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## Considerations of elderly factors to manage the complication of liver cirrhosis in elderly patients

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### Abstract

The aging of the organ function causes sensitivity to the disease progression and need careful consideration for the medical treatment. With the increase of aging population, the opportunity to provide medical treatment for people in very old age is rapidly increasing therefore, the understanding of the various physiological changes of cellular function, size and function of organs are essential for the decision of therapeutic options. Among the various chronic conditions seen in elderly people, we have focused on liver cirrhosis, since despite specific therapeutic options for many of liver diseases including direct acting antivirals for hepatitis C virus, nucleoside analogs for hepatitis B, and corticosteroids for autoimmune hepatitis, there is currently no standard therapy to treat liver cirrhosis, which is the final stage of these liver diseases. Therefore, management of the various symptoms of liver cirrhosis is essential, and aging-related parameters must be considered in the decision making for therapeutic strategies and dosage of the available medicine. In this mini-review, we have summarized the therapeutic options to manage various symptoms of liver cirrhosis, carefully considering the physiological changes of various organs associated with aging.

**Key words:** Liver cirrhosis; Elderly patients; Quality of life; Aging

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**Core tip:** The increasing aging population is a worldwide issue and societies are facing various problems including long-term care for populations with a high prevalence of chronic conditions including the liver diseases. It is clear that management of hepatitis and cirrhosis is important to maintain hepatic function as well as activities of daily living and quality of life of liver disease patients. While various therapeutic options have been

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available including newly developed medicines and techniques, the aging-related parameters must be considered in the decision making for therapeutic strategies and dosage of the available medicine. However, as there is no information available to date in this field, to fill this gap, we have summarized the points that must be considered upon the management of liver cirrhosis in elderly patients. The information summarized will be helpful for physicians treating the elderly patients with the understanding of the aging-related changes of the body and organs.

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## INTRODUCTION

The increasing aging population is a worldwide issue<sup>[1]</sup>, and societies are facing various problems including long-term care for populations with a high prevalence of chronic conditions<sup>[2]</sup>. Previous studies have demonstrated that aging well requires activities of daily living<sup>[3]</sup> and appropriate care for elderly patients<sup>[4,5]</sup>. Therefore, these crucial factors need to be considered to understand the features of physiological changes when considering therapeutic options for chronic diseases<sup>[5-7]</sup> due to the impact of aging on cellular function, size and function of organs, and vascular cognitive impairment and dementia<sup>[8]</sup>.

Among the various chronic conditions seen in elderly people, we have focused on liver cirrhosis, as liver disease is a major issue as its symptoms vary and there are various considerations involved in the treatment of these patients. The general management guidelines have been published for the any age<sup>[9]</sup>, however, due to the physiological changes in the organs and body, special considerations are essential for the elderly patients.

Morphological and functional aging of the liver includes reduced liver weight and blood flow in the liver<sup>[10,11]</sup> due to decreased cardiac output<sup>[12]</sup>, decreased number of hepatocytes<sup>[13]</sup>, loss of metabolic function, and loss of detoxification in the liver. Ginsberg *et al.* reported that the total volume of cytochrome p450 decreases to 70% of its original level in people > 70 years old, resulting in decreased metabolism and detoxification in the liver<sup>[14]</sup>. These age-related changes in pharmacokinetics are correlated with a decrease in renal function<sup>[15]</sup> and should be considered when administering medicines to elderly patients<sup>[16]</sup>. It was reported that growth factor expression decreases with aging; therefore, elderly patients have difficulties tolerating liver injury<sup>[17,18]</sup>. The etiologies of liver diseases include viral hepatic diseases, autoimmune hepatic diseases, alcoholic liver diseases, and non-alcoholic steatohepatitis. Despite specific therapeutic options for many of these diseases including direct acting antivirals for hepatitis C virus, nucleoside analogs for hepatitis B, corticosteroids for autoimmune hepatitis, ursodeoxycholic acid for primary biliary cholangitis, stopping of alcohol for alcoholic hepatitis, control of body weight, vitamin E, pioglitazone, peroxisome proliferator-activator receptor agonists, farnesoid X receptor, and glucagon-like peptide for non-alcoholic steatohepatitis, there is currently no standard therapy to treat liver cirrhosis, which is the final stage of these liver diseases and may be complicated with hepatocellular carcinoma. Therefore, management of the various symptoms of liver cirrhosis is essential, and aging-related parameters must be considered in the decision making for therapeutic strategies and dosage of the available medicine. In this mini-review, we have summarized the therapeutic options to manage various symptoms of liver cirrhosis, carefully considering the physiological changes associated with aging.

