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*EDITORIAL*

# Systemic abnormalities in liver disease

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## Abstract

Systemic abnormalities often occur in patients with liver disease. In particular, cardiopulmonary or renal diseases accompanied by advanced liver disease can be serious and may determine the quality of life and prognosis of patients. Therefore, both hepatologists and non-hepatologists should pay attention to such abnormalities in the management of patients with liver diseases.



**Key words:** Systemic abnormality; Risk of surgery; Drug dosage; Liver disease

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## INTRODUCTION

Systemic abnormalities are often seen in liver disease, possibly because of the following characteristics of the liver as an organ[1]. (1) The liver is the key organ for the metabolism of protein, carbohydrate and fat. The liver produces many proteins, including coagulation factors. (2) The liver is a major organ for drug metabolism and the removal of hormones and other substances. (3) The liver is frequently invaded by various pathogens, and hepatitis virus infection causes not only serious liver diseases, but also exhibits extrahepatic manifestations through either immunological or non-immunological mechanisms. (4) The liver has a high blood flow supplied from the portal vein and the hepatic artery, leading to changes in portal, systemic or cardiopulmonary circulation in severe or advanced liver disease. (5) The liver is a major hematopoietic organ in the fetus and produces hematopoietic growth factors such as thrombopoietin[2].

In this review, in addition to systemic abnormalities often found in liver disease, dosage adjustment of drugs and risks of surgery in patients with liver disease are summarized. These factors should always be considered in the diagnosis or management of patients with liver disease.

## CARDIOPULMONARY SYSTEM IN LIVER DISEASES

Patients with advanced liver disease have mild hypoxemia attributable to an alteration in ventilation-perfusion matching[3]. When a patient with liver disease exhibits dyspnea in the absence of detectable primary cardiopulmonary disease, hepatopulmonary syndrome (HPS) or portopulmonary hypertension (PPHTN) should be considered[4]. Clinical features and diagnostic criteria for HPS and PPHTN are shown in Table 1.

### *Hepatopulmonary syndrome*

HPS is defined as the triad of liver disease, pulmonary gas exchange abnormalities leading to arterial deoxygenation and evidence of intrapulmonary vascular dilatation (IPVD)[4-7]. Although the mechanism for the development of HPS is complex and unclear, ventilation-perfusion mismatch and enhanced production of nitric oxide in the lung have been proposed as the predominant mechanisms[7].

A diagnosis of HPS requires demonstration of IPVD and an increased alveolar-arterial oxygen difference (AaDO2) (> 15 mmHg[8] or > 20 mmHg[6,9])

**Table 1 Difference between HPS and PPHTN modified from Rodríguez-Roisin *et al*[4]**

| | HPS | PPHTN |
|---|---|---|
| Prevalence | 11%-32% of patients with liver cirrhosis | 2% of patients with portal hypertension |
| Pathogenesis | Increased intrapulmonary shunting | Unknown |
| Intrapulmonary vascular dilatations | (+) | (-) |
| Pulmonary arterial hypertension | (-) | (+) |
| Symptom | Dyspnea, platypnea | Dyspnea on exertion, syncope, chest pain |
| Clinical manifestations | Cyanosis | No cyanosis |
| | Orthodeoxia | Accentuated pulmonary component of Ⅱs |
| | Spider nevi | Systolic murmur, edema |
| ECG findings | None | RVH, RBBB, right axis deviation |
| Arterial blood gas levels | Moderate-to-severe hypoxemia (< 60-80 mmHg) | No/mild hypoxemia |
| Chest radiography | Normal | Cardiomegaly, hilar enlargement |
| CEE | Positive finding; left atrial opacification for > 3-6 heart beats after right atrial opacification | Usually negative finding |
| $^{99m}$TcMAA shunting index | ⩾ 6% | < 6% |
| Pulmonary hemodynamics | Normal/low PVR | Elevated PVR<br>mPAP > 25 mmHg at rest or > 30 mmHg with exercise |
| OLT | Indicated in severe stages | Only indicated in mild-to-moderate stages |

HPS: Hepatopulmonary syndrome; PPHTN: Portopulmonary hypertension; RVH: Right ventricle hypertrophy; Ⅱs: Second heart sound; ECG: Electrocardiography; RBBB: Right bundle-branch block; $AaPO_2$: Alveolar arterial oxygen gradient; CEE: Contrast-enhanced echocardiography; $^{99m}$TcMAA: Technetium-99m-labelled macroaggregated albumin; PVR: Pulmonary vascular resistance; mPAP: Mean pulmonary artery pressure; OLT: Orthotopic liver transplantation.

on breathing of air at room temperature and pressure. In order to diagnose IPVD, trans-thoracic contrast-enhanced echocardiography[4], technetium-99m-labeled macroaggregated albumin scanning[10] and pulmonary arteriography are useful. HPS is reported to occur in 11%-32% of patients with chronic liver disease, mainly among those with liver cirrhosis[11-15]. HPS patients who experience severe hypoxemia at rest should receive continuous long-term low-flow oxygen therapy, although no data on its long-term effectiveness is available. Complete resolution of HPS following orthotopic liver transplantation (OLT) has been observed in > 80% of reported cases[16]. At present, OLT appears to be the most effective therapy for patients with HPS.

