphoid organs and tissues. Lymphatic vessels are classified anatomically into capillaries and collecting vessels. Further, the lymphatic capillaries are closed-ended and composed of a single layer of lymphatic endothelial cells (LECs). The initial lymphatics are highly permeable for transport of interstitial fluid macromolecules and immune cells. LECs have anchoring filaments that contract and relax, which enable them to "flap" open to allow interstitial fluid uptake[10,11]. The lymphatics capillaries merge into larger collecting lymphatic vessels, which possess a continuous basement membrane and have unidirectional bicuspid valves with contractile smooth muscle cells' (SMCs) covering for assisting the flow of lymph. Similar to lymphatic capillaries, the liver has

sinusoids, consisting of a single layer of liver sinusoidal endothelial cells (LSECs), without the basement membranes[12]. Hepatic lymph is produced by plasma components filtered through the LSECs into the space of Disse. In the gastrointestinal tract, lymphatics are present in mucosal, submucosal, and muscular layers; they merge with collecting lymphatic vessels near the mesenteric border. The lymphatics present in the center of each intestinal villus are referred to as lacteals, which have a structure similar to the lymphatic capillaries elsewhere, consisting of a single layer of LECs, without a basement membrane[13].

There is constant filtration of plasma into the interstitial space during the passage of blood through the capillaries. The rate of filtration is primarily dictated by the hydrostatic pressure and plasma oncotic pressure in the capillaries. Due to the change in interstitial pressure, interstitial fluid enters the lymphatic capillaries, as lymph, and moves towards larger lymphatic vessels[14]. The contractile activity of SMCs, of the collecting lymphatic vessels, is believed to be one of the major driving forces of lymphatic circulation[15]. The Ca^{2+} channels of SMCs and nitric oxide (NO) produced in LECs is thought to contribute to the regulation of lymphatic flows, by modulating the contractility of SMCs[16]. In liver, most of the lymph from space of Disse drains into lymphatic vessels in the area near portal triads. Some part of the lymph also circulates into the interstitium around the central vein or underneath the Glisson's capsule. Finally, all the liver lymphatic vessels converge into the hepatic hilum and flow into the lymph nodes arranged in the lesser omentum along the hepatic vessels and hepatic ducts[5,17]. The collecting lymphatic vessels, from all organs, connect to one or more lymph nodes and, finally, lymph trunks, which ultimately drain into the subclavian vein *via* thoracic duct or right lymph trunk (Figure 1). Thus, interstitial fluid, collected as lymph, is finally returned to the blood circulation through the lymphatic vessels. It is estimated that approximately 3 L to 5 L of lymph fluid travel through the thoracic duct each day, of which 50% to 90% comes from the intestines and liver[18]. Being capillary ultrafiltrate, all plasma proteins are present in lymph. However, several proteins derived from extracellular matrix, cellular metabolism, and cell death are enriched in lymph instead of the plasma[19]. Therefore, the composition of the lymph arising from various areas varies to a degree.

FUNCTIONS OF LYMPHATIC SYSTEM

The lymphatic system plays an important role in maintaining tissue homeostasis, by transporting interstitial fluid, serum protein, and lipids from tissues to the systemic circulation. After plasma filtration through the capillaries, the only way the fluid can be returned to blood circulation is *via* the lymphatic system[20]. When there is a mismatch between capillaries filtration and lymphatic removal, fluid accumulation occurs in the extravascular space. Lymphatic system plays a key role in adaptive immunity. It delivers antigen and antigen-presenting cells to the regional lymph nodes, where they evoke immune responses. Lymphatics also play a role in controlling the inflammatory response, by influencing the drainage of extravasated fluid and inflammatory mediators, and by facilitating the discharge of infiltrated immune cells from inflamed sites[21,22]. Moreover, lymphatic vessels are essential for the removal of cholesterol from peripheral tissues[23]. LECs are known to take up cholesterol carried by high-density lipoprotein, and dysfunctional LECs can lead to the development of hepatic steatosis[24]. Furthermore, intestinal lacteals play important role in the absorption of fat and fat-soluble vitamins as chylomicrons.

LYMPHATIC SYSTEM CHANGES IN CIRRHOSIS

In patients with cirrhosis, capillary filtration increases steadily and gradually, primarily due to an increase in hydrostatic pressure. This contributes to an enhanced lymph production, with consequent lymphatic compensatory responses, such as an increase in the number and size of lymphatic vasculature, to enhance the drainage of interstitial fluid[8,25,26]. Several structural and functional changes in the lymphatic system have been reported in patients with cirrhosis.

Increase in the lymph flow

An increased architectural distortion in cirrhosis causes resistance to sinusoidal blood flow, increased hydrostatic pressure in the sinusoid, and increased filtration of plasma.