Japan has the oldest population in the world and has one of the most advanced aging societies (<https://www.mhlw.go.jp/english/database/db-hw/lifetb16/index.html>), with 35.215 million (27.8%) people aged ≥ 65 years, and more than 10 million (7.9%) people over 80. One in 10 women in the country is over 81, and the number of people > 65 years is also growing (<https://www.stat.go.jp/english/data/kokusei/2015/summary.html>). Under these circumstances, defining the elderly as those aged ≥ 65 years does not seem appropriate, and the distinction of categories of old, old-old, and oldest

old is under discussion worldwide<sup>[1]</sup>. In Japan, there are 5.5 million elderly people aged  $\geq 85$  years, accounting for just under 5% of the total population (<https://www.mhlw.go.jp/english/database/db-hw/lifetb16/index.html>), and the opportunity to provide medical treatment for people in very old age is rapidly increasing.

It is clear that management of hepatitis and cirrhosis is important to maintain hepatic function as well as activities of daily living and quality of life (QoL) of patients. While direct acting antiviral drugs have made it possible to control chronic hepatitis C infection, it is important to understand the changing characteristics of diseases in the elderly, as well as continuously increasing lifestyle diseases and associated non-alcoholic steatohepatitis that leads to liver cirrhosis and liver cancer, in order to fully understand the disease concept and select the appropriate treatment methods. Furthermore, various complications of liver cirrhosis, such as liver cancer and gastrointestinal tract bleeding, affect QoL in the elderly. As there have been no literatures focusing on these problems, we have summarized the main points that must be considered in the management of current liver cirrhosis treatment in elderly patients.

## LIVER CIRRHOSIS IN ELDERLY PATIENTS

It is clear that the removal of etiological factors, if possible, is the most important part to prevent the progression of liver cirrhosis, particularly alcohol consumption, and control of viral hepatitis as stated in the guidelines<sup>[9]</sup>. It is also true for elderly patients while the careful consideration of renal function is essential using medications. And various complications in liver cirrhosis patients including ascites, hepatic encephalopathy, gastrointestinal tract bleeding from varices, and skin symptoms could be severer in elderly patients and the diagnosis and treatments of hepatocellular carcinoma, which is the final stage of the chronic liver disease need careful consideration as it affects the both renal and hepatic functions. In addition, sarcopenia is a condition, which the liver cirrhosis patients could be easily suffered and therefore, the management of the condition is necessary to continue the treatment. Therefore, with the increase of elderly populations, the understanding of the pathophysiological changes in this population is important for the physicians. For this point, we have reviewed the body changes with aging affecting these points.

Physiological changes that occur with age in the liver include a decrease in volume, blood flow, and metabolic capacity. Furthermore, liver injury by various factors such as viruses and drugs tends to be more severe (Table 1). While there are no liver diseases unique to elderly patients, it was reported that in non-alcoholic fatty liver disease, which continues to increase in the elderly, exacerbation and carcinogenesis decreased in patients aged  $\geq 70$  years<sup>[19]</sup>. However, in general, falls and related disorders are common in elderly patients not only by autonomic dysfunction, cognitive impairment, muscle abnormalities, and drug intake, but also with chronic liver diseases<sup>[20]</sup>, suggesting that therapeutic intervention is necessary for patients with chronic liver diseases and cirrhosis (Table 2). Treatments for each symptom are summarized below, and the complications and management of liver cirrhosis in elderly patients need careful considerations are summarized in Table 3.