### Portopulmonary hypertension

PPHTN refers to pulmonary arterial hypertension that is associated with portal hypertension. PPHTN should be suspected in hypoxemic patients without pulmonary vascular dilatation[4,7,17]. The most common symptoms are dyspnea on exertion, syncope and chest pain. Although the cause of PPHTN is unknown, it has been reported that vasoactive substances could reach the pulmonary circulation at abnormally high concentrations owing to portosystemic shunts or decreased hepatic metabolism, leading to the pathological pulmonary vascular lesions exhibited in PPHTN[4,18]. Severe PPHTN is a contraindication of OLT, which can result in perioperative death from acute right ventricular failure[19,20]. Therefore, it is very important to distinguish between HPS and PPHTN in patients who are candidates for liver transplantation[4,7,21].

### Idiopathic pulmonary fibrosis

Chronic hepatitis C virus (HCV) infection has been associated with a variety of extrahepatic complications, and an association between idiopathic pulmonary fibrosis (IPF) and HCV infection has been reported[22]. Studies undertaken in Japan and Italy suggest that the incidence of anti-HCV antibody positivity in patients with IPF is significantly higher than in those without IPF[22,23]. Arase *et al*[24] reported that the cumulative rate of IPF development is 0.9% at 20 years after HCV infection, which is significantly higher than that after hepatitis B virus (HBV) infection.

### Coronary artery disease

It has been reported that atherosclerosis-related coronary artery disease (CAD) is less frequent in patients with liver cirrhosis than in controls matched with cirrhotic patients according to age, sex or cigarette smoking[25-28]. The prevalence of myocardial infarction was found to be significantly lower in cirrhotic patients than that in non-cirrhotic patients (1.7% *vs* 6.4%)[28]. The mechanisms of this protective effect on coronary atherosclerosis are unclear, but it may be associated with liver-related cholesterol metabolism and hematologic changes in cirrhotic patients. In contrast to the reported effect of cirrhosis on CAD, Alyan *et al*[29] demonstrated that HCV infection is an independent predictor of increased coronary atherosclerosis when patients with severe liver disease and cirrhosis are excluded from the analysis. It is thus suggested that the incidence of coronary atherosclerosis in patients with liver disease could be influenced by the severity of the liver disease and by hepatitis virus infection.

Recently, nonalcoholic steatohepatitis (NASH) has become well known as one of the leading causes of cirrhosis, and NASH is known to be strongly related to insulin resistance[30]. Kadayifci *et al*[31] reported that the prevalence of all CAD risk factors and metabolic syndrome was significantly higher in NASH-related cirrhotic patients than in cirrhotic patients with other etiologies.

### High cardiac output and increased circulatory volume

In patients with advanced cirrhosis, cardiac output and circulatory volume are increased because systemic vascular peripheral resistance is reduced and oxygen consumption is decreased by arteriovenous shunting[32,33]. However, it is also known that these circulatory changes rarely result in heart failure.

### Cardiomyopathy

Dilated and hypertrophic cardiomyopathies associated with HCV infection have been reported[34-36]. Although HCV has been isolated from the myocardium of patients with myocarditis and cardiomyopathy[37], there are conflicting reports on the incidence of HCV infection in these patients[38-41]. International epidemiological studies examining the incidence of HCV infection in patients with non-ischemic cardiomyopathy should be conducted. Some HLA haplotypes have been identified in a particular population of patients with HCV-associated cardiomyopathy, suggesting that genetic predisposition may be involved in the development of the disease[42]. Although the mechanisms of myocardial damage by HCV have not been characterized, HCV core protein may damage the myocardium either directly or indirectly through immunological mechanisms[43-45]. The treatment of chronic hepatitis C with interferon is sometimes contraindicated in patients with myocardial dysfunction[46]. Therefore, understanding and assessing cardiomyopathy as an extrahepatic manifestation of HCV infection is important.

## ENDOCRINE SYSTEM IN LIVER DISEASES

Because the liver is involved in the synthesis and metabolism of many kinds of hormones, various abnormalities of circulating hormone levels are found in patients with advanced liver disease. HCV infection is known to be linked to some endocrine disorders.

### Diabetes mellitus

Type-2 diabetes mellitus is present in more patients with chronic HCV infection than in those with HBV infection (21% and 12% in the United States, 23.6% and 9.4% in the United Kingdom, respectively)[47-50]. The association between HCV infection and diabetes mellitus is thought to be responsible for insulin resistance, which is shown to be directly induced by HCV core proteins[51]. Insulin resistance is also reported to be closely associated with the progression of fibrosis[52]. Diabetes mellitus is considered to increase the risk of the development of hepatocellular carcinoma and to increase mortality[53,54]. The monitoring of blood glucose should be performed on patients with chronic HCV infection, and in particular on those with advanced fibrosis, and appropriate treatment may be required when diabetes mellitus is diagnosed. The treatment of diabetes should be performed carefully owing to existing liver damage and hepatotoxicity of oral hypoglycemic drugs, particularly in cirrhotic patients. Oral hypoglycemic drugs, like biguanides which improve insulin resistance, for advanced liver diseases may be useful because insulin resistance is considered to be the main cause of glucose intolerance in patients with advanced liver disease[55]. $\alpha$-glucosidase inhibitors may also be effective, because they reduce the absorption of glucose from the intestine and improve postprandial hyperglycemia[56]. Insulin treatment should be carefully performed in cirrhotic patients, because insulin resistance is increased and the metabolism of insulin decreases as liver diseases advance[55].