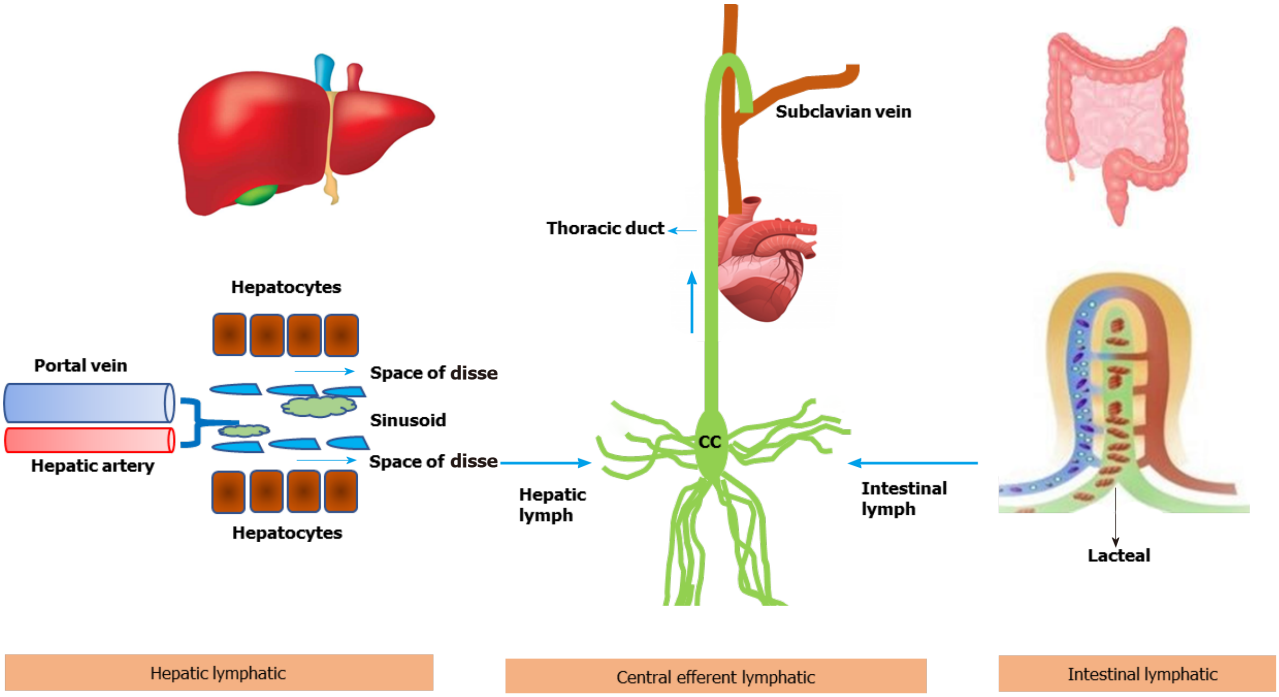

Figure 1 Schematic diagram showing lymph flow kinetics from liver and intestine to the systemic circulation. The capillary filtrate enters the lymphatic capillaries, as lymph, and moves towards larger lymphatic vessels. In liver, lymph is produced by filtration of plasma through the sinusoidal endothelial cells into the space of Disse. The collecting lymphatic vessels from all organs connect to one or more lymph nodes, and finally to the lymph trunks which ultimately drain into subclavian vein *via* cysterna chyli and thoracic duct. Approximately 80% of thoracic duct lymph comes from the intestines and liver.

This process may be further enhanced by concomitant hypoalbuminemia and increased capillary permeability under certain circumstances. Thus, lymph production and flow is greatly increased (up to 30 folds) in patients with cirrhosis[27,28]. Witte *et al*[7] demonstrated that lymph in the thoracic duct of cirrhosis patients had a high protein concentration. Because the protein concentration of hepatic lymph is higher (50%-80% of plasma), such overproduction of lymph in cirrhosis appears to come primarily from the liver. However, with advancement of cirrhosis, the protein content of hepatic lymph also decreases because of a dysfunctional lymphatic transport system. In an animal study of cirrhotic livers, a positive correlation between hepatic lymph flow and increasing portal pressures was found. Moreover, this study also demonstrated a compromised functional capacity of lymphatic vessels to absorb interstitial fluid[29].

Increase in the number and density of lymphatic vessels

Dumont and Mulholland[30] were the first to describe an increased diameter and lymph flow in the thoracic duct, in patients with cirrhosis. Such expansion of lymphatic vasculature has also been reported by Sadek *et al*[31] on computed tomography and Shimada[32] on laparoscopy. The expansion of lymphatic density correlates positively with the severity of fibrosis around the portal tracts of human liver. Yamauchi *et al*[26] found that the intrahepatic lymphatic vessels remain stable during the early stages of liver disease, but when it progresses to advanced cirrhosis, it increases significantly. In addition, Yokomori *et al*[33] recently calculated the density of lymph vessels by immunohistochemistry in patient specimens and found that the density increased with the progression of liver disease, peaking at the most advanced stages of cirrhosis. In cirrhotic livers, a substantial increase in vascular endothelial growth factors (VEGF)-D expression, an inducer of lymphangiogenesis, was observed and in addition, VEGF-D expression was found to be positively associated with liver fibrosis progression[8]. This lymphangiogenic response may help to enhance the drainage of increased interstitial fluid.