### Ascites/edema

As a symptom of liver cirrhosis, accumulation of ascites above the physiological level can cause symptoms by compressing various organs, and edema can cause difficulty in walking and falls leading to the impairment of patients' social life and to the hospitalization. As it also related to the poor prognosis<sup>[9]</sup>, therapeutic intervention is necessary. Firstly, it should be diagnosed with the grading and count of neutrophil, culture, and measurement of protein concentration to exclude the possibility of bacterial peritonitis. The grading of the ascites is described as follows: Grade 1, mild ascites only detected by ultrasound examination; Grade 2, moderate ascites manifested by moderate symmetrical distension of abdomen; and Grade 3, large/gross ascites resulted in the abdominal distension. Based on the guidelines available<sup>[9]</sup>, a moderate sodium restriction (4.6-6.9 g of salt per day) is recommended for grade 2 ascites although the diets with a very low sodium content should be avoided to prevent the other complications<sup>[9]</sup>.

Especially for the elderly people tend to consume excessive amounts of salt, therefore, the mild restriction is effective. And as described in guidelines, the prolonged bed rest cannot be recommended, as for elderly patients, increased rest decreases muscle mass, treatment should be promptly being shifted to drug therapy where possible. For the medication, anti-mineralcorticoid, furosemide, torasemide,



**Table 1 Morphological and functional aging of the liver**

Reduced liver weight
Reduced blood flow to the liver
Loss of metabolic function
Loss of detoxification
Decreased growth factor expression

and albumin infusion can be considered with the careful follow of electrolytes. The patients with the first episode of grade 2 should be treated with anti-mineralcorticoid with stepwise increasing followed by the combination of furosemide for the patients with recurrent ascites. Torasemide can be given for the patients with poor response to furosemide, and baclofen and albumin can be considered especially for the patients with muscle cramps<sup>[9]</sup>. With these therapies, as rapid changes in circulation dynamics and electrolyte abnormalities may cause complications in elderly patients, it is important to carefully follow up observations such as body weight, waist circumference, pulse, and blood pressure, and verify treatment effects and adverse effects by blood biochemistry and urinalysis. In addition, it is not safe to continue increasing the dose of furosemide unnecessarily because elderly patients have relatively lower serum creatinine levels that reflect their decreased muscle mass, renal function tends to decline easily, and complications of acute renal failure reduce the survival rate in patients with decompensated cirrhosis<sup>[21]</sup>.

Tolvaptan, a selective vasopressin receptor inhibitor, was recently approved and is attracting attention as a diuretic<sup>[22,23]</sup>. It is believed to be useful even in hypoalbuminemia, and its use will be recommended for renal protection in elderly patients<sup>[15,23]</sup>. On the other hand, the use of these diuretics readily causes changes in electrolytes in addition to circulation dynamics; therefore, physicians need to consider the age-related changes in the cardiac system of elderly patients<sup>[24]</sup>. It is also advisable to decide the treatment methods under inpatient management based on blood and urine measurements and in conjunction with the appropriate specialists.

Other therapeutic options include large volume paracentesis, non-selective beta-blockers, and transjugular intrahepatic portosystemic shunts can be considered for the patients with refractory ascites<sup>[9]</sup>, however, as these intervention may affect the cardiovascular conditions, careful consideration should be given to the elderly patients. It is clear further clinical information and trials are necessary to develop the safer procedure of medication for the elderly patients.