### Thyroid disease

Thyroid disease often accompanies chronic HCV infection, particularly in elderly women (13% in patients with HCV infection)[56]. Anti-thyroid autoantibodies are also found in patients with chronic HCV infection (0% in men and 14.7% in women)[57]. Interferon-$\alpha$ therapy has been independently associated with the development of thyroid disorders[58,59]. Therefore, thyroid function or anti-thyroid autoantibodies should be evaluated before and during anti-viral treatment with interferon. Furthermore, thyroid cancer is also reported in patients with chronic HCV infection, particularly in those with thyroid autoimmunity[60,61].

### Nonalcoholic fatty liver disease (NAFLD)

NAFLD is the most common cause of chronic liver disease in the western world, and NAFLD is known to be accompanied by type-2 diabetes and hyperlipidemia in about 30% of patients[62]. In addition, endocrine disorders such as hypopituitarism or hypothyroidism have been associated with NAFLD (the prevalence is reported to be 2.3% and 15% in NAFLD cases, respectively), although the precise mechanism for this association is unknown[62-64]. Patients with NAFLD accompanied by hypopituitarism may be susceptible to central obesity, dyslipidemia and insulin resistance, leading to disease progression.

## HEMATOLOGICAL ABNORMALITIES IN LIVER DISEASES

### Erythrocyte abnormalities

About 50%-75% of patients with chronic liver disease develop anemia by various mechanisms[65] including hemodilution, hypersplenism, myelosuppression caused by viral infection or hemolysis (by either immunological or non-immunological mechanisms). Alcoholism has a close association with low dietary intake of folate and vitamin B12, and is known to inhibit the absorption of both nutrients from the gut leading to macrocytic anemia[66,67]. Alcoholic liver cirrhosis is associated with spur cell hemolytic anemia[68], although a recent report revealed that this can also be induced by NASH[69]. Other anemia-causing factors found in liver diseases include hemolysis in Wilson disease, alcoholic liver disease (Zieve syndrome), pregnancy (HELLP syndrome) and myelosuppression followed by viral hepatitis[65].

### *Leukocyte abnormalities*

Leukocytopenia, especially neutropenia, is often found in advanced chronic liver disease. Although splenic sequestration of leukocytes due to hypersplenism or serum hematopoietic progenitor inhibitory factors has been thought to be the main mechanism causing leukocytopenia[70,71], a shortened neutrophil lifespan caused by increased apoptosis may also be responsible[72]. Lymphocytopenia is also often found in patients with liver cirrhosis, possibly due to malnutrition[73]. In contrast, HCV infection can cause monoclonal proliferation of B lymphocytes leading to the induction of various autoimmune disorders[74], and an increased association with the development of non-Hodgkin's lymphoma has been reported[75]. Interestingly, the functional maturation of B lymphocytes has been proven to occur in the livers of patients with hepatitis C[76].

### *Platelet abnormalities*

Patients with chronic liver disease show a reduction in both number and function of platelets[65], and platelet count is shown to decrease with disease progression, especially in the case of HCV infection. The aspartate aminotransferase to platelet ratio index has recently been reported to be a useful predictor of the progression of liver fibrosis in HBV infection[77] and recurrent HCV infection after liver transplantation[78]. The mechanisms responsible for the decrease in platelet count in chronic liver disease include splenic platelet sequestration due to hypersplenism[79] and a reduced level or activity of thrombopoietin[80], which is a hematopoietic factor for thrombocytes produced by mature hepatocytes[2]. In chronic HCV infection, bone marrow suppression by HCV itself[81], or immune-mediated destruction of platelets through production of anti-platelet antibody or formation of immune complexes[81], has been reported to be the cause of thrombocytopenia. Because platelet-associated immunoglobulin (Ig) G is found in as many as 88% of hepatitis C patients[82], it is not unusual for hepatitis C patients with thrombocytopenia to be diagnosed with idiopathic thrombocytopenic purpura.

With regard to platelet function, deficiency in platelet aggregation[83] or platelet-vessel wall interaction[84] has been reported in patients with cirrhosis, resulting in a tendency to bleed profusely.

Recently, the platelet count to spleen diameter ratio has proven to be effective for ruling out the presence of esophageal varices[85]. Therefore, platelet count is an important parameter for assessing disease progression and the presence of complications in advanced liver disease.

### *Abnormal coagulation*

Because most coagulation factors are only synthesized in the liver[86], liver damage can easily lead to abnormal coagulation or a tendency to bleed profusely. Moreover, disseminated intravascular coagulation (DIC) is often seen in seriously ill patients with conditions including sepsis, malignancies and liver failure. Since both liver failure and DIC present with prolonged prothrombin time (PT), it is sometimes difficult to distinguish the two. It has been reported that a decrease in factor Ⅷ (not synthesized in the liver) and decreasing fibrinogen levels and platelet counts over time could indicate DIC accompanying liver failure rather than liver failure alone[87]. Levels of factor V are also reported to be useful for distinguishing the two conditions, since they are < 10% of normal levels in DIC and 10%-40% of normal levels in cirrhosis[87]. Vitamin K deficiency can also cause prolonged PT, but in contrast to liver failure and DIC, it leads to near normal levels of factor V[87].

In addition to prolonged PT, liver diseases are associated with hyperfibrinolysis[88], dysfibrinogenemia[89], endothelial dysfunction[90] and low count and/or decreased function of platelets[81,83], which all increase the risk of profuse bleeding in patients with advanced liver diseases.