Lymphatic oversaturation and flow dysfunction

The lymphatic system keeps tissue edema free, by returning excess tissue fluid back to the bloodstream. In cirrhotic patients, when interstitial fluid is increased, expansion of lymphatics and increased lymphatic flow initially tries to prevent development of ascites and edema[7]. However, it is not clear as to what extent the lymphatic

vasculature may compensate for enhanced lymph production. In a sustained increase of the hydrostatic pressure, fall in plasma oncotic pressure, compounding effects of capillarization/defenestration of sinusoidal endothelium, and neurohormonal changes, the compensatory mechanism is gradually overwhelmed, resulting in fluid accumulation in the extravascular space[34,35]. In the splanchnic circulation of cirrhosis patients, arteriolar vasodilation occurs; it increases the production of splanchnic lymph beyond the ability of the lymphatic system to transport and, thus, triggers lymph leakage into the peritoneal cavity. Moreover, an increased splanchnic vascular permeability and chronic retention of renal sodium and water plays a major role in the sustained development of ascites[36,37]. Over time, increased pressure and flow stasis in the intestinal lymphatic channels may lead to lymphangiectasia, followed by the rupturing of dilated lacteals and intestinal loss of protein, chylomicrons, and lymphocyte[38]. Rarely, the rupture of subserosal lymphatic, secondary to a sustained high pressure, results in the development of CA[39].

Apart from lymphatic oversaturation, functional defect in the lymphatic transport system has also been reported in patients with cirrhosis. Henriksen[40] have described a model of lymphatic conductivity (flow rate per unit pressure difference), based on protein kinetic and hemodynamic measurement in patients with cirrhosis. They found that lymphatic conductance in the thoracic duct was three times higher than normal in patients without ascites, while in patients with tense ascites, these values were close to normal. Moreover, conductance in the right lymphatic duct system was ten times below that of thoracic duct of cirrhotic patients with ascites. The results of this study suggest that a relatively insufficient lymphatic drainage plays an important role in the accumulation of ascites in decompensated cirrhosis. Recently, the functionality of the splanchnic and peripheral lymphatic system was studied by fluorescent lymphangiography, in an experimental model of rats exposed to chemokine ligand 4 (CCL4). A substantial decrease in fluorescence-labeled lymphatics was observed in cirrhotic rats, in both peripheral and splanchnic regions, indicating a deficiency in lymphatic drainage[9].

PATHOPHYSIOLOGY OF LYMPHATIC DYSFUNCTION IN CIRRHOSIS

The pathophysiological mechanism behind lymphatic dysfunction in cirrhosis is an area yet to be explored at cellular and molecular level (Figure 2). In a study on cirrhotic rats with ascites, Ribera *et al*[9] found that an impaired lymphatic drainage in the splanchnic and peripheral regions was accompanied by increased activity of endothelial nitric oxide synthase (eNOS) and production of NO by LECs. In addition, SMC coverage of lymphatic vessels was found to be significantly decreased. Interestingly, when cirrhotic rats were treated with inhibitor of eNOS activity (L-NG-methyl-L-arginine, L-NMMA), a significant improvement of lymphatic drainage, reduction in ascetic fluid volume, and an increase in lymphatic smooth muscles were seen. Therefore, this study demonstrated a role of NO in the lymphatic dysfunction of cirrhotic rats. Whether the same applies for human cirrhosis remains to be seen. Lymphangiogenesis observed in cirrhosis appears to be due to increased expression of several induces of lymphogenesis, such as VEGF-D and VEGF-C. Their levels have been found to be significantly elevated during hepatic fibrosis and positively correlated with fibrosis progression[8,41]. Study on cirrhotic rat has found a four-fold increase in VEGF-D, in the endothelial cells. Additionally, the receptor of this VEGF (VEGR-3) was found to be overexpressed in the LECs of cirrhotic rats[42]. It has recently been shown that autonomic nervous system is a key modulator of the lymphatic vessels' function[43].

Lymphatic function, in general and in patients with cirrhosis, can be modulated by numerous factors including age, obesity, diabetes, dyslipidemia, neurohormonal alterations, and chronic inflammation. Neurohormonal changes are known to occur in advanced cirrhosis, and the levels of a number of vasoactive substances such as noradrenaline, histamine, substance P, prostaglandins, and endothelin are altered, which can affect contractility of lymphatic vessels[44-46]. Intestinal motility plays an important role in the propulsive motion of intestinal lymph, and by inducing VEGF-C, intestinal microbiota is an important regulator of intestinal lacteal integrity[13,47]. Therefore, the intestinal dysmotility and intestinal dysbiosis that are frequently seen in advanced cirrhosis may interfere with intestinal lymphatic function. Moreover, Cirrhosis and portal hypertension (PHT) is known to create a state of low-grade chronic inflammation[48]. Furthermore, gut dysbiosis, bacterial translocation, and release of Inflammatory cytokines such as tumor necrosis factor alpha, and