### **Hepatic encephalopathy**

Hepatic encephalopathy associated with liver cirrhosis is a general term for neuropsychiatric symptoms mainly consisting of disturbance of consciousness, which appear due to severe acute or chronic liver failure. Therefore, in elderly patients, it is necessary to differentiate this from dementia and cerebrovascular diseases, which may prove difficult from examination findings and requires comprehensive evaluation including measurement of blood ammonia levels and the presence of a shunt. However, as the increased level of ammonia in the elderly patients can also be seen in the uremia due to renal failure, which can present like hepatic encephalopathy. It was recently proposed that astrocyte senescence may be related to persistent cognitive impairment in hepatic encephalopathy<sup>[25]</sup> and Soriano *et al*<sup>[26]</sup> reported the effectiveness of psychometric hepatic encephalopathy score which could help identifying the patients with a risk for falls. These findings highlight the importance of working closely with neurologists. Further, as the bowel movement abnormality is a typical trigger of hepatic encephalopathy that often occurs in elderly patients, the other chemicals including byproducts of bacterial metabolisms from the gut may play an important role in this condition which may be related to age-related changes in gut function and gut microbiota<sup>[27,28]</sup> leading to the gut-brain axis alterations. Optimization of bowel movement and suppression of ammonia production should be achieved using laxatives, branched-chain amino acids, and synthetic disaccharide lactulose. However, these chemicals especially lactulose should be administered to the elderly patients with caution as it could induce the diarrhea and dehydration in the cases. Rifaximin, a poorly absorbed antimicrobial agent, is used to treat hyperammonemia in hepatic encephalopathy<sup>[29,30]</sup>. Rifaximin has few systemic adverse effects and is considered to have little impact on renal function due to its poor absorbability; therefore, it may be a therapeutic option for the treatment of hepatic encephalopathy in elderly patients. Furthermore, recent reports showed that rifaximin reduced mortality<sup>[29]</sup> and did not affect glomerular filtration rate or levels of



**Table 2** Conditions to consider when determining therapeutic options

Change	Risk
Decreased cardiac function	Use of endoscopic therapy Use of beta-blockers Increase in blood pressure caused by molecular targeted agent
Decreased renal function	Use of contrast medium Use of interventional radiology for hepatocellular carcinoma
Decreased respiratory function	Rapid change in circulation dynamics Aspiration pneumonia
Ease of electrolyte abnormalities	Higher risk of using diuretics
Dementia	Difficulty in differentiating hepatic encephalopathy from dementia and cerebrovascular diseases
Aging of gut microbiota	Hepatic encephalopathy
Loss of bone density	Osteoporosis Risk of fall-related injury
Loss of muscle volume	Sarcopenia Risk of fall-related injury
Dry skin	Pruritus Hand-foot syndrome caused by molecular targeted agent

vasoactive hormones<sup>[30]</sup>. In addition, it was recently reported that rifaximin ameliorates hepatic encephalopathy and endotoxemia without changing gut microbiome diversity, implying its potential use in elderly patients<sup>[31]</sup>. On the other hand, it is important to be aware that oral administration compliance may be lowered due to frequent diarrhea that causes electrolyte abnormalities and skin troubles from frequent defecation. Treatment for encephalopathy involves an intravenous drip infusion of Fischer solution; however, careful management is necessary because this could easily increase cardiac stress and fluctuation of electrolytes in elderly patients.