## GASTROENTEROLOGICAL ABNORMALITIES IN LIVER DISEASES

The liver has a unique anatomical characteristic in that a large amount of blood is supplied directly to the organ from the intestines *via* the portal vein. Consequently, various complications of the gastrointestinal tract are seen in advanced liver diseases.

### *Portal hypertensive gastropathy and esophageal varices*

In a recent large-scale study, 37% of patients with HCV infection and advanced fibrosis in the liver were found to have portal hypertensive gastropathy (PHG)[91]. Biochemical markers of liver disease severity such as low serum albumin, high bilirubin or low platelet count may be correlated with the prevalence of PHG[91]. The presence of PHG may be predictive of esophageal varices[91], and low platelet count could be an indicator of the development of varices[92]. Some previous reports suggested that patients with primary biliary cirrhosis (PBC) may develop esophageal varices at a relatively early stage of the disease when other symptoms related to cirrhosis are not exhibited[93,94]. In recent studies, it has been recommended that PBC patients with a decreased platelet count (140 000-200 000/mm$^3$) should be screened for esophageal varices[95,96]. Nonselective beta-blockers may be effective for the treatment of PHG[92].

### *Pancreatic and biliary cancer*

In a recent report, it was found that past exposure to HBV may be associated with the development of pancreatic or biliary tract cancer[97,98]. Anti-HBc antibody tests were positive in 7.6% of pancreatic cancer cases and 3.2% of controls[97], and a 2.4-fold increased risk of extrahepatic bile duct cancer in chronic HBV infection was reported[98]. HBV DNA integration in these tissues may have a pathogenetic influence. However, it is debatable whether the risk of biliary or pancreatic cancers is increased by HCV infection[98,99].

## SKIN LESIONS IN LIVER DISEASES

Vascular spiders and palmar erythema are well known as skin lesions in patients with liver cirrhosis[100]. These skin lesions are thought to be related to excess estrogen, although the level of serum estrogen has been reported to be normal in patients with liver cirrhosis[100,101].

Chronic hepatitis infection is thought to be associated with various extrahepatic manifestations such as cutaneous lesions[102,103], including mixed cryoglobulinemia, porphyria cutanea tarda (PCT), lichen planus (LP), pruritus and urticaria. When these skin lesions are found, hepatitis virus infection should be considered.

### *Mixed cryoglobulinemia*

Mixed cryoglobulin contains both a polyclonal IgG and a monoclonal IgM rheumatoid factor, and about 80% of mixed cryoglobulinemia is associated with HCV infection. Diagnosis of mixed cryoglobulinemia is made by skin palpable purpura, low serum complement levels and detection of circulating cryoglobulin[104-107]. Palpable purpura is a major finding suggestive of vasculitis. It is reported that a reduction in HCV load by treatment with interferon[108-110] could decrease serum cryoglobulin levels and improve skin lesions.

### *Porphyria cutanea tarda*

PCT is caused by reduced activity of the enzyme uroporphyrinogen decarboxylase, and exposure to the sun can induce the development of skin erythema, vesicles and bullae[111]. A strong association between sporadic PCT and HCV infection has been reported, and a systematic review showed HCV infection in about 50% of patients with sporadic PCT[112]. Chronic HCV infection may impair porphyrin metabolism and cause sporadic PCT, but the mechanism for this is unclear.

### *Lichen planus*

Although LP is a relatively rare skin disorder, it can be seen in patients with chronic liver diseases, particularly those with HCV infection[113]. It has been reported that anti-HCV antibodies are present in 10%-40% of these patients, but the relationship between HCV infection and LP is still uncertain[113,114]. During interferon treatment for chronic HCV infection, the development or exacerbation of LP has been reported[115]. In contrast, the improvement of oral LP in HCV-infected patients treated with interferon has also been reported[116].

### *Gianotti-crosti syndrome (GCS)*

GCS is characterized by a symmetric papular eruption, which is mainly observed on the cheeks, buttocks and extensor surfaces of the forearms and legs[117]. GCS usually occurs in association with several viral infections, and acute HBV infection has been reported to be one of the most common causes of GCS in infants and young children[118,119]. It is, however, reported that GCS rarely occurs in adults[120].

## RENAL DISEASES ASSOCIATED WITH LIVER DISEASES

Renal diseases in patients with liver disease can be classified into two major categories by etiology. One is hepatitis virus-associated nephropathy including membranous nephropathy, membranoproliferative glomerulonephritis (MPGN) and mesangioproliferative glomerulonephritis[121-123]. The other is hepato-renal syndrome (HRS), which is a serious complication of advanced liver cirrhosis[124]. When a patient with chronic liver disease has proteinuria and/or hematuria, hepatitis virus-associated nephropathy should be considered (Figure 1)[122].

### *Hepatitis virus-associated nephropathy*

HBV infection may be directly associated with a variety of renal diseases, including membranous nephropathy and MPGN[121,125]. The diagnosis is based on an assessment of the status of HBV replication (HBeAg/Ab and HBV DNA levels)[126], laboratory findings (urinalysis and liver function test) and a kidney biopsy, although it is sometimes difficult to detect the deposition of viral antigens in the kidney by routine immunohistochemical analysis. HBV-associated nephrotic syndrome due to membranous nephropathy is not uncommon in children, and spontaneous recovery has been reported, which is often associated with seroconversion of HBeAg to anti-HBe[127]. In adults, on the other hand, spontaneous resolution is relatively uncommon and antiviral therapy may be effective[128].