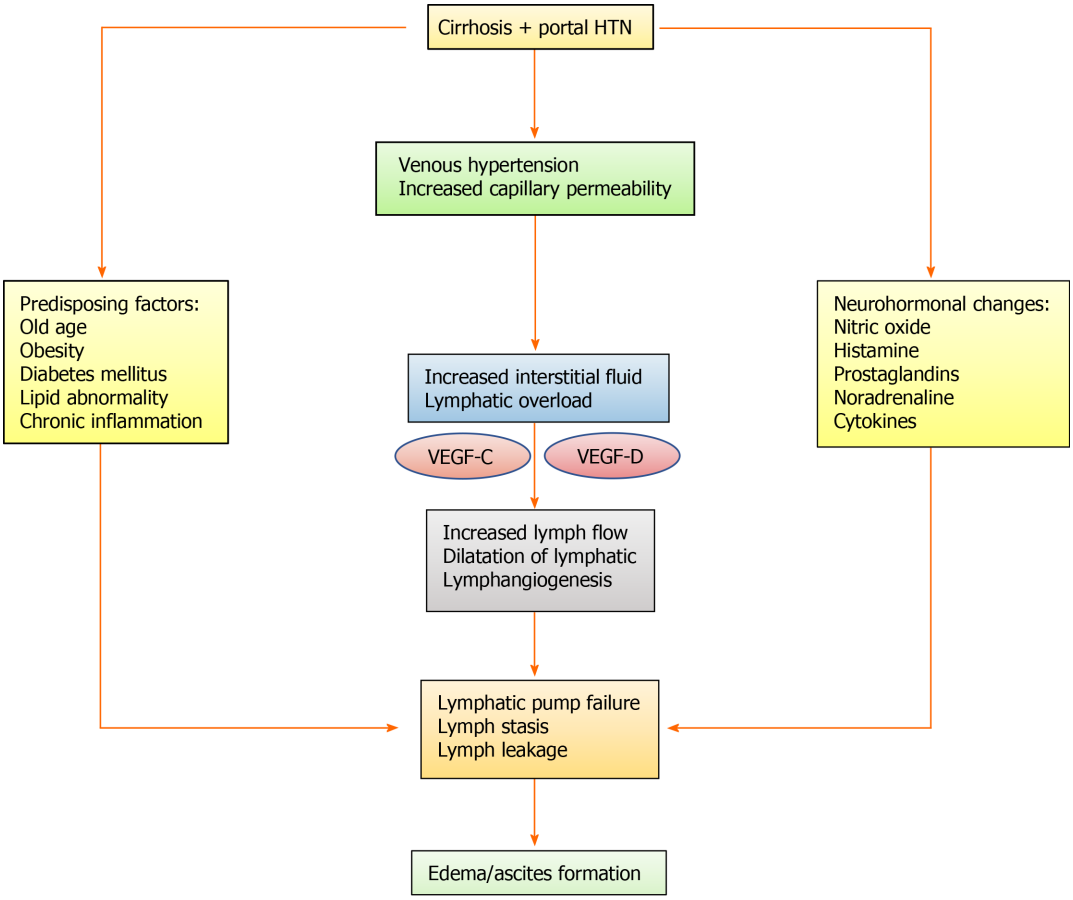

Figure 2 Flow diagram showing the possible pathophysiological mechanism behind lymphatic abnormalities in cirrhosis patients leading to fluid imbalance. The exact pathophysiological mechanism, at cellular and molecular level, is poorly understood in human cirrhosis. Some of the information has been derived from the experimental study on animal. VEGF: Vascular endothelial growth factor; HTN: Hypertension.

interleukin-1β occur in cirrhosis[49]. Consequently, chronic inflammation and neurohormonal disturbances, in advanced cirrhosis, can lead to structural and physiologic changes in the lymphatic system. Dysfunctional lymphatics, with lymph stasis, can impair lipid transport and stimulate adipogenesis in the affected area[50,51].

Old age and obesity also affect lymphatic functions. Aging induces structural changes in the lymphatic vessels, such as loss of extracellular matrix, reduced contractile protein expression, and changes in eNOS and histamine gradients, which tend to decrease the lymphatic transport of interstitial fluids[52,53]. Obesity results in several structural and physiological changes in the lymphatic system, including increased lymphatic leakiness, decreased contractility of the collecting vessel, and changes in the architecture of the lymph node, which significantly affect lymphatic transport functions[54,55]. Notably, most cirrhosis patients belong to the old age group, and obesity is presently a growing cause of non-alcoholic fatty liver disease (NAFLD)-related cirrhosis. Given that obesity is a growing cause of NAFLD-related cirrhosis and that most patients with cirrhosis are older, they may be at a higher risk of developing lymphatic dysfunction.

CLINICAL IMPLICATIONS OF LYMPHATIC DYSFUNCTION

Lymphatic dysfunctions have been aptly described in patients with cirrhosis; however, little has been described about the clinical consequences of such dysfunctions. Given the role of lymphatic vasculature in the body fluid homeostasis, adaptive immunity, and the transport of lipid and waste materials, it is tempting to speculate that lymphatic dysfunctions, in cirrhosis, may have several clinical implications, particularly with regard to the body fluid homeostasis.

