

106564_Auto_Edited_005118.docx

WORD COUNT

4643

TIME SUBMITTED

14-MAY-2025 05:56PM

PAPER ID

116228659

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 106564

Manuscript Type: MINIREVIEWS

Pay attention to ¹ the value of liver regeneration in the re-compensation of decompensated cirrhosis

Wang JY, *et al.* Liver regeneration in cirrhosis re-compensation

Jiaying Wang, Bo Yi, Chunyan Li, Huaqian Xu, Shan-hong Tang

Abstract

Conventional wisdom holds that progression from compensated cirrhosis to decompensated cirrhosis is a point of no return in the natural history of the disease. However, in recent years, more and more clinical evidence suggests that liver cirrhosis can achieve re-compensation, that is, after effective etiological treatment and complication management, the liver function of partially decompensated patients with cirrhosis has improved and gradually stabilized, and decompensation is no longer occurring for a long time. Liver regeneration, as one of the powerful intrinsic abilities of the liver, is the key to the restoration of the structure and complex physiological functions of the damaged liver. Studies have shown that the restoration of liver regeneration in patients with cirrhosis can promote the occurrence of re-compensation, thereby improving the prognosis of patients. At the same time, monitoring liver regeneration indicators helps us assess patients' re-compensation potential for early selection of appropriate treatment options. Insufficient attention has been paid to the role of liver regeneration in the course of liver cirrhosis. Therefore, this article aims to review the value of liver regeneration in the re-compensation of decompensated cirrhosis.

Key Words: Liver regeneration; Decompensated cirrhosis; Re-compensation; Prognosis; a-fetoprotein

Wang J, Yi B, Li C, Xu H, Tang SH. Pay attention to ¹the value of liver regeneration in the re-compensation of decompensated cirrhosis. *World J Gastroenterol* 2025; In press

Core Tip: Regeneration is key to the restoration of the structure and complex physiological functions of the damaged liver. When liver regeneration is stagnant, the deterioration of liver function cannot be reversed. Studies have shown that the restoration of liver regeneration in patients with cirrhosis can promote the occurrence of re-compensation, thereby improving the prognosis of patients. Therefore, we should pay attention to ¹the value of liver regeneration in the re-compensation of decompensated patients with cirrhosis.

INTRODUCTION

Cirrhosis is a wound-healing response (fibrogenesis) to liver injury caused by various causes. As the disease progresses, the typical structure of the liver is gradually replaced by regenerating nodules[1,2]. Clinically, the progression of cirrhosis is usually silent until the portal venous pressure increases and the liver function deteriorates into a clinical phenotype. At this time, complications such as ascites, variceal hemorrhage, and hepatic encephalopathy may occur, marking the occurrence of liver decompensation. The prognosis of decompensated cirrhosis is poor, with ²a median survival of only 2 to 3 years in patients with decompensated cirrhosis compared with the median survival of patients with compensated cirrhosis of more than 12 years[3].

Therefore, the occurrence of decompensation is an important watershed in the clinical course of liver cirrhosis, which means that the risk of further decompensation events and mortality is significantly increased. Fortunately, studies have shown that after effective etiological treatment, the liver function and tissue structure of some patients with decompensated cirrhosis can gradually return to the compensated phase and