HBV-related MPGN is characterized by the deposition of antigen-antibody complexes in the mesangium and subendothelial space. Antiviral therapy with interferon[129,130] or lamivudine[131] has been reported to induce remission in HBV-associated MPGN.

HCV infection is more often associated with renal diseases such as mixed cryoglobulinemia, MPGN and membranous nephropathy[122] than is HBV infection. The prevalence of MPGN in patients with HCV infection is higher than that of patients with HBV infection[123]. A high incidence of mixed cryoglobulinemia (35%-90%) has been reported in patients with HCV infection[132-134]. Mixed cryoglobulinemia is a systemic vasculitis and can frequently cause renal disease. MPGN associated with mixed cryoglobulinemia is the predominant type of glomerulonephritis, and the incidence of MPGN in patients with mixed cryoglobulinemia is approximately 30%[123,135,136]. The pathogenesis of HCV-related cryoglobulinemic MPGN is unknown, but the glomerular damage may be caused by the deposition of immune complexes of HCV, and IgG and IgM rheumatoid factors[135]. The clinical manifestations of renal diseases may include hematuria, nephritic range proteinuria and renal insufficiency. HCV-infected patients should be screened for proteinuria, hematuria, hypertension and renal function, as well as for cryoglobulinemia, complement and rheumatoid factors[124]. A kidney biopsy should be performed when

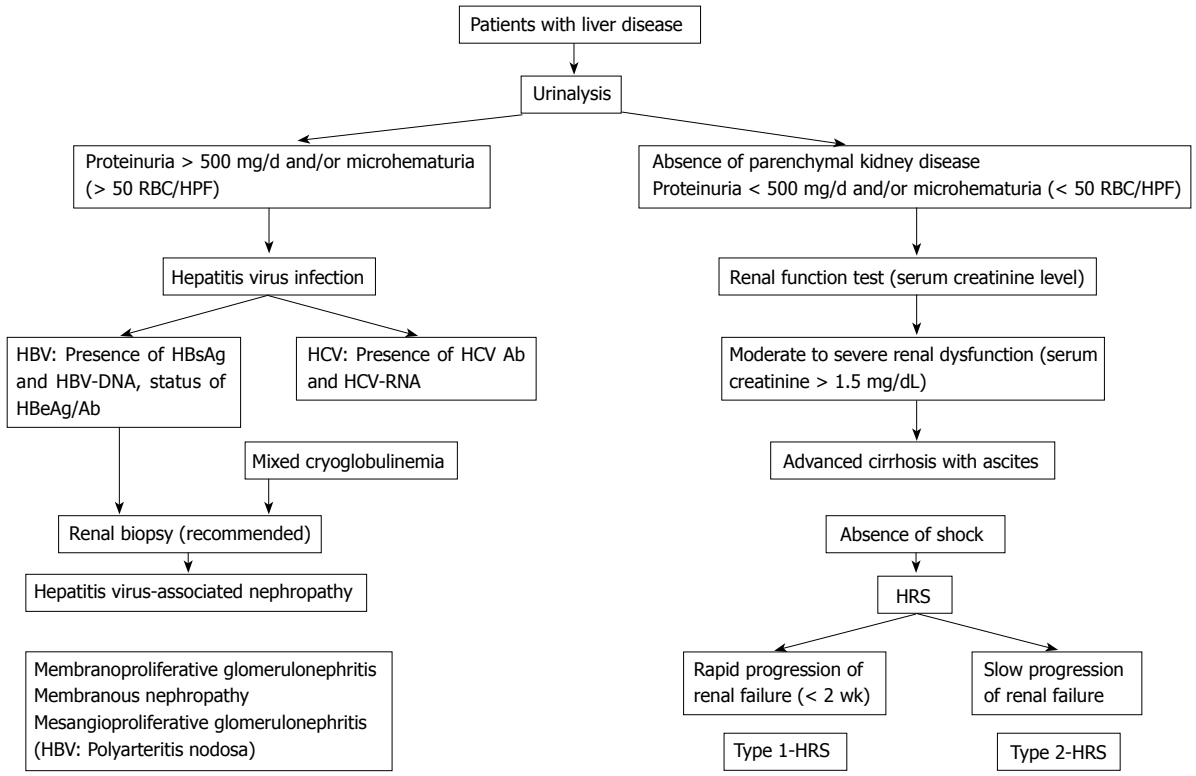


**Figure 1 Diagnostic strategy for renal disorders found in patients with liver disease.** RBC: Red blood cell; HPF: High power field; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

**Table 2 New diagnostic criteria for hepatorenal syndrome in cirrhosis[146]**

| |
|---|
| Cirrhosis with ascites |
| Serum creatinine > 133 μmol/L (1.5 mg/dL) |
| No improvement of serum creatinine level (decrease to ≤ 133 μmol/L) after at least 2 d with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/d |
| Absence of shock |
| No current or recent treatment with nephrotoxic drugs |
| Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/d, microhematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasonography |

significant proteinuria and/or impaired renal function are observed (Figure 1).

There have been many reports on beneficial responses of patients with HCV-induced renal disease to antiviral therapy with interferon[137-139]. Improvements in both serum cryoglobulin levels and plasma creatinine concentration have been reported in patients who exhibited undetectable levels of serum HCV RNA after interferon therapy. A recently developed combination therapy involving pegylated interferon and ribavirin improved the rate of sustained virologic clearance. It has also been reported that this combination regimen improved HCV-associated mixed cryoglobulinemia[140,141], although the efficacy of ribavirin is limited when renal insufficiency is complicated. Recently, the effectiveness of anti-CD20 chimeric monoclonal antibody (rituximab) in the treatment of cryoglobulinemic glomerulonephritis has been reported[142].

