



EDITORIAL

Critical issues in the diagnosis and treatment of liver cirrhosis

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Liver cirrhosis (LC) is a worldwide health problem that is associated with various complications and high mortality. Although, in the past four decades, the incidence of hepatitis B continuously decreased and a promising cure for hepatitis C was developed, LC remains a formidable challenge in clinical practice due to the ever-increasing incidences of alcoholic and non-alcoholic fatty liver diseases, autoimmune-related liver disease and drug-induced liver disease [1–3]. Our survey data showed a significant increase in the inpatient percentages of alcoholic LC and autoimmune LC, with concomitant decreases in viral hepatitis LC, which contributes to the overall increasing incidence of LC in China [4]. As a spacious country with a large population, a discrepancy exists in medical specialties and several topics should therefore receive more attention in the management of LC. To aid broad gastroenterologists and hepatologists as well as physicians, we identified the following critical issues in the diagnosis and treatment of LC.

Etiological overlap must receive attention in LC

Cirrhosis with two or more mixed etiologies should be carefully identified, despite high prevalences of hepatitis B virus (HBV) and hepatitis C virus (HCV) cirrhosis. We conducted a large-scale, cross-sectional study and found that the proportions of LC inpatients with HBV/HCV coinfection, HBV/alcohol coexistence and HBV/HCV/alcohol coexistence were 0.58%, 4.81% and 0.14%, respectively [4]. We also observed cases of HBV with fatty liver disease, cases of HBV with Wilson's disease and cases of HBV with hemochromatosis; cases with as many as four overlapping etiologies were not rare. HBV/HCV coinfection has been reported to be associated with higher rates of severe liver disease and with a

2- to 5-fold increased risk of hepatic decompensation [5], whereas multicenter studies have shown that alcohol abuse significantly increased long-term incidences of hepatocellular carcinoma (HCC) in HBV-related and HCV-related cirrhotic patients [6]. When considering the fact that multi-etiological cirrhosis may result in a worse prognosis, treatments that target all of the underlying etiologies are necessary to achieve favorable curative effects.

Hepatic and systemic inflammation should be evaluated for LC

Activated Kupffer cells and monocytes initially induce inflammatory reactions in LC, after which the levels of TNF- α and other pro-inflammatory cytokines increase, and natural killer cells, natural killer T cells and macrophages are activated to aggravate systemic inflammation [7]. Inflammatory evaluations have always been ignored when staging fibrosis, but the measurement of liver stiffness is emphasized. Instead, more attention should be focused on the focal inflammation of the liver parenchyma by liver biopsies and on systemic inflammation by the detection of serum or humoral inflammatory biomarkers. The control of the liver parenchyma and systemic inflammation has been observed to be able to slow the progression of decompensated LC or even reverse fibrosis to some extent [8].

Non-invasive measurements should be developed for LC diagnosis

Cirrhosis usually develops from chronic hepatitis and transitions into compensated cirrhosis, after which there is a

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progression into decompensated cirrhosis. The early diagnosis of LC is difficult due to the absence of overt symptoms, the patient's neglect and a lack of appropriate biomarkers. Traditional liver biopsies have been widely accepted as the gold standard for the evaluation of liver fibrosis and liver parenchymal inflammation. Although liver biopsies are very safe with the use of ultrasonic guidance, these biopsies are still invasive procedures. Non-invasive serum fibrosis biomarkers are highly applicable and easily repeatable, and newly developed markers, including procollagen type III N-terminal peptide (PIIINP) and YKL-40, have been demonstrated to be of great value in detecting advanced fibrosis or cirrhosis with both a sensitivity and specificity of approximately 80%. However, none of the fibrotic markers is liver-specific; thus, these markers may be influenced by non-hepatic inflammation. On the other hand, numbers of composite score models combining multiple serum markers have been developed to accurately evaluate the degree of liver fibrosis. As two of the most validated models, the AST-platelet ratio index and fibrosis-4 (FIB-4) index have shown comparable results in excluding advanced, but not moderate, fibrosis [9]. Liver-specific markers and new score models are being exploited and show promise for more specific diagnoses in the near future. With regard to imaging methods for the diagnosis of liver fibrosis, routine ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) is not accurate enough for early diagnoses, whereas FibroScan and FibroTouch tests have certain reference values but are subject to inter-observer variation. Increasing amounts of data have shown that real-time shear wave elastography and magnetic resonance elastography are the most promising and efficient evaluations for the early diagnosis of LC with respect to multi-sectional inspection, objectivity, sensitivity for early fibrosis and the ability to examine the entire liver [10, 11]. Recent studies have observed that the ultrasound measurements of the stiffnesses of the liver or spleen are promising tools for detecting clinically significant portal hypertension and for excluding severe portal hypertension, although these methods were limited by heterogeneous values and an inapplicability in hepatic decompensation [12].