remain stable for a long time. In a prospective cohort study by Premkumar *et al* [4], 1152 patients with hepatitis C virus (HCV)-associated decompensated cirrhosis, 284 (24.7%) achieved re-compensation after treatment with effective direct-acting antivirals; In a multicenter prospective study by Wang *et al*[5], 56.2%(159/283) of patients with hepatitis B virus (HBV)-associated cirrhosis decompensated achieved re-compensation after 120 wk of antiviral therapy; An observational study by Hofer *et al* [6] on decompensated alcohol-related cirrhosis showed that persistent abstinence resulted in hepatic re-compensation in 18.1% (37/204) of patients. This re-compensation breaks the traditional concept that liver cirrhosis is irreversible and is of great significance for improving the prognosis of patients. However, the current high-quality research and clinical data on liver re-compensation are still limited, and the re-compensation of decompensated cirrhosis of some etiologies has not been fully proven. In addition, not all patients can achieve re-compensation after effective treatment of the etiology, which requires us to consider the possible factors that affect the occurrence of re-compensation and adopt an individualized treatment strategy according to the re-compensation situation of different patients. For patients with high re-compensation potential, patients should be encouraged to continue active etiological treatment, anti-inflammatory, anti-fibrotic therapy, and prevention and treatment of complications if necessary, to promote hepatocyte repair and regeneration, to improve the quality of life of patients; For those who are unlikely to achieve re-compensation, they should be prepared for liver transplantation in the long term. The liver has a high regenerative potential, key to hepatic homeostasis and maintaining liver function and structure after liver injury. The lack of liver tissue regeneration ability based on cirrhosis may be one of the factors leading to the difficulty of recovery or even continuous deterioration of liver function in decompensated patients, thus affecting the re-compensation and long-term prognosis of patients. At present, some studies have pointed out that gender, severity of liver disease, severity of portal hypertension, systemic inflammatory response, and other factors may affect the re-compensation of patients with decompensated liver cirrhosis. However, there is still a lack of sufficient understanding of the role of liver

regeneration. The purpose of this article is to review the potential of liver regeneration in the re-compensation of decompensated cirrhosis, to promote the establishment of personalized treatment for such high-risk patients.

LIVER REGENERATION AFTER LIVER INJURY

The liver is a vital organ of the human body, which has the functions of metabolism, detoxification, excretion, and biotransformation[7]. Among them, liver regeneration is one of the most striking and powerful innate abilities of the liver[8], which allows the liver to regain its original size and function quickly after injury. A variety of pathological factors can lead to liver damage, such as hepatitis virus infection, exposure to hepatotoxic drugs, and liver resection. Sometimes, these conditions are triggers for liver regeneration, but damage, if severe and persistent, can impair liver regeneration, leading to fatal liver failure[9]. There is a strong association between chronic liver damage and decreased liver regeneration. A retrospective study by Aierken *et al*[10] found that the rate of liver regeneration decreased with the increase in the degree of liver fibrosis, and that liver regeneration in patients with cirrhosis was significantly slower and incomplete than that of normal liver, which may be related to a significant reduction in the key factors affecting liver regeneration [tumor necrosis factor α , interleukin (IL)-6, and hepatocyte growth factor].

The pattern of liver regeneration varies greatly depending on the degree and type of liver injury, and the proliferation of mature hepatocytes and the expansion of liver progenitor cells (LPCs) are the two main pathways of liver regeneration. The liver has a slower renewal rate under homeostatic conditions. It relies on the self-replication of different hepatocyte subsets to achieve dynamic reproduction and maintain the function and quality of the liver. In partial hepatic resection or other models of acute liver injury, residual hepatocytes not only proliferate to refill the damaged area of the liver but also upregulate their gene expression levels to compensate for lost liver function, resulting in a significantly higher rate of regeneration than hepatocytes during steady-state[7,11]. LPCs are proliferative epithelial cells that grow in Hering's ducts,