### HRS

HRS involves renal failure in patients with severe liver disease in the absence of any identifiable renal pathology[124,143,144]. The incidence of HRS in patients with cirrhosis and ascites is 18% and 39% after 1 and 5 years of follow-up, respectively[145]. New criteria for a diagnosis of HRS were reported by the International Ascites Club in 2007 (Table 2)[146]. HRS may be classified into two types: type-1 HRS is characterized by a rapid progression of renal failure (within 2 wk) with the mortality rate at 2 wk being about 80%. In contrast, the degree of renal failure is less severe in patients with type-2 HRS, and median survival is around 4-6 mo[144]. Type-1 HRS is often induced by a precipitating event, in particular spontaneous bacterial peritonitis[147]. HRS is related to renal vasoconstriction following a reduction of effective circulating volume due to peripheral vasodilation[148]. OLT is the ideal treatment for cirrhotic patients with HRS, but the survival rate after OLT is lower in those patients than in patients without HRS (60% *vs* 70%-80% at three years)[149]. The combined use of vasoconstrictors and albumin is one of the most useful options in treatment of patients

with HRS[150].

The diagnostic strategy for hepatitis virus-associated nephropathy and HRS is shown in Figure 1.

## NUTRITIONAL ABNORMALITIES IN LIVER DISEASES

Protein-energy malnutrition is often found in patients with liver cirrhosis, and is reported to have an incidence as high as 30%-90%[151]. Malnutrition has been reported to be associated with survival and surgical outcome in cirrhotic patients, and nutritional intervention such as supplementation of branched-chain amino acids (BCAA) could improve patient outcome[152,153]. Hypermetabolism, which is indicated by increased resting energy expenditure, has been reported to be associated with malnutrition, and the measurement of energy metabolism could thus be used to predict the prognosis of liver cirrhosis[154,155]. Hypermetabolism may be explained by increased α-adrenergic activity[156], and further investigation is required to determine whether the administration of beta-blockers is effective for the treatment of malnutrition in patients with liver cirrhosis.

The administration of BCAA has been reported to not only reduce malnutrition and improve energy metabolism, but also to improve the liver function and quality of life of patients with cirrhosis[157-159]. However, BCCA supplementation may be harmful because glucose intolerance can be exhibited by cirrhotic livers[55]. The administration of BCAA and α-glucosidase inhibitors in combination may improve the therapeutic effects[160].

In addition, hepatic glycogen stores decrease in patients with liver cirrhosis because of liver atrophy, leading to the development of a severe catabolic state after fasting. Late evening snacks including BCAA are recommended in order to avoid such problems during the night-time[158,159].

## NERVOUS SYSTEM IN LIVER DISEASES

Liver diseases frequently affect the nervous system.

### *Hepatic encephalopathy*

Hepatic encephalopathy (HE) is a major complication of chronic liver diseases with neuropsychiatric manifestations ranging from sleep disturbance to deep coma. The swelling of astrocytes and oxidative stress induced by ammonia, inflammatory cytokines, benzodiazepines and hyponatremia have been regarded as essential causes of HE[161]. Psychometric tests such as the number connection test may be effective for assessing HE[162], and neuropsychiatric function should be carefully evaluated in patients with chronic liver diseases including alcoholic liver disease and Wilson disease (WD). Minimal hepatic encephalopathy (MHE) occurs in 30%-80% of cirrhotic patients, which could be a serious problem because of the associated impaired quality of life[161,163]. For the management of patients with HE, removal of precipitating causes, such as gastrointestinal bleeding, excessive protein intake, hypokalemic alkalosis, infection, constipation (which can all increase blood ammonia levels), hypovolemia, hypoglycemia, hypoxia and the administration of sedatives, is important. Lactulose is the most effective therapy for HE so far, and has been reported to even be effective for patients with MHE[164].

### *Polyneuropathy and neurocognitive dysfunction*

Nervous system disorders such as neuropathy, fatigue and depression are often associated with chronic HCV infection, even without advanced cirrhosis[165-167]. Mixed cryoglobulinemia in HCV causes peripheral neuropathy as a moderate axonal sensory polyneuropathy[168], and chronic sensory polyneuropathies were found in 13% of HCV infected patients with cryoglobulinemia in southern Italy[169]. In addition, paresthesia has been found in about 20% of patients with chronic HCV infection, particularly among those with cryoglobulinemia[170,171]. The therapeutic response to antiviral treatment for neuropathies is generally unsatisfactory[172]. Furthermore, fatigue or depression is found in many patients with chronic HCV infection, with incidences of about 50% and 35%, respectively[173-175]. These neurocognitive dysfunctions have been characterized epidemiologically or pathophysiologically in chronic HCV infection[166,167,176], and may be explained by the neuroinvasion of HCV, because HCV has been reported to be found in monocytes/microglia of the central nervous system[176,177]. However, antiviral treatment with interferon, particularly interferon-α, is known to exacerbate depression[178].

### *Guillain-Barre syndrome*

Guillain-Barre syndrome accompanying hepatitis virus infection, which is primarily associated with HBV and rarely with HCV or hepatitis A virus, has also been reported[179-181]. Immune complexes have been found in the serum of these patients, which may be the cause of the development of the disease.