Edema and ascites

In advanced cirrhosis, the activation of compensatory vasoconstrictor pathways compromises glomerular filtration, causing greater renal retention of sodium and water. This further increases the production of lymph, burdening the already inefficient lymphatic system with the responsibility for drainage. Moreover, inability of the lymphatic system to recirculate extravasated albumin may worsen pre-existing hypoalbuminemia, leading to a change in the transcapillary oncotic pressure gradient and worsening of fluid imbalance. Additionally, serum albumin is also required for furosemide to work properly[56]. Therefore, severe lymphatic dysfunction can lead to the development of refractory edema and ascites in patients with cirrhosis.

Lymphedema should be fairly common in patients with advanced cirrhosis for obvious reasons; however, its description is lacking in existing literature. Lymphedema is deposition of protein-rich lymph fluid within the tissues, as a consequence of lymphatic leak and an imbalance between the rate of lymph production and drainage. Recent evidences suggest that lymphedema can also occur as an immune response secondary to lymphatic injury or metabolic derangements, including adiposity and infection[57]. Furthermore, fat deposition is present in lymphedema due to failure of lipid transport and stimulation of adipogenesis[50,51]. Clinically, a diagnosis of lymphedema can be made by physical characteristics, including pitting edema, peau-d'orange appearance, and a positive Stemmer sign. Patients with lymphedema are often susceptible to various skin infections, such as cellulitis.

Intestinal lymphangiectasia

An increase in lymphatic pressure secondary to PHT may lead to dilatation of the intestinal lymphatics, known as intestinal lymphangiectasia[58]. A sustained rise in lymph pressure leads to the rupture of lymphangiectasia and lymph leakage into the lumen of the intestines, with many clinical consequences (Figure 3). As intestinal lymph contains many proteins, lipoproteins, and lymphocytes, its loss would result in hypoproteinemia, hypoalbuminemia, lymphocytopenia, and hypogammaglobulinemia[59,60]. Hence, in patients with advanced cirrhosis, lymphangiectasia can lead to worsening of ascites, by causing severe hypoalbuminemia. The disruption of lymphatic flow, in lymphangiectasia, leads to malabsorption of fats and fat-soluble vitamins (vitamins A, D, E, and K), which may cause steatorrhea, vision problems, muscles weakness, osteopenia, and coagulopathy in cirrhosis patients. In addition, loss of lymphocytes may contribute to an increased susceptibility to infection in cirrhosis[60].

Chylous ascites

Chylous ascites (CA) results from the leakage of lipid-containing lymph (chyle) into the peritoneal cavity[61]. Elevated lymphatic pressure secondary to PHT can rarely cause rupture of dilated subserosal intestinal lymphatics, leading to the formation of CA[39]. Intestinal lymph, which constitutes 50%-75% of intra-abdominal lymph, contains fat droplets rich in triglyceride and appears to be milky in color. CA is found in 0.5%-1% of patients with cirrhosis, and cirrhosis is responsible for 11% of cases of atraumatic CA[62,63]. In patients with cirrhosis, CA may also develop due to complications of shunt surgery, sclerotherapy-related thoracic duct injury, or hepatocellular carcinoma[62,64]. A diagnosis of CA is made when triglyceride concentration of fluid is ≥ 110 mg/dL. It is to be noted that a rupture of hepatic lymph, which drains 25%-50% of abdominal lymph, does not produce CA, as hepatic lymph is devoid of fat droplets.

Other clinical implications

Patients with lymphatic dysfunction often exhibit impaired immune function predisposing them to a variety of infections[65,66]. Recurrent cellulitis/erysipelas and interdigital fungal infections are common in presence of lymphedema. The lymphatic vasculature is preferential route for the spread of cancer cells. Therefore, lymphangiogenesis can promote tumor metastasis if patients with cirrhosis have hepatocellular carcinoma[67]. Moreover, lymphatic dysfunction may interfere with the removal of inorganic material, dying cells, and mutant cells from the body, but such adverse effects are unknown in patients with cirrhosis. Furthermore, lymphatic dysfunction can affect oral bioavailability of lipophilic drugs, which require functional intestinal lacteals for absorption.