express the hepatoblast marker alpha-fetoprotein (AFP), and are considered dual-potent precursor cells due to their ability to differentiate into hepatocytes and cholangiocytes in vitro. LPCs are not observable in the liver of normal adults, but they occur and dilate in severe or chronic liver injury. Their number depends on the severity of the disease[12]. In severe liver fibrosis/cirrhosis, a large amount of parenchymal tissue is lost, and the ability of hepatocytes to proliferate is impaired due to excessive inflammation, scarring, and epithelial abnormalities. At this time, necrotic hepatocytes and immune cells can produce LPCs proliferation activator to initiate the liver regeneration process induced by LPCs, and the activated LPCs differentiate into hepatocytes and cholangiocytes, refill the damaged epithelial cells, and promote the recovery of liver function[13]. LPCs are mainly derived from the dedifferentiation of hepatocytes or cholangiocytes, and it has been suggested that hematopoietic stem cells and myofibroblasts can also transform into LPCs[14]. In addition, in some cases, hepatocytes and cholangiocytes can also proliferate as "facultative stem cells" into each other. When one of the epithelial cells cannot regenerate, an alternative regeneration regimen is activated. Elevated serum AFP levels in patients with active cirrhosis after hepatocellular carcinoma have been excluded, which may indicate hepatic progenitor cell mobilization and proliferation. However, the origin and characteristics of such AFP-expressing cells are not fully understood. The study by Nakano *et al* [15] identified a unique population of AFP-expressing cells induced by Jagged1/Notch2 signaling in mouse fibrotic liver. It was found that in fibrotic liver tissues, the expression of Jagged1 (ligand protein) in myofibroblasts was significantly increased, which stimulated the Notch2 (receptor protein) signaling of adjacent AFP-expressing cells, thereby inducing the mobilization and proliferation of AFP-expressing cells. These AFP-positive cells exhibit the characteristics of immature hepatocytes and have high proliferative capacity, which may contribute to the regeneration of fibrotic liver and are associated with the prolonged survival time after partial hepatectomy in mice with fibrotic liver. Acute-on-chronic liver failure (ACLF) is an acute liver injury and rapid deterioration of liver function based on chronic liver disease, often complicated by bacterial infection, and its

short-term mortality rate is high. Xiang *et al*[16] found that liver fibrosis and bacterial infection had significant inhibitory effects on liver regeneration induced by acute liver injury by constructing a mouse model of ACLF, which was achieved by impairing the IL-6/signal transduction and activator of transcription (STAT)3 pathway, which promotes regeneration and enhancing the interferon (IFN)- γ /STAT1 pathway, which inhibit regeneration. STAT3 and STAT1 are both members of the STAT protein family and are key intracellular signal transduction proteins, which are complementary and often antagonistic. IL-6 and IL-22 predominantly activate STAT3, and IFN- γ predominantly activates STAT1. The balance of the two plays a key role in controlling liver damage and regeneration (Figure 1). IL-22Fc is a recombinant fusion protein consisting of two human IL-22 molecules linked to a constant region of immunoglobulin. IL-22Fc has been found to activate STAT3 and attenuate STAT1 in the liver, promoting liver regeneration and mitigating bacterial infections to improve ACLF survival. It can be seen that effective restarting of liver regeneration in patients with cirrhosis is essential to improve the prognosis, and adjusting the signaling pathways related to liver regeneration is a therapeutic strategy worthy of our consideration.

CONCEPT OF RE-COMPENSATION AND ITS CURRENT RESEARCH PROGRESS

The concept of re-compensation implies that the structural and functional changes in cirrhosis are at least partially restored after the etiology of cirrhosis has been eliminated. In 2021, the Baveno VII consensus proposed for the first time a unified standard for the definition of liver re-compensation, namely: (1) clearance/inhibition/cure of the primary cause of liver cirrhosis, *i.e.*, elimination of HCV, continuous inhibition of HBV, and continuous abstinence from alcohol for the treatment of alcoholic cirrhosis; (2) resolution of ascites (discontinuation of diuretics), resolution of hepatic encephalopathy (discontinuation of lactulose/rifaximin) and absence of recurrent variceal bleeding for at least 12 mo; and (3) stable improvement in liver function indicators [albumin (ALB), international normalized ratio (INR) and bilirubin] [17]. Since its inception, the Baveno VII standard has been validated in several studies. However, the generation of

new concepts always has to go through a long and iterative process of revision and refinement, and we need to pay attention to the current limitations of the Baveno VII standard.