### **Gastrointestinal bleeding**

Gastrointestinal bleeding occurs due to gastro-esophageal varices or to non-variceal lesions including portal hypertensive gastropathy and intestinopathy. The acute gastrointestinal bleeding may lead to the high risk of mortality in decompensated cirrhosis<sup>[9]</sup> and elderly patients, therefore the therapeutic intervention is essential. In addition, it should particularly be emphasized that patients with decompensated liver cirrhosis should have esophagogastroduodenoscopy performed to screen for the lesions and if the risky varices with red wale marking were found, therapeutic intervention should also be considered including the administration of non-selective beta-blocker. Patients with medium-sized varices should be treated with NSBB or endoscopic band ligation (EBL)<sup>[9]</sup>. It is however, obvious that the administration of beta-blocker should be more careful for the elderly patients as it may cause, arrhythmia and fluctuation of blood pressure which may lead to the cardiac failure. Therefore, referring to the guidelines for the patients with hypotension and intercurrent conditions for beta-blockers, elderly patients with high risk using beta-blockers can be considered for management by expeditious EBL. Focusing on the elderly patients, there are only a few reports on treatments of esophageal and gastric varices in elderly patients; however, this conventional method should be used as an emergency response to ruptures to control the bleeding and manage the general condition. The development of endoscopic techniques has highlighted the usefulness of endoscopic procedures such as EBL and injection sclerotherapy (EIS) in the management of esophageal varices<sup>[32]</sup>. Furthermore, recent developments in this field have facilitated this procedure and may contribute to improving the control of bleeding from varices<sup>[33]</sup>. However, due to the general risks in elderly patients during endoscopic examination<sup>[34]</sup>, careful preparation and monitoring of vital signs are necessary, even during elective EBL and EIS. Furthermore, treatment-related complications, such as aspiration pneumonia associated with sedation and delirium caused by inpatient management and fasting, required careful attention in elderly patients. Complications such as myocardial ischemia may often occur in elderly patients due to blood pressure fluctuations and tachycardia due to stress undergoing upper gastrointestinal endoscopic examination, and sedation may also cause a sudden drop in blood pressure<sup>[35]</sup>. Appropriate risk management involves carefully explaining these issues to family members prior to treatment, and taking account of old age in

**Table 3 The complications and management of liver cirrhosis in elderly patients need careful considerations**

Complications	Management (general)	Considerations should be given in elderly patients
Ascites	Sodium restrictions Anti-mineral corticoid Furosemide Torsemide Albumin infusion	Electrolyte abnormalities Changes in circulation dynamics Body weight Pulse and blood pressure Verification of blood biochemistry and urinalysis
Hepatic encephalopathy	Optimization of bowel movement Laxatives Branched-chain amino acids Synthetic disaccharide lactulose Rifaximin Intravenous drip infusion of Fischer solution	Diarrhea Frequent diarrhea that causes electrolyte abnormalities Skin troubles from frequent defecation Dehydration Cardiac stress and fluctuation of electrolytes
Gastrointestinal bleeding/varices	Non-selective beta-blockers	Arrhythmia Fluctuation of blood pressure Cardiac failure
Sarcopenia	Endoscopic therapy Risk of fall-related injury	Aspiration pneumonia Nutritional monitoring (serum markers including the albumin, cholesterol level) Muscle volume Administration of branched-chain amino acid preparations
Skin symptoms	Skin moisturisers Bile salts Rifampicin Anti-histamines	Likely to have dry skin Frequently suffer from wound infections and persistent skin inflammation Nalfurafine hydrochloride
Hepatocellular carcinoma	Use of phase contrast for the diagnosis Surgical therapy Transarterial chemotherapy Needle guided local therapy Molecular targeted therapies	Renal function Cardiac function Bone marrow function History of cerebral bleeding, Hypertension Renal function Cardiac function
Cirrhotic cardiomyopathy		Sarcopenia
Spontaneous bacterial peritonitis		
Hepato-renal syndrome		
Acute and chronic kidney injury		
Hyponatremia		Further clinical trials and information from retrospective studies are necessary

addition to disease condition, treatment methods, and general complications. In a report of treatments for esophageal and gastric varices in elderly patients aged  $\geq 85$  years, Nakamura *et al.* stated that preventive treatment should be limited to those at high risk of bleeding<sup>[36]</sup>. Endoscopically large hematocystic spots and white fibrin plugs are considered to be indications for preventive treatment. For other therapies, a balloon-occluded retrograde variceal sclerotherapy for gastric varices and a transjugular intrahepatic portosystemic, it is necessary to consider the risk of renal injury in elderly cases<sup>[15,21]</sup> due to sclerosant and contrast agents.

