Research Progress of Artificial Liver in the Treatment of Severe Liver Disease

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Abstract: Acute-on-chronic liver failure (ACLF) presents high mortality with limited treatments. Artificial liver support systems (ALSS), including non-biological (NBAL) and bioartificial (BAL) types, offer key supportive strategies. NBAL removes toxins and cytokines, while BAL provides metabolic and regenerative functions. Recent developments in BAL — such as stem cell sourcing, 3D scaffolds, and clinical trials — show promise in improving outcomes. This review outlines the advances, clinical applications, and future prospects of ALSS in achieving individualized, efficient liver failure management.

***Keywords*:** ACLF; artificial liver; NBAL; BAL

1. Introduction

Acute chronic liver failure (ACLF) has become a global public health problem, often accompanied by multiple organ failure, and the 90-day mortality rate is as high as 58%[1]. [2]The incidence of ACLF remains high in Asia due to chronic hepatitis B (HBV) infection, while in Western countries, the prevalence of alcohol abuse and metabolic syndrome has led to a continuous increase in the incidence of ACLF. [3]lthough liver transplantation is an effective treatment for end-stage liver disease, the shortage of organs seriously limits its application. Traditional treatment methods have many limitations in the treatment of acute liver failure and ACLF, such as poor therapeutic effect, significant drug side effects, and limited effect on prolonging the survival of patients. Artificial liver system (ALSS) has emerged to provide temporary support for patients with liver failure by simulating partial liver function. However, there is still a lack of high-quality clinical evidence on the long-term efficacy and safety of artificial liver, especially the specific application prospects in the treatment of ACLF need to be further explored.

2. Classification of artificial liver

2.1 Non-biological Artificial Liver

The main mechanism of action of NB-ALSS includes the removal of a variety of harmful substances such as medium and large molecular toxins, cytokines (TNF-α, IL-6), bilirubin and bile acids in the plasma. By removing these toxic substances, the burden on the liver is reduced, the internal environment is improved, the systemic inflammatory response is reduced, and favorable conditions are created for liver regeneration and functional recovery[4]. In addition, plasma exchange can also help restore the function of the liver and the balance of the immune system[5], regulate the immune response, reduce the inflammatory response, and improve the function of multiple organs by supplemating coagulation factors, albumin and immunoglobulin.

The combination of plasma infusion and low volume plasma exchange showed good short-term efficacy in patients with HBV-ACLF. A multicenter randomized controlled study found that the 28-day transplantation-free survival rate was significantly improved in the combination therapy group, accompanied by a significant decrease in the MELD score, indicating that the combination therapy was superior to the single therapy, showing advantages in the clearance of bilirubin and inflammatory mediators, and reducing the risk of impaired coagulation function and bleeding[6-9].

Since the large amount of plasma required for treatment is dependent on plasma supply, this can lead to limitations of treatment[10]. Anticoagulants used during plasma exchange may cause further damage to the patient's coagulation function and increase the risk of bleeding. Based on the artificial liver support system (NB-ALSS), the strategies of "albumin regeneration" and "inflammatory pathway intervention" have been further developed by DIALIVE and MARS systems. The main advantage of MARS (Molecular adsorption Recycling System) is that it can recycle albumin dialysate and effectively remove toxins bound to albumin. Although it can improve symptoms such as jaundice and hepatic encephalopathy, clinical trials have shown that it has no significant improvement in 90-day overall survival[11]. This suggests that MARS is more

suitable as a short-term "bridging therapy" rather than a long-term intervention, and its efficacy is restricted by factors such as the baseline liver function of patients and the timing of intervention.In contrast, DIALIVE further shows unique advantages in improving inflammation and endothelial function through replacement albumin supplementation and removal of PAMPs and DAMPs.Although it did not significantly reduce 28-day mortality in a small sample study, its performance in improving albumin function, shortening recovery time, and optimizing inflammatory biomarkers, provide strong clues for the future.

2.2 Bioartificial liver

Bioartificial Liver (BAL) is designed to temporarily replace the detoxification and metabolic functions of the liver, help patients through the emergency period, and promote the recovery of the damaged liver, and even become an independent therapy or liver transplantation bridge therapy.

Animal studies have shown that in a pig model of D-Gal-induced acute liver injury, the survival rate of patients treated with BAL was significantly better than that of the control group[12]. Genetic engineering methods have also shown good application prospects. For example, genetic engineering methods (such as those studied by Ke et al.) also show the potential to significantly reduce the levels of bilirubin and ammonia[13]. NHBLS also showed excellent ammonia clearance and metabolic support in simulated liver failure serum in vitro[14]. In recent years, the combination of cell and cell free therapies, such as hUCMSC-BAL and hiHep-BAL, has become a research hotspot in the field of BAL. BAL of Human umbilical cord mesenchymal stem combined with exosome therapy has been validated to inhibit cytokine storm, improve liver function, and promote liver regeneration in porcine and mouse models[15]. At the same time, hiHep-BAL based on GMP conditions has been shown to significantly improve the survival rate and liver function indexes in the pig postoperative liver failure model and clinical trials[16-17]. In addition to cell and model optimization,[18] the combination of decellularized liver matrix (DLM), Gelatin-based hydrogel (GelMA) and oxygen-rich perfusion bioreactor provides new ideas for the construction of biomimetic scaffolds and the optimization of oxygen supply environment, thereby significantly improving ammonia metabolism and detoxification functions. Such BLSS with excellent function and structure provide new ideas for the construction of biomimetic scaffolds and the optimization of oxygen supply environment. It brings a new direction and hope for the clinical application of engineered liver in the future.

3. Clinical application and effect

A meta-analysis of 19 randomized controlled trials (RCTs) showed that artificial LSS significantly reduced the mortality of ACLF patients without increasing the risk of hepatic encephalopathy or bleeding, especially the advantages of BAL in acute liver failure[19].

[20]Several prospective and retrospective studies have shown that PE-based NBALSS significantly improves survival at 28 days, 90 days, and 1 year, especially in severe patients with ACLF grade 2 or MELD score of 30-40.

[21-23]Meta-analysis also showed that ALSS significantly reduced the short-, medium- and long-term mortality risk of ACLF patients, and improved the survival rate by about 30-50%, especially in patients with bacterial infection, and also significantly improved the survival rate. Importantly, ALSS not only improves overall short-term survival, but also shows more significant benefits in specific high-risk subgroups, such as HBV-ACLF patients with bacterial infection. These evidence-based studies collectively show that ALSS and its emerging extension technology play an important role in improving the short-term and long-term survival rates of patients with ACLF.

4. Conclusions and Prospects

Artificial liver support systems (ALSS) as a key therapeutic approach for severe liver diseases, particularly ACLF. Future research should focus on optimizing the treatment plan of artificial liver support system (ALSS), including accurately screening suitable patients, identifying the best intervention time, exploring combined treatment strategies, and promoting the development of low-cost and high-performance materials and devices to reduce the treatment burden and improve clinical accessibility.

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