According to Baveno VII, the core of the concept of hepatic re-compensation is to address the underlying etiology of cirrhosis, which is essential to initiate the re-compensation process. However, most of the existing studies on etiological treatment are based on patients with HBV, HCV, and alcohol-related liver cirrhosis, and there are still insufficient data on the effect of etiological treatments other than alcohol abstinence and antiviral therapy on re-compensation. For liver diseases of different etiologies, particularly less common diseases such as autoimmune hepatitis, primary biliary cholangitis (PBC), and primary sclerosing cholangitis, there is still a lack of accepted criteria for success in treating the cause. In addition, the definition of successful etiological treatment in patients with multiple overlapping etiologies of liver disease is debatable. In a retrospective study of 42 patients with PBC and decompensated cirrhosis, Hofer *et al* [18] defined the criteria for etiological treatment success as normalization of bilirubin and alkaline phosphatase (ALP) reduced to ≤ 1.5 times the upper limit of normal (ULN) (determined to be a biochemical response to UDCA by reference to Paris II criteria) with ursodeoxycholic acid (UDCA, the first-line agent for PBC), and 7 patients (16.7%) received re-compensation. Another pilot study demonstrated that decompensated cirrhosis due to autoimmune hepatitis (AIH) can achieve re-compensation in some patients after successful immunosuppressive therapy (4/21) [19]. These studies have small sample sizes, limited statistical power, and limited extrapolation of results. However, they also suggest the feasibility of re-compensation in cirrhosis of multiple etiologies, which still needs further study.

In addition to successful etiological treatment, the Baveno VII criteria emphasize the resolution of complications related to hepatic decompensation. Transjugular intrahepatic portal system shunt (TIPS) is an effective intervention for variceal hemorrhage or refractory ascites in patients with cirrhosis by reducing the portal pressure gradient and not directly addressing the removal of the cause of cirrhosis[20].

Gao *et al*[21] studied patients with decompensated cirrhosis of different etiologies, including chronic hepatitis B, hepatitis C, alcoholic liver disease, metabolic dysfunction-associated steatotic liver disease (MASLD), autoimmune liver disease, and cholestatic liver disease. Approximately one-third of decompensated patients were found to recompensate for cirrhosis after TIPS, and re-compensation was more likely to occur in younger patients and in patients whose portal venous pressure gradient dropped below 12 mmHg after TIPS. This suggests that therapeutic interventions for portal hypertension may be a key factor in promoting the re-compensation of cirrhosis of different etiologies. Although the Baveno VII consensus emphasizes the importance of addressing the underlying cause to achieve complication re-compensation, there is still a lack of sufficient data to support whether etiological treatment can achieve re-compensation in patients with advanced cirrhosis and severe complications. Gao *et al*[21] concluded that since the occurrence of cirrhosis decompensation is mainly based on the progression of portal hypertension, reversal of portal hypertension by TIPS is essential to achieve re-compensation, and etiological treatment alone is far from sufficient to suppress the recurrence of life-threatening complications of portal hypertension. More data are needed to evaluate the relationship between portal hypertension mitigation and re-compensation to complement and refine the concept of cirrhosis re-compensation.

Although the Baveno VII consensus regards "stable improvement in liver function" as one of the re-compensation definitions and provides reference indicators (albumin, INR, bilirubin), the specific critical value of the relevant parameters is not established. Different studies may have chosen different variables and cutoff values for liver function re-compensation. For example, the study of Aravinthan *et al*[22] improved the MELD score to < 15 as the standard for liver function re-compensation in patients with decompensated alcohol-related liver disease, and the study of Kim *et al*[23] defined re-compensation as the recovery of cirrhosis status to a Child-Pugh score of 5 points. Formulating unified and accurate re-compensation standards for liver function will help in future related research and the diagnosis of re-compensation groups in clinical

practice. Wang *et al*[4] proposed a precise definition of stable improvement in liver function [model for end-stage liver disease (MELD) score < 10 and/or Child-Pugh class A, *i.e.*, ALB > 35 g/L and INR < 1.50 and total bilirubin (TBIL) < 34 μmol/L]. This was included in China's latest *Guidelines for the Prevention and Treatment of Chronic Hepatitis B* (version 2022). However, that study only included patients with HBV-related decompensated cirrhosis treated with entecavir, and it is still unclear whether these criteria can be applied to other causes of cirrhosis or other treatments. As for whether liver function indicators other than albumin, INR, bilirubin, or scores other than MELD and Child-Pugh can better evaluate liver function re-compensation, few studies are currently available. Future research needs to continue to improve the definition of liver function improvement to meet the needs of re-compensation.