Careful use of beta-blockers could prevent rebleeding and even first bleeding of varices<sup>[37]</sup>; therefore, medication may also be considered for managing and preventing the progression of the varices in elderly cases. However, beta-blockers should be introduced with caution as they may increase the risk of bradycardia, development and exacerbation of heart failure, and syncope due to atrioventricular block in elderly patients with low cardiac function. Widespread use of capsule endoscopy may also be used to detect small-bowel varices; however, some studies have reported no

advantage of this technique compared with regular endoscopy<sup>[38]</sup>, and endoscopic examination and treatment is currently considered to be the optimal treatment regimen.

### **Sarcopenia**

It is presumed that protein synthesis and degradation are not well balanced in elderly patients<sup>[7]</sup>, which increases risk of fall-related injury. Loss of bone density and muscle volume, known as osteoporosis and sarcopenia, respectively, significantly affect the general condition of elderly patients<sup>[39-41]</sup>. Primary sarcopenia is a decrease in muscle mass associated with aging, while secondary sarcopenia is a decrease in muscle mass and muscle strength associated with underlying diseases such as liver diseases, malignant tumors, and inflammatory diseases<sup>[42]</sup>. It has long been known that skeletal muscle mass tends to be decreased in patients with chronic liver diseases and that complications such as falls and bone fractures are common<sup>[20]</sup>. Therefore, understanding the concept and pathophysiology of sarcopenia and focusing on its prevention are important in elderly patients with liver diseases. Patients with liver diseases are more likely to have sarcopenia compared with those of the same age due to the involvement of protein energy malnutrition, an imbalance between protein synthesis and degradation, increased levels of myostatin that inhibits myogenesis of skeletal muscles, and increased levels of inflammatory cytokines and reactive oxygen species<sup>[20]</sup>. In patients with liver cirrhosis, skeletal muscle atrophy progresses due to reduced glycogen storage in the liver that promotes amino acid and glycogen supply from skeletal muscles, including branched-chain amino acids<sup>[20]</sup>. Therefore, administration of branched-chain amino acid preparations, which have a strong anabolic action among essential amino acids, is considered useful to inhibit the progression of this disease state. In addition, the serum markers including the albumin, cholesterol level, and muscle volume are useful for nutritional monitoring.

### **Skin symptoms**

Patients with liver diseases exhibit jaundice as well as various other skin symptoms such as telangiectasia, purpura, and pruritus, among which pruritus interferes with sleep, causing deterioration of rhythm and QoL. In addition, chronic pruritus is a general and major skin problem in elderly patients which is caused by abnormalities of the epidermal barrier, immune system, and nervous system<sup>[43]</sup>. The causes of pruritus include both histaminergic (peripheral) and non-histaminergic (central nervous system) mechanisms. The latter is mainly due to cholestasis and scratches of the skin induce a peripheral type of itching and worsen the symptoms, forming a vicious cycle.

As elderly patients are likely to have dry skin, they frequently suffer from wound infections and persistent skin inflammation. Generally, skin moisturisers, bile salts, rifampicin, and anti-histamines have been used to reduce pruritus. In addition to these traditional medicines, nalfurafine hydrochloride has been approved in Japan although not approved in Europe currently. Nalfurafine hydrochloride, which was approved for its use for pruritus in liver diseases, is a  $\kappa$ -receptor agonist that suppresses itching via central mechanisms and is expected to control skin symptoms as extrahepatic lesions of patients with liver diseases<sup>[44]</sup>. Its clinical effects were confirmed in various chronic liver disease patients including those with primary biliary cholangitis, for which pruritus is the major symptom and could affect QoL<sup>[45]</sup>. We recently reported that administration of nalfurafine hydrochloride in 18 cases of liver disease patients with a median age of 69 years (45-82 years) led to alleviation of symptoms for long periods of time. During the observation period up of to 41 wk, there were no systemic adverse effects such as deterioration of liver function; however, four cases were excluded due to discontinued administration due to oral dryness, progression of anemia (the causal relationship with the drug administration was unknown), progression of liver disease, and financial reasons<sup>[45]</sup>. Control of extrahepatic lesions including the skin is an important issue in the treatment of cirrhosis from the viewpoint of QoL and maintaining the reserve capacity of the liver.