LC stage and liver function classification must be accurately estimated

The Child-Pugh-Turcotte classification system is still of clinical value and has long been regarded as the most convenient measurement for LC clinical staging, although the score may be influenced by inter-observer variance. The Model for End-Stage Liver Disease (MELD) score incorporates serum creatinine levels, serum bilirubin levels and the international normalized ratio (INR); thus, it is likely to be more accurate in evaluating the disease severity and in predicting prognoses. Furthermore, the MELD score is crucial in assessing the need for liver transplantations. The Metavir score system has been widely used for the staging of liver fibrosis, with scores ranging from F0 (no fibrosis) to F4 (cirrhosis), and ultrasound elastography has been increasingly accepted as a non-invasive and valuable approach for distinguishing patients with no or minimal fibrosis (F0/F1), as well as those with severe fibrosis or cirrhosis (F3/F4) [13].

Measures of hepatic venous pressure gradient (HVPG) should be recommended

HVPG is the best indicator for portal pressure. A HVPG ≥ 10 mmHg is associated with an increased risk of developing gastroesophageal

varices (GEV), whereas a HVPG ≥ 12 mmHg can identify a risk of bleeding and a HVPG ≥ 20 mmHg can predict the failure to control acute variceal bleeding, early rebleeding and bleeding-related deaths [14]. Hepatic vein catheterization with the use of a balloon-tipped catheter is currently the preferred technique in determining HVPG, which is highly recommended in qualified liver care centers. Given that HVPG measurements are invasive, costly and difficult in terms of obtaining real-time continuous surveillance, the Baveno VI guideline recommended a combination of liver stiffness that is less than 20 kPa in transient elastography and a peripheral platelet count that is higher than 150,000/ μ L to preclude the risk of a variceal hemorrhage [15]. Non-invasive HVPG measurements have been introduced; however, these measurements are pending until they can be proved to be effective in clinical practice and practically accurate, non-invasive approaches for HVPG measurements are highly expected.

Etiological treatment is vital

The etiological treatment of LC is critical, although it is usually ignored in the decompensated stage. Patients should be initially treated with a direct-acting antiviral (DAA) treatment as soon as HCV is identified. Hepatitis B cirrhosis is the predominant etiology in China and mounting data have shown that the early use of antiviral therapy may alleviate cirrhotic progression and reduce the risk of HCC [16]. Moreover, both the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) guidelines advocate that the patient should undergo antiviral therapy regardless of the levels of HBV-DNA and alanine aminotransferase, as well as the HBeAg status, when the patient has a positive result for HBV-DNA test [17, 18]. Alcohol cessation is the key issue for alcoholic LC treatment, whereas psychological interventions may be essential for alcohol addicts. Adequate physical exercise, the treatment of comorbid metabolic syndrome and an early referral to a dietician are helpful for patients with non-alcoholic fatty liver disease that is related to LC. With regard to AIH-related LC, physicians should optimize a therapy of steroids and immunosuppressants for the etiological treatment.

Maintenance of a sufficient blood supply of the portal vein

Given that the liver is an organ with a dual blood supply from the portal vein and the hepatic artery, the maintenance of sufficient perfusion is significant for ensuring the nourishment of this organ. Injuries to the portal vein, which may occur as a result of devascularization surgery, a surgical portosystemic shunt, a splenectomy, an endoscopic tissue glue injection or radio-interventional therapy, should be carefully avoided to reduce the possibility of a portal vein thrombosis (PVT). PVTs have long been a difficult clinical problem. Although warfarin has been a traditionally efficient treatment, the dose titration highly relies on repeated INR tests and may result in poor patient compliance [19]. New generations of oral anticoagulants, including rivaroxaban and dabigatran, have been proved to be effective, but they are also expensive. Failed cases that result from the use of anticoagulation therapy should consider the use of interventional portal vein recanalization techniques, including balloon angioplasty, stent placement, thrombectomy and thrombolysis [20].