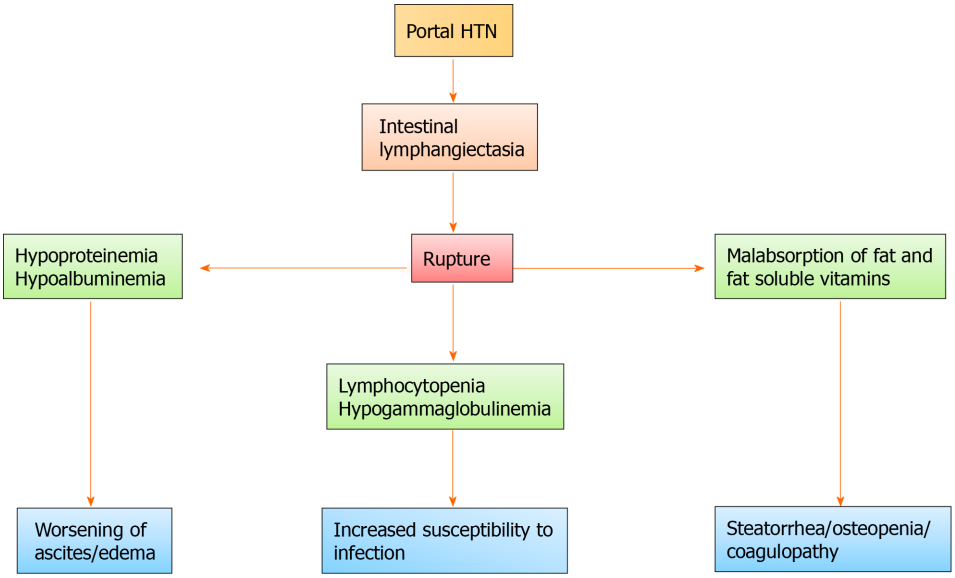

Figure 3 Flow diagram showing clinical consequences arising from the rupture of intestinal lymphangiectasia. HTN: Hypertension.

ASSESSMENT OF LYMPHATIC DYSFUNCTIONS IN CIRRHOSIS

No recommendation exists with regard to the diagnosis and assessment of lymphatic dysfunction in patients with cirrhosis. Table 1 provides a rational overview of the assessment of lymphatic dysfunction in cirrhosis patients. Techniques to evaluate the lymphatic system radiologically are still evolving[68]. There are various imaging techniques available, such as X-ray or magnetic resonance lymphography, lymphoscintigraphy, and duplex ultrasonography. The gold standard that offers insight into the lymphatic anatomy as well as lymph flow dynamics is lymphangioscintigraphy. However, these imaging modalities are often limited by sub-optimal resolution, lack of standardization, invasiveness, risk of radiation exposure, and low availability[69]. Therefore, as of now, no recommendation can be made with respect to the use of a radiological technique for assessment of lymphatic dysfunction in patients with cirrhosis.

Lymphatic dysfunction, especially in elderly cirrhosis with diabetes and dyslipidemia, should be considered when there is severe generalized edema, sctrotopenile swelling, diuretic-resistant ascites, and peripheral lymphedema. On blood investigation, the presence of disproportionate hypoproteinaemia, combined with severe lymphocytopenia, may also suggest lymphatic dysfunction. Intestinal lymphangiectasia is an endoscopic manifestation of lymphatic abnormality in cirrhosis. It is characterized by swollen mucosa with scattered white spots, white villi, and chyle-like substances covering the mucosa (Figure 4). This must be confirmed *via* histopathological examination, which should reveal dilated intestinal lacteals in the lamina propria region of the intestinal villi. Morphologically, it is often difficult to distinguish lymphatic vessels from blood vessels. Therefore, use of specific lymphatic endothelium markers may be necessary for accurate identification of lymphatic vessels on pathological specimens[25,70]. These markers include LYVE-1 (lymphatic vessel endothelial hyaluronan receptor), Prox-1 (a transcription factor), and podoplanin or D2-40 (lymphatic vessel endothelial hyaluronic acid receptor-1). However, even these markers may not be exclusive to lymphatic vessels. Mouta Carreira *et al*[25] found that LYVE-1 is also present in Kupffer cells and normal LSECs. Therefore, a combination of lymphatic markers should be used for accurate identification. Finally, presence of CA, as evident by milky appearance of ascitic fluid with triglyceride levels > 110 mg/dL, indicates lymphatic abnormality related to cirrhosis, after exclusion of alternative causes such as malignancy, tuberculosis, post-operative or post-radiation status, and cardiac diseases.

THERAPEUTIC PERSPECTIVE

From a pathophysiological point of view, a number of therapeutic options are available for lymphatic dysfunctions, but no adequate evidence is available for the use

Table 1 Assessment of risk factors, clinical markers and investigations for lymphatic dysfunction in cirrhosis

Parameters	Findings that support or indicate lymphatic dysfunction
Risk factors	(1) Old age; (2) metabolic syndrome (obesity, diabetes, dyslipidemia); and (3) concomitant inflammatory disorders
Clinical examination	(1) Diuretic-resistant ascites; (2) severe generalised edema, scrotal/penile swelling; (3) lymphedema: Peau-d'orange appearance and a positive stemmer sign; (4) frequent cellulitis/lymphangitis of affected limbs; and (5) hyperkeratotic skin lesions, yellow nail
Blood investigations	(1) Hypoproteinaemia and hypoalbuminemia; (2) lymphocytopenia; and (3) hypogammaglobulinemia
Ascitic fluid analysis	Chylous ascites: Milky appearance, fluid triglyceride level ≥ 110mg/dL
Upper endoscopy	Intestinal lymphangiectasia: Whitish congested villi in duodenum
Radiological imaging: (lymphography, lymphoscintigraphy)	Abnormal lymphatic structure and/or lymph flow dynamics: Dilated lymphatic vessels, lymph stasis, lymph leakage
Histopathological examination (liver/intestine)	(1) Increase in number and size of lymphatic structures; and (2) specific lymphatic endothelial markers for accurate identification: Prox-1, podoplanin, LYVE-1

LYVE-1: Lymphatic vessel endothelial hyaluronan receptor.