### **Hepatocellular carcinoma**

Surveillance of hepatocarcinogenesis in patients with liver cirrhosis involves screening by ultrasound and imaging findings using dynamic computed tomography and magnetic resonance imaging, particularly that using gadolinium-ethoxybenzyl diethylemetriaminepentaacetic acid. However, in elderly patients with decreased renal<sup>[15,21]</sup> and cardiac<sup>[24]</sup> function, more personalized regimens for individual patients are required, such as frequency of examination according to the situation of the patient based on previous medical history and performance status and estimation using measurements of tumor markers.

Regarding treatment, consideration of general conditions such as cardiac output,

respiratory function, renal function, and hepatic function is essential for elderly patients; however, if these parameters can tolerate invasion, surgical treatment including the transplantation should be considered<sup>[12,46,47]</sup>. While the liver itself ages in terms of size, blood flow<sup>[9,10]</sup>, and capacity for regeneration after hepatectomy<sup>[17,18]</sup>, the appropriate post-procedure management could lead to improved QoL and patient survival.

Understanding the disease stages, such as reserve capacity, extrahepatic metastasis, vascular invasion, tumor number, and tumor diameter is essential when determining treatment options. The options other than the surgical treatment include the traditional chemoembolization, transarterial chemotherapy, and needle guided local therapy of radiofrequency ablation, ethanol injection, microwave ablation, and thermal therapy. For these therapeutic options, the understanding of the physiological changes in the elderly patients especially for the cardiac function<sup>[24]</sup> and renal function<sup>[15,21]</sup> is essential as these organs are easily injured upon the chemotherapy and embolization.

Recently, molecular targeted therapies such as sorafenib, regorafenib, and lenvatinib have become available for the treatment of hepatocellular carcinoma. However, it is difficult to use these therapies in patients with poor hepatic reserve capacity or elderly patients with heart problems or a history of cerebral bleeding, as they could cause severe adverse events including hand-foot syndrome, hypertension, anorexia, or diarrhea. Therefore, maintaining a good reserve capacity, even in elderly patients, is necessary to increase the available treatment options. It is also important to preserve many treatment options in cases of liver cancer to optimize recovery after treatment and maintain QoL.

### Others

Other various complications including the bacterial infections, renal impairment, cardiopulmonary complications should also be paid attentions as they could cause the severe damage on the patients' conditions especially for the weaker cases such as elderly patients. The conditions may be introduced include spontaneous bacterial peritonitis, acute, chronic kidney injury, cirrhotic cardiomyopathy, hepato-renal syndrome, and hyponatremia. As a feature of elderly liver cirrhotic patients, it may also be related to the structural and functional changes of organs<sup>[15,21,24]</sup> and conditions of gut microbiota<sup>[27,28]</sup>. To avoid to be in the severe conditions, for the bacterial infections, empirical antibiotic therapy should be started with caring the drug induced hepato-, and renal injuries<sup>[9]</sup>. Therefore, for the elderly patients, careful follow up of laboratory examinations should be given. For renal impairment, early diagnosis of the acute and chronic kidney disease and acute kidney injury is essential, as even a mild increase of serum creatinine may underlie a marked decrease of glomerular filtration<sup>[9]</sup>. For cardiomyopathy, although the data relating cardiac function with survival is variable, however, as diastolic dysfunction and mortality seems to be related, cardiac functions should be carefully monitored in the elderly patients with potentially lower functions<sup>[24]</sup>.