PAY ATTENTION TO THE VALUE OF LIVER REGENERATION IN RE-COMPENSATION OF DECOMPENSATED LIVER CIRRHOSIS

Role of liver regeneration in the re-compensation of cirrhosis

Although the Baveno VII consensus emphasizes that re-compensation should be accompanied by improvement in liver histological structure, the current clinical judgment of re-compensation is mainly based on the evaluation of complications and liver function, and liver histopathological studies supporting re-compensation of cirrhosis are still lacking. The pathophysiology of hepatic re-compensation is currently unclear, but understanding the mechanisms of cirrhosis decompensation can help identify potential compensatory targets. By reviewing the pathological features of the formation of cirrhosis, Bedossa *et al*[24] proposed three significant cirrhosis mechanisms of reversal: Collagen degradation, hepatocyte regeneration, and reconstitution of liver lobular structure. Portal hypertension is an essential driver of decompensation in cirrhosis. Its associated complications are key to determining the prognosis of cirrhosis and develop based on changes in liver structure and function. Severe structural disturbances in the liver, because of progressive fibrosis and vascular occlusion of the liver, followed by parenchymal disappearance and tissue collapse, are the main

mechanisms of portal hypertension. Patients with cirrhosis and severe lobular structural disorders lack an appropriate structural framework (basement membrane scaffold), which prevents neohepatocytes from filling collapsed lobules. In this case, hepatocyte regeneration is blocked, resulting in a single regenerative nodule that fails to produce normal liver structure, and the enlarged regenerated nodule continues to compress the hepatic vein, resulting in tissue congestion, hepatocyte necrosis, and a new regeneration cycle, ultimately leading to end-stage irreversible liver disease[25-27]. Successful etiological treatment and antifibrosis can promote collagen degradation, hepatocyte regeneration, and replacement of disappeared fibrotic tissues by newly formed hepatocytes, which can lead to the reconstitution of hepatic lobular structure and translobular blood flow, as well as reduction of portal hypertension and promotion of re-compensation. If the liver lacks fibrosis resolution potential and internal regeneration, cirrhosis may not be reversed, even if the cause is effectively controlled[24]. Many studies have shown that factors such as baseline liver function, gender, age, portal venous pressure gradient, and systemic inflammation may affect the re-compensation of patients. However, there is still insufficient attention to the role of changes in liver regeneration capacity in the re-compensation of cirrhosis.

A few studies have confirmed liver regeneration's effect on the re-compensation of decompensated cirrhosis. Previous studies have demonstrated that AFP is a biomarker of hepatic progenitor cell proliferation. Treating AFP as a cancerous indicator alone is very one-sided, and ¹¹ elevated AFP levels may also indicate the severity of liver destruction and subsequent liver regeneration, which is often observed in patients with a variety of acute and chronic liver diseases, including cirrhosis. Under normal physiological conditions, AFP is produced by the yolk sac and the hepatocytes of the fetus and is gradually replaced by ALB at 2-3 mo after birth. After liver injury, serum AFP levels positively correlate with hepatocyte regeneration capacity, possibly because of immature hepatic progenitor cells with characteristics similar to those of fetal hepatocytes. Wen *et al*[28] conducted a study on patients with HBV-associated liver cirrhosis with ascites as the single first decompensation event. They found that AFP was