Strengthening nutritional support therapy

Malnutrition occurs in up to 80% of overall cirrhotic patients and in nearly all decompensated patients [21]. This complication comprises protein malnutrition, energy malnutrition and mixed malnutrition, which are highly related to insufficient intake, absorption dysfunction and a high catabolic status. Impaired nutritional situations will induce ascites and infection, will aggravate variceal bleeding and will increase mortality; therefore, cirrhotic patients should adhere to an adequate diet of sufficient calories and protein. Food supplements involving essential amino acids are able to promote protein synthesis and improve the outcomes of malnutrition, whereas proper physical exercise also helps in energy intake and nutritional rehabilitation [22].

Endoscopic sequential therapy is able to eradicate gastroesophageal varices and reduce the death rate of rebleeding

As the most lethal complication of LC, gastroesophageal variceal bleeding (GEVB) occurs in 0%–40% of compensated cirrhosis and in 70%–80% of decompensated cirrhosis. Moreover, 20%–50% of patients will rebleed after the first bleeding episode and this proportion of patients is associated with 20% of 6-week mortality and 15% of in-hospital mortality [23]. When considering that LC patients also have intestinal variceal bleeding risks due to portal hypertension, early endoscopy screening should be advocated for the evaluation of the bleeding risk of not only GEV, but also of the small intestinal and colorectal varices. The endoscopic management of GEV has been proven to be effective and has been widely used in primary hospitals. However, it is common in China that patients will attend one or two treatment sessions for acute bleeding but will not attend subsequent follow-up sessions until recurrent bleeding occurs. Our preliminary data from a cirrhotic cohort showed that, after variceal eradication by endoscopic sequential therapy that combined band ligation, tissue glue injection and sclerotherapy, the 5-year occurrence rate of rebleeding and all-cause death rate were reduced to 9.6% and 3.4%, respectively (data not shown). Furthermore, endoscopic treatments should be repeated and sequenced until complete variceal eradication occurs, after which the patients should receive follow-ups with regular 6- to 12-month intervals.

Early diagnosis and early treatment are pivotal for LC-supervised HCC

Primary liver cancer contributes to 4.7% of global malignancies and 8.2% of cancer mortalities. Cancer statistics in China showed that the incidence of liver cancer ranks third in men and sixth in women, and the mortality ranks third in men and fourth in women [24]. Early interventions with DAA drugs may prevent cancerization and may prolong the cancer-free survival period. The early diagnosis rate of HCC is still low, which is partially due to asymptomatic features and neglect by the patients. Ultrasound screening is still the first choice that is applicable for primary healthcare institutions, whereas CT/MRI is more accurate but costly. Biomarkers represent a promising direction. However, even though alpha-fetoprotein (AFP) is a classical marker, its sensitivity and specificity are not high. We recently identified a novel biomarker (Lnc-PCDH9-13: 1) that has >80% of sensitivity and >98% of specificity for early HCC diagnoses, and the biomarker is detectable in both serum and saliva. Therefore, the use of this biomarker is more convenient for clinic follow-

ups and community surveys than traditional AFP detection [25]. For every LC patient, ultrasound should be administered every 6 months and a subsequent CT/MRI is necessary when a suspicious carcinoma is discovered. Regular surveillance will promote early detection and may benefit subsequent treatments.

Standardized follow-up and management, as well as health education, are important for LC patients

Regular follow-ups involving clinic visits and laboratory tests are able to monitor disease progression and modulate the timely use of therapies. Patients should undergo complete blood counts, liver biochemistry tests, electrolyte tests, coagulation measurements, AFP measurements and tests for viral loads of HBV and/or HCV every 3 months. Nutritional evaluation should also be carried out every 3 months to investigate the risk of hypoalbuminemia, as well as to treat malnourishment. Ultrasonic examination should be performed every 6 months to examine the liver parenchyma and to detect changes in the portal vein, in order for occurrences of HCC and PVT to be quickly identified. Furthermore, an annual CT or MRI is necessary for the surveillance of cirrhosis progression and HCC. Regular endoscopic examinations of the upper and lower gastrointestinal tract are recommended to investigate the variceal situation and bleeding risk. The medical center should establish a comprehensive follow-up database to systematically manage patients. In addition, health education for the patients themselves, as well as their family members, is also important to guide rehabilitation, to improve the quality of life and to increase the survival of LC patients.