The dysfunction of immune system caused by immunosenescence due to the toxic protein aggregation<sup>[48]</sup> and autophagy<sup>[49]</sup> leading to the organ dysfunction, carcinogenesis, and neurodegeneration can be the next target of anti-aging therapy in the hepatology field. Further basic researches are essential for the clarification of the association to develop the management strategies. For the patients with severe liver cirrhosis and liver cancers satisfying the criteria, the liver transplantation is one of the therapeutic options even for the elderly patients; however, the situation is different between the countries and correct understanding of the conditions of aging of the organs and physiological changes are essential considering the candidates for the transplantation (Figure 1).

## CONCLUSION

The increase in the number of elderly patients has prompted an increase in the opportunity to treat elderly patient and development of medical technology to treat these patients. In the treatment of liver cirrhosis associated with non-alcoholic fatty liver disease, which is predicted to increase in the future, circulatory dynamics, organ function, and immune function are deteriorated in elderly patients, and it is essential to recognize that careful observation of progress is required when implementing the same treatment as would be used in young patients. While assessing electrolyte balance and physiological function is important to avoid treatment-related complications, careful treatment tailored to the individual condition of each patients should be implemented, observing the general condition and preventing deteriorating

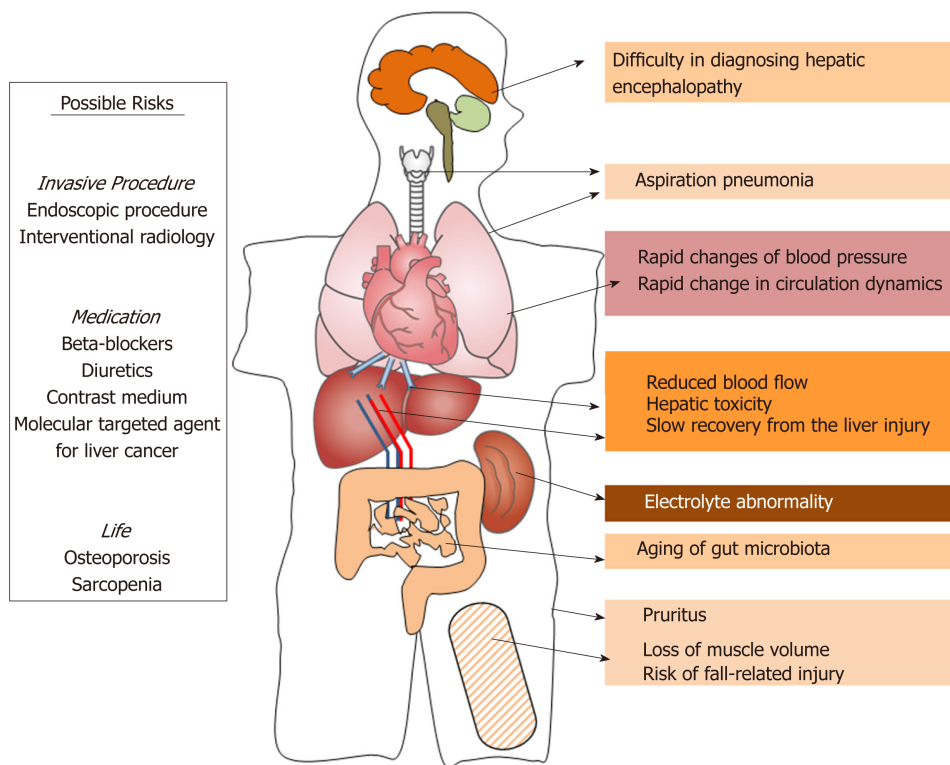


Figure 1 Summary of the changes of the body and possible risks treating the complication of the liver cirrhosis.

liver cirrhosis and maintaining the reserve capacity of the liver. To this end, treatment should be implemented by a medical team consisting of multiple specialists including nurses, pharmacists, nutritionists, and social workers in addition to doctors. As there have been no reviews focusing on these points, this mini-review should help to maintain QoL in patients, and further prolong life expectancy worldwide.

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