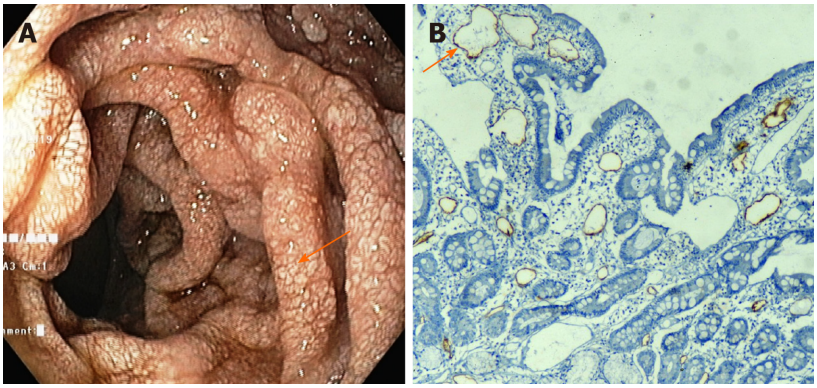

Figure 4 Intestinal lymphangiectasia in a patient with cirrhosis. A: Upper gastrointestinal endoscopy of a patient showing whitish swollen villi in the duodenum, suggestive of intestinal lymphangiectasia; B: On immunohistochemistry (× 10), markedly dilated vessels were seen in the lamina which showed strong D2-40 positivity indicating dilated lymphatics.

of several of them in patients with cirrhosis (Table 2). The mobilization of fluid is particularly difficult in cirrhosis patients with lymphatic dysfunction. An effort should be made to minimize capillary filtration into the interstitial space. Local skincare and compression therapy remains the cornerstone for lymphedema affecting limbs. Common infections, such as cellulitis, should be vigorously treated, as they can deteriorate lymphedema very rapidly. Limb elevation may facilitate lymphatic drainage and prevent the transfer of tissue fluid to an affected limb due to gravity. Pressure effect of compression therapy with elastic stockings/gloves or bandages may help to minimize capillary leakage, reduce lymph regurgitation, and avoid the movement of fluid related to gravity[71]. However, compression therapy should be avoided when cellulitis, venous thrombosis, and congestive heart failure are present. Obesity and salt consumption may worsen lymphedema; therefore, salt and calorie diet should be restricted. Role of conventional diuretic therapy in lymphatic edema, per se, is limited; however, it may be beneficial in mixed-origin edema which occurs in cirrhosis patients. In addition, diuretics may also render lymphedema worse by removing fluid and increasing lymph protein concentration, resulting in a reversed gradient of oncotic pressure and increased vulnerability to infection. The role of newer molecules with diuretic activity, such as V2-receptor antagonist and sodium-glucose cotransporter 2 (SGLT2) inhibitors, needs to be explored in cirrhosis patients with lymphatic dysfunction. Tolvaptan is an oral selective V2-receptor antagonist and a novel water diuretic. Unlike loop diuretics, tolvaptan has a different effect on fluid distribution, and it can ameliorate fluid retention with a low risk of a worsening renal function[72,73]. SGLT2 inhibitors are the new class of antihyperglycemic agents with a good safety profile in cirrhosis patients. SGLT2 inhibitors have been shown to have

Table 2 Possible therapeutic strategies for treatment of lymphatic dysfunction in cirrhosis

To decrease formation of lymph	
Decrease water retention	Low salt diet, diuretic therapy
Control of portal hypertension	Beta-blocker, octreotide, transjugular intrahepatic portosystemic shunt
Increase interstitial pressure	Compression therapy
To promote lymphatic drainage	
Facilitate fluid movement into the lymphatic vessels	Compression therapy, limb elevation, diuretic therapy (limited role)
Increase contractility of the lymphatic vessels	Nor-adrenaline, phenylephrine, nitric oxide-inhibitors (experimental)
Facilitate lysis of interstitial protein	Benzopyrones (coumarin and flavoids)
Promote lymphangiogenesis	Prostaglandins E2 (experimental), vascular endothelial growth factor-C (experimental)
To control aggravating factors for lymphatic dysfunction	
Care of lymphedema	Control of infection (aggressive use of antibiotics), avoidance of trauma, hot bath and other heat-producing treatment
Control risk factors	Control of diabetes, dyslipidemia and obesity
To decrease leakage of lymph	
Decrease stimulants of intestinal lymph flow	Low fat diet, octreotide
Decrease leakage of lymph by intervention	Compression therapy, antiplasmin (tranexamic acid); radiological intervention to obliterate the site of leak
To correct underlying condition	
Definitive therapy of cirrhosis	Liver transplantation

significant diuretic effects and, interestingly, without altering the intravascular volume, they can induce interstitial fluid clearance[74]. In addition to inducing glycosuria and natriuresis, these agents have beneficial effects on neurohormonal regulation and hepatorenal fibrosis[75]. Given that DM is also a risk factor for lymphatic dysfunction, SGLT2 inhibitors may be potentially helpful in diabetic patients with cirrhosis, with lymphatic dysfunction.