### *Autonomic and sensory nerve dysfunction*

Autonomic and sensory nerve dysfunction presenting as reduced 24 h heart rate variability and lower current perception threshold has also been reported to be common in patients with PBC, particularly those suffering a severe form of the disease for a long period[182]. Peripheral sensory nerve dysfunction may contribute to hyperesthesia, leading to the itching that is a characteristic symptom of PBC[182].

### *Wilson disease*

WD is an autosomal recessive inherited disorder of copper metabolism, resulting in excessive accumulation of copper in virtually all organs, especially in the liver. The clinical spectrum of liver diseases in WD is broad from asymptomatic with only mild biochemical

abnormalities, chronic active hepatitis, liver cirrhosis to fulminant hepatitis[183]. Copper accumulation is also remarkable in the cornea (Kayser-Fleischer rings) and brain in patients with WD. The patients show various neuropsychiatric symptoms such as dysarthria, dyspraxia, ataxia, a tremor-rigidity syndrome and psychoses, and progressive extrapyramidal neurological disorder is the typical sign of neurologic WD[183,184]. The initial neurological symptoms usually develop in mid-teenage years or in the twenties and are frequently misdiagnosed as behavioral problems associated with puberty[184].

## BONE DISEASE ASSOCIATED WITH LIVER DISEASES

Metabolic bone disease is a common complication of chronic liver disease, particularly in patients with end-stage liver disease due to cholestatic disorders such as PBC. It has been reported that osteoporosis occurs in approximately 20%-30% of patients with PBC[185,186], and older age and severity of the disease were the main risk factors for osteoporosis[187]. Moreover, there were 2-fold relative increases in the risk of bone fractures in patients with PBC compared with the general population[188]. Although the mechanisms responsible for osteoporosis in liver diseases are not well understood, cirrhotic patients show reduced osteoid thickness, osteoblast surfaces and bone formation rate, suggesting the presence of an osteoblast defect[189].

In post-liver transplantation populations, osteoporosis is known to be a major complication[190]. Several studies suggest that bone loss is remarkable within the first year after liver transplantation. The etiology is multifactorial, consisting of both preexisting low bone mineral density associated with underlying liver disease and post-transplantation factors[190]. High-dose corticosteroids and immunosuppressive agents such as cyclosporine A are thought to contribute to bone loss[191]. Although few prospective studies are available, vitamin D and calcium supplementation are generally recommended for those patients[192].

## ARTHROPATHY IN LIVER DISEASES

Arthralgia or arthritis is often seen in patients with liver diseases, and it is not rare that arthropathy may be the first presentation of the disease[193]. In acute viral hepatitis, especially in HBV infection, patients may show polyarthralgia or polyarthritis during the prodromal period and immune complex is thought to be responsible for the pathogenesis[194]. Similar arthropathies are seen in patients with chronic hepatitis C, autoimmune hepatitis, PBC, hemochromatosis or WD[193]. Arthralgia or arthritis is reported to be the most common extrahepatic manifestation in patients with hemochromatosis, autoimmune hepatitis and PBC. Polyarthralgia is also the most common symptom of mixed cryoglobulinemia[195], which often occurs secondary to HCV infection.

## SEXUAL DYSFUNCTION IN LIVER DISEASES

Erectile dysfunction (ED) is frequently problematic in patients with chronic liver diseases such as hemochromatosis[196], alcoholic liver disease[197] or liver transplant patients[198], leading to worsening of quality of life in those patients. Hypogonadism or protein malnutrition found in patients with advanced liver disease may induce ED[199,200]. Removal of causative factors such as iron or ethanol, or administration of testosterone may improve ED in such patients[197,198]. ED is also more frequent in patients with chronic HCV infection than in control subjects (39% *vs* 14%, respectively) probably due to a direct effect of HCV on neurovascular and hormonal systems (i.e. low testosterone levels)[201]. Successful antiviral treatment such as interferon plus ribavirin may improve such sexual dysfunction in patients with chronic HCV infection[202].

## DOSAGE ADJUSTMENT OF DRUGS IN LIVER DISEASES

The liver is the main organ of biotransformation and elimination of drugs. Thus, liver diseases could affect drug metabolism, resulting in abnormally high concentrations of drugs in the body.

Drug elimination by the liver may be determined mainly by first-pass effect, hepatic metabolism and biliary extraction. In addition, since the liver produces most plasma proteins, decreased liver function could influence the binding of drugs to plasma proteins, leading to changes in the distribution and elimination of such drugs[203].

The first-pass effect of each drug is variable and drugs with high first-pass effects are listed in Table 3[204]. The serum concentration of these drugs could easily be elevated by a decrease in hepatic blood flow (especially portal blood flow) or total hepatocyte mass. For drugs with a high first-pass effect, both initial dose and maintenance dose should be reduced in cirrhotic patients if the drug is orally administered.