Integrating palliative care into routine clinical management is a contentious issue for LC

End-stage liver disease (ESLD), encompassing advanced liver disease, liver failure and decompensated cirrhosis, is associated with a high mortality and a high degree of symptom burden and it affects approximately 6 million people in the USA [26]. Palliative care (PC) as an approach for improving the quality of life of patients and families who are facing a life-limiting illness has become an emerging debated issue in the field of ESLD treatment. Increasing amounts of data have shown beneficial effects of PC, including the alleviation of patient-reported symptoms, a reduction in the overall cost of care and even prolonged survival. However, PC consultation is still underused in cirrhotic patients and only approximately 5% of hospitalized patients with decompensated cirrhosis received this kind of service [27]. The broader implementation of PC is hindered by a shortage of qualified providers, a lack of public reimbursement, the misconceptions of patients and healthcare providers, and a dearth of relevant research. Access to PC services is mainly limited to Western countries and little is known about the clinical application of PC in developing countries, including China. Better organization and financing of PC services are greatly needed and more data focusing on how to best integrate PC into the ESLD workflow are highly needed in the future.

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Conflict of interest

The authors declare that they have no conflicts of interest.

References

- Allen AM, Kim WR, Moriarty JP et al. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. *Hepatology* 2016;**64**:2165–72.
- Tapper EB, Parikh ND. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: observational study. *BMJ* 2018;**362**:k2817.
- GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2018;**392**:1015–35.
- Wang X, Lin SX, Tao J et al. Study of liver cirrhosis over ten consecutive years in Southern China. *World J Gastroenterol* 2014;**20**:13546–55.
- Mavilia MG, Wu GY. HBV-HCV coinfection: viral interactions, management, and viral reactivation. *J Clin Transl Hepatol* 2018;**6**:296–305.
- Lin CW, Lin CC, Mo LR et al. Heavy alcohol consumption increases the incidence of hepatocellular carcinoma in hepatitis B virus-related cirrhosis. *J Hepatol* 2013;**58**:730–5.
- Noor MT, Manoria P. Immune dysfunction in cirrhosis. *J Clin Transl Hepatol* 2017;**5**:50–8.
- Bernardi M, Caraceni P. Novel perspectives in the management of decompensated cirrhosis. *Nat Rev Gastroenterol Hepatol* 2018;**15**:753–64.
- Lurie Y, Webb M, Cytter-Kuint R et al. Non-invasive diagnosis of liver fibrosis and cirrhosis. *World J Gastroenterol* 2015;**21**:11567–83.
- Wang K, Lu X, Zhou H et al. Deep learning radiomics of shear wave elastography significantly improved diagnostic performance for assessing liver fibrosis in chronic hepatitis B: a prospective multicentre study. *Gut* 2019;**68**:729–41.
- Procopet B, Berzigotti A. Diagnosis of cirrhosis and portal hypertension: imaging, non-invasive markers of fibrosis and liver biopsy. *Gastroenterol Rep (Oxf)* 2017;**5**:79–89.
- Song J, Huang J, Huang H et al. Performance of spleen stiffness measurement in prediction of clinical significant portal hypertension: a meta-analysis. *Clin Res Hepatol Gastroenterol* 2018;**42**:216–26.
- Li C, Li R, Zhang W. Progress in non-invasive detection of liver fibrosis. *Cancer Biol Med* 2018;**15**:124–36.
- Garcia-Tsao G, Abraldes JG, Berzigotti A et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017;**65**:310–35.
- de Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015;**63**:743–52.
- Marcellin P, Gane E, Buti M et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet* 2013;**381**:468–75.
- Terrault NA, Lok ASF, McMahon BJ et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;**67**:1560–99.
- European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017;**67**:370–98.
- Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. *Vascu Pharmacol* 2019;**113**:86–91.
- Priyanka P, Kupec JT, Krafft M et al. Newer oral anticoagulants in the treatment of acute portal vein thrombosis in patients with and without cirrhosis. *Int J Hepatol* 2018;**2018**:8432781.
- European Association for the Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. *J Hepatol* 2019;**70**:172–93.
- Moctezuma-Velazquez C, Garcia-Juarez I, Soto-Solis R et al. Nutritional assessment and treatment of patients with liver cirrhosis. *Nutrition* 2013;**29**:1279–85.
- Cabrera L, Tandon P, Abraldes JG. An update on the management of acute esophageal variceal bleeding. *Gastroenterol Hepatol* 2017;**40**:34–40.
- Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**:394–424.
- Xie Z, Zhou F, Yang Y et al. Lnc-PCDH9-13:1 is a hypersensitive and specific biomarker for early hepatocellular carcinoma. *EBioMedicine* 2018;**33**:57–67.
- Potosek J, Curry M, Buss M et al. Integration of palliative care in end-stage liver disease and liver transplantation. *J Palliat Med* 2014;**17**:1271–7.
- Rush B, Walley KR, Celi LA et al. Palliative care access for hospitalized patients with end-stage liver disease across the United States. *Hepatology* 2017;**66**:1585–91.