a relevant factor in re-compensation, suggesting that liver regeneration is not negligible in cirrhosis re-compensation. A retrospective study by Kim *et al*[23] found that high AFP level at baseline (≥ 50 ng/mL) was an essential predictor of re-compensation after antiviral therapy in patients with HBV-associated cirrhosis decompensation. A prediction score model for re-compensation, including AFP, was also constructed, namely the BC2AID (Bilirubin-severe Complication-Alphafetoprotein-Alanine aminotransferase-International normalized ratio-Duration of decompensation before NUC therapy) score. The value of this scoring model in predicting re-compensation of decompensated cirrhosis within 1 year after antiviral treatment is better than that of traditional prediction models [Child-Pugh, MELD, MELD-Na, and BE3A (BMI, encephalopathy, ascites, and serum levels of ALT and ALB) scores]. It can better predict the long-term mortality of patients at 6–36 mo. It can be seen that the clinical prediction model that integrates the evaluation of liver regeneration ability has potential research value in predicting the re-compensation of decompensated cirrhosis. Zhang *et al* studied 136 patients with ACLF based on HBV-associated cirrhosis, and found that 56 (41.18%) patients recovered to the compensated phase within 1 year of antiviral therapy. The AFP in the recompensated group was significantly increased, suggesting that a stronger capacity for liver regeneration may be more conducive to re-compensation[29]. Some clinical studies have shown that serum AFP levels are a good prognostic indicator, especially in patients with ACLF. Wang *et al*[30] found that the parameter \log_{10} AFP was a valuable predictor of HBV-ACLF prognosis and that the short-term survival rate of ACLF patients with \log_{10} AFP ≥ 2 was higher. To evaluate the prognosis of patients from both the dimensions of liver regeneration and impaired liver function, Wang *et al*[31] created and validated a new prognostic model for HBV-ACLF with the following mathematical formula: TACIA score = $0.003 \times \text{TBiI} (\mu\text{mol/L}) + 0.036 \times \text{age} + 0.009 \times \text{creatine} (\mu\text{mol/L}) + 0.525 \times \text{INR} - 0.003 \times \text{AFP} (\text{ng/mL})$. The new scoring system combines the clinical parameters of organ damage and liver regeneration, which can effectively assess the re-compensation of liver function and predict the prognosis of 90-d survival. In addition to AFP, platelets have been reported to predict liver

regeneration. A study by Yamazaki *et al*[32] showed a significant delay in liver volume recovery after hepatectomy when platelet recovery rates were low. This may be related to the regeneration of liver parenchyma between platelets and hepatocytes through cytokines such as hepatocyte growth factor, vascular endothelial growth factor, serotonin, and thrombopoietin. Platelet-mediated liver regeneration is inhibited when platelet-hepatocyte interactions are interrupted. Thrombocytopenia is often the first problem in chronic liver disease and early cirrhosis, and the severity of cirrhosis is also an important factor in platelet count. Therefore, focusing on changes in platelet count may help us monitor disease progression in patients with cirrhosis and assess the patient's regeneration ability to predict re-compensation. This is supported by the study of Deng *et al* [33], which explored the predictors of re-compensation after entecavir in treating HBV-related decompensated cirrhosis and found that higher platelets at 24 wk of treatment were among the best predictors. The construction of a new re-compensation prediction model based on platelet indexes may be worthy of further research in the future, which can comprehensively reflect liver regeneration, inflammatory response, coagulation function, *etc.* However, both the BC2AID score and the TACIA score still lack validation in different large and diverse cohorts, and the scores are all based on patients with HBV-related liver disease. In contrast, patients with other causes of liver disease are not included. In the future, the predictive value of AFP, platelets, and other indicators on re-compensation should be further studied in patients with liver cirrhosis caused by different etiologies (including alcoholic, autoimmune, *etc.*), to build a more versatile clinical prediction model. Liver regeneration capacity is the key to structural reversal and liver function recovery in cirrhosis, and actively maintaining liver regeneration capacity to achieve re-compensation is a therapeutic strategy worth considering.

Different complications also affect the re-compensation and prognosis of patients with cirrhosis. Wen *et al*[29] included only patients with decompensated ascites, and studies on other complications are lacking. He *et al*[34] found that after effective etiological treatment, the re-compensation rate was significantly lower in patients with

variceal hemorrhage as the first decompensated event than in patients with ascites as the first decompensated event. In addition, there is a higher risk of further decompensation, hepatocellular carcinoma, death or liver transplantation after re-compensation. This suggests that patients with decompensation who have variceal bleeding as their first decompensated event have a worse prognosis. More and more extensive studies should be conducted to explore the re-compensation of this subset of patients and to pay attention to the role of liver regeneration.