Drug metabolism in the liver largely depends on the activity of the cytochrome P (CYP) 450 enzymes, which is known to be affected in different ways in patients with cirrhosis. The activities of CYP3A, 1A and 2C19 are reported to be substantially reduced, whereas those of CYP2D6, 2C9, 2B and 2E1 are also reduced, but to a lesser extent[205]. The severity of liver cirrhosis is estimated using Child-Pugh (C-P) classification, and patients with C-P grade A show mild to moderate deterioration of CYP activities. On the other hand, patients with C-P grade B or C are shown to have prominent reduction in CYP activity. Therefore, the doses of drugs mainly metabolized by CYP 3A, 1A or 2C19 in the liver may need to be reduced in these patients (Table 3)[206]. Moreover, cirrhotic patients often have impaired renal function, despite a normal serum

**Table 3 Drugs that may need to be administered at reduced doses in patients with liver cirrhosis[187]**

| Drugs with high first-pass effect | Drugs metabolized mainly by | | |
|---|---|---|---|
| | CYP 1A2 | CYP3A4 | CYP2C9 |
| Amitriptyline | Acetaminophen | Quinidine | Diclofenac |
| Bromocriptine | Caffeine | Amiodarone | Ibuprofen |
| Diltiazem | Mexiletine | Lidocaine | Mefenamic acid |
| Flumazenil | (R)-Warfarin | Midazolam | Tolbutamide |
| Fluorouracil | Imipramine | Diazepam | Phenytoin |
| Imipramine | Theophylline | Amitriptyline | Phenobarbital |
| Isosorbide dinitrate | Propranolol | Imipramine | (S)-Warfarin |
| Labetalol | Tamoxifen | Carbamazepine | Losartan |
| Lidocaine | Estradiol | (R)-Warfarin | Piroxicam |
| Morphine | | Erythromycin | |
| Nifedipine | | Clarithromycin | |
| Pentazocine | | | |
| Propranolol | | | |
| Verapamil | | | |

creatinine level[207]. Therefore, creatinine clearance should be measured or estimated in cirrhotic patients to determine the appropriate dose of drugs with predominant renal excretion.

## RISK OF SURGERY IN PATIENTS WITH LIVER DISEASES

Patients with liver diseases face relatively high risks during surgery, and these risks could be increased according to the progression of liver disease. A decrease in hepatic blood flow during anesthesia or surgery is thought to be mainly responsible for postoperative liver damage, and Cowan *et al*[208] reported that a major reduction in hepatic blood flow occurs after the induction of anesthesia, but not during or after surgery.

In acute viral hepatitis, as well as acute alcoholic hepatitis, the risk of surgery might be extremely high. Therefore, surgery should be avoided unless the situation is life-threatening[209]. In contrast, surgery on patients with chronic hepatitis can generally be considered safe[210], and there have been no deaths or complications reported in patients with chronic hepatitis C undergoing laparoscopic cholecystectomy[211]. In patients with liver cirrhosis, complications and mortality rates of surgery are high[212], especially if one or more of the following factors apply to the patient: elevated bilirubin, prolonged PT, ascites, decreased albumin, encephalopathy, portal hypertension, elevated creatinine concentration, intraoperative hypotension and emergent surgery[213]. The outcome of surgery also depends on the invasiveness or duration of the operation[214]. There are two scores for the assessment of the progression of liver cirrhosis: the model for end-stage liver disease (MELD) score and the C-P grade[215]. Both scores are useful for assessing the risk of surgery, and C-P classification was reported to be useful in stratifying the risk of death. Two studies showed that patients in class A had mortality rates of about 10%, those in grade B had mortality rates of around 30%, and those in grade C had mortality rates above 70%[216,217]. A recent study in Italy also reported similar mortality rates of surgery for patients with liver cirrhosis (C-P grade A; 7.1%, C-P grade B; 23%, C-P grade C; 84%)[218]. Teh *et al*[219] recently reported that MELD score, age and American Society of Anesthesiologists class are important predictors for the risk of postoperative mortality in patients with cirrhosis. Interestingly, they also reported that the risk was not associated with the type of surgery performed. For MELD, operation risks increase according to the score, and one report showed that a MELD score $\geqslant$ 14 or plasma hemoglobin levels < 10 g/dL were independent predictors of poor outcomes in patients undergoing abdominal surgery excluding hepatic surgery[220]. For patients undergoing laparoscopic cholecystectomy, a preoperative MELD score of 8 was linked to high morbidity, and was suggested as the cutoff value for avoiding the operation in patients with liver cirrhosis[221]. However, Schiff *et al*[222] recently reported that preoperative platelet levels and PT (international normalized ratio) are more important factors for the safety of cholecystectomy than C-P grade.

In patients undergoing cardiac surgery, the risk of mortality or complications may be high when a cardiopulmonary bypass is performed on patients with chronic liver disease[223]. In general, the mortality of cirrhotic patients with C-P grade A is low, but that of patients exhibiting C-P grade B for a long period and that of all patients with C-P grade C is high, especially when open heart surgery is performed. Therefore, open heart surgery should be avoided for patients with C-P grade C, and cardiac operation on the beating heart is recommended for patients with C-P grade B[224]. The results of another study led to the recommendation that patients with a C-P score > 7 avoid cardiac surgery involving cardiopulmonary bypass[225].

In summary, surgery should be avoided for patients with acute hepatitis. However, surgery is generally safe for patients with chronic hepatitis and cirrhotic patients with C-P grade A. The risks are elevated for cirrhotic patients with C-P grade B or C, or patients with a MELD score of $\geqslant$ 8, though this might vary according to the type of surgery performed. Other predictive factors for safe surgery are platelet count and PT, both of which are markers for the tendency to bleed profusely and for the progression of liver disease.

## CONCLUSION

Liver diseases often cause systemic abnormalities, and it is not uncommon that these complications, rather than the liver disease itself, determine the quality of life and prognosis of patients. Therefore, both hepatologists and non-hepatologists should always pay attention to the abnormalities caused by liver diseases, and should be concerned with their management in addition to the actual treatment of the liver disease itself.

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