The contractile function of lymphatic vessels is very important for the reabsorption of extravascular fluid. While lymphatic vessels can modulate their contractile function in response to various neural, hormonal endothelial and humoral factors, no specific therapeutic agent has been approved for this purpose. In an animal study, intravenous adrenaline infusion has been found to increase the frequency of lymphatic contraction and lymph flow in efferent lymphatic vessels[76]. In an experimental study, significant improvements were observed in lymphatic vessels' contractility and lymphatic drainage, when treated with an eNOS inhibitor[9]. Inhibition of eNOS can, therefore, be a useful therapeutic target for lymphatic dysfunction in cirrhosis. However, any attempt to inhibit NO must take into account the fact that inhibition of intrahepatic NO may increase intrahepatic pressure, so that the resulting increased lymph production may negate its impact on improving the drainage of the lymph. As a result, to target only eNOS of extra-hepatic lymphatic vessels, a tissue-specific delivery strategy is required. Benzopyrones (flavonoids and coumarin) have been found to be effective in lymphatic edema treatment[77]. These drugs facilitate removal of accumulated interstitial proteins, by binding and causing phago-proteolysis by macrophages. However, there are some concerns regarding coumarin hepatoxicity, and there is a lack of evidence on the use of this medication in cirrhosis.

Low fat diets are currently recommended for the treatment of intestinal lymphangiectasia, as intestinal lymph flow is highly affected by oral fat intake[77]. For fat nutrition, medium-chain triglycerides supplementation should be used as they are directly absorbed through the portal venous system, without involvement of intestinal lacteal. Additionally, octreotide has been found helpful in patients with intestinal lymphangiectasia, by reducing splanchnic blood flow and the leakage of intestinal lymph[78]. Moreover, tranexamic acid has been found to cause significant reduction in protein loss in patients with intestinal lymphangiectasia, possibly due to the inhibition of tissue fibrinolytic activity that decreases the capillary permeability to protein[79]. Finally, transjugular intrahepatic porto-systemic shunt and liver transplantation have

been found to be effective therapy of PHT-induced protein-losing enteropathy, possibly caused by intestinal lymphangiectasia[80,81]. Regarding CA, a number of treatment options have been identified, including low-fat diet, medium-chain triglyceride, octreotide, total parenteral nutrition, embolization of leaking lymph vessel by radiological intervention, and surgical peritoneovenous shunt[39,82]. Nevertheless, there are no research reports comparing either of these treatment modalities. Initially, these patients should be managed with conservative approaches, and when they fail, repeated paracentesis should be used for symptomatic relief, and further invasive therapies may be considered.

It has been found that splenectomy effectively decreases portal pressure and corrects hypersplenism in patients with cirrhosis[83,84]. Since the progression of cirrhosis may result in a parallel increase in portal pressure, it would be worth investigating whether a reduction in portal pressure, after splenectomy, contributes to decreased lymph formation and decreased overload of the lymphatic system. However, in patients with advanced decompensated cirrhosis, where lymphatic dysfunction is maximal, splenectomy may not always be feasible[84]. Furthermore, caution is needed while contemplating albumin therapy in cirrhotic patients with lymphatic dysfunction. Henriksen *et al*[85] have recently found that in patients suffering from advanced cirrhosis, with diuretic-resistant ascites, the transport rate of albumin from plasma into the peritoneal cavity is highly elevated and exceeds the back transport rate of albumin into the plasma. Patients with advanced cirrhosis have accelerated trans-capillary escape rate of albumin, due to greater hydrostatic pressure and capillary permeability[86]. Hence, the molecules of albumin are more likely to extravasate rapidly into the interstitium. To recirculate the escaped albumin back to plasma, proper lymphatic functions are needed. However, in patients with advanced cirrhosis, the escaped albumin is less likely to be recirculated back into the plasma, due to deficient lymphatic function. This would not only fail to correct circulating hypovolemia, the reason for which it is given, but accumulation of albumin in the interstitium would facilitate development of reversed oncotic pressure gradient and extravascular movement of fluid, leading to worsening of edema and ascites[87]. Albumin, however, also has anti-inflammatory, immunomodulatory, and anti-oxidant properties[88]. It would be interesting to investigate these non-oncotic properties of albumin on lymphatic functions, as chronic inflammation and neurohormonal alterations play a significant role in lymphatic dysfunction of cirrhosis.

CONCLUSION

In conclusion, a greater understanding of the lymphatic vascular system has emerged over the last two decades, following the discovery of specific lymphatic endothelial markers and technical advances in lymphatic imaging. However, the role of lymphatic dysfunctions in the pathophysiology of advanced cirrhosis is still poorly understood. Given the major role of the lymphatic system in body fluid homeostasis, immunity, and metabolism, it is plausible to understand that in patients with cirrhosis, a defective lymphatic system may have several clinical consequences. This field is, therefore, largely open to new research. A better understanding of lymphatic pathophysiology in cirrhosis will significantly enhance our ability to manage such patients and design targeted therapy.

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