Liver cirrhosis re-compensation was evaluated in combination with the liver regeneration index

The evaluation of liver cirrhosis re-compensation mainly includes liver histopathology (degree of liver fibrosis, hepatocyte regeneration, and liver lobular reconstruction), liver function, and complications, but hepatocyte regeneration evaluation still needs improvement (Table 1). After decompensation of cirrhosis, the restoration of liver function includes the restoration of liver reserve capacity and regeneration. When the ability of liver regeneration is more potent than that of injury, hepatocyte regeneration repairs damaged tissues to rebuild liver lobules, promoting the reversal of liver structure and function, and the prognosis of patients is better. However, when the damage is too extensive or the liver's regeneration ability is weakened, it may be difficult for patients to achieve compensation, and the prognosis is poor[36]. Therefore, evaluation of hepatocyte regeneration deserves our attention.

Clinically, the assessment of liver regeneration ability should be comprehensively judged through multi-dimensional indicators, including laboratory indicators, imaging evaluation, histological examination, *etc.* AFP is an essential indicator for evaluating liver regeneration ability. It can be combined with dynamic monitoring of platelets, liver function indicators (albumin, bilirubin, INR, *etc.*), Child-Pugh scores, and regularly undergo abdominal CT or MRI examinations for patients with decompensated cirrhosis to rule out the existence of hepatocellular carcinoma. On this basis, AFP increases, platelets rise, and an improvement in liver function may indicate hepatocellular

regeneration in patients. Laboratory indicators have low specificity and are susceptible to interference factors. For example, nutritional status affects albumin indicators, and hypersplenism disturbs platelets. Based on the patient's situation, comprehensive consideration should be taken during clinical application. Imaging methods such as ultrasound, CT, MRI examination, *etc.*, are non-invasive and intuitive, which can quantify liver volume changes, but cannot distinguish regenerated liver cells from fibrotic tissue. Hepatic elastography can evaluate dynamic changes in liver fibrosis. A decrease in cirrhosis value (LSM) may indicate that liver regeneration is accompanied by reduced fibrosis, but this examination cannot directly reflect the proliferation activity of hepatocytes. In addition, since hepatocyte regeneration mainly comes from precursor cells, the evaluation value of precursor cell markers such as epithelial cell adhesion molecule (EpCAM), cytokeratin 19 (CK 19), and SRY-Box transcription factor 9 (SOX9) is also worth our consideration[27]. Liver biopsy tissue can be used in clinical practice to perform immunohistochemistry, intuitively localize precursor cells expressing specific markers, and evaluate their distribution and number. The increase in marker-positive cellularity in chronic liver disease/cirrhosis may indicate compensatory activation of liver precursor cells, while sustained high expression may indicate the risk of liver failure or a tendency to cancer. However, this operation requires an invasive biopsy and is unsuitable for dynamic monitoring. Serological markers, such as soluble CK19 fragments (CYFRA21-1) and EpCAM ectodomain (EpEX) in the serum, can also be detected through enzyme-linked immunosorbent assays (ELISA). They can be dynamically monitored to observe peaks and downward trends to evaluate regeneration. However, serum markers have low sensitivity and specificity, and interference from other diseases, such as malignant tumors, is required. The clinical application is limited. In general, clinical evaluation of liver regeneration should be multi-dimensional and combined. The existing methods are still lacking and need further research in the future.

CONCLUSION

In recent years, increasing clinical evidence points to the possibility of re-compensation in decompensated cirrhosis, in which structural and functional changes in cirrhosis are at least partially reversed after the cause of cirrhosis has been eliminated. Studies have confirmed that the recovery of liver regeneration ability in patients with cirrhosis can promote the occurrence of re-compensation and improve the patient's prognosis. Clinical practice can evaluate patients' liver regeneration ability in multiple dimensions by monitoring the levels of AFP, platelets, and other indicators, detecting precursor cell-specific markers, *etc.*, and establishing reasonable individualized treatment strategies. In short, we should actively maintain the liver regeneration ability of patients with decompensated cirrhosis to promote the occurrence of re-compensation and further improve the clinical evaluation methods on hepatocyte regeneration.

ACKNOWLEDGEMENTS

All authors thank the reviewers for their efforts.

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