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Clinical Significance of Alpha-Fetoprotein Levels in Artificial Liver Therapy for Liver Failure

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Abstract: *Objective:* Through the treatment of liver failure using artificial liver plasma exchange (PE), this study aims to explore the predictive value and clinical significance of alpha-fetoprotein (AFP) levels in the prognosis of liver failure patients. *Methods:* A retrospective analysis was conducted on the clinical data of 96 liver failure patients, all of whom underwent artificial liver plasma exchange therapy in addition to standard medical treatment. Based on AFP test values, patients were divided into three groups: low AFP group (AFP < 100 ng/mL, $n = 32$), medium AFP group (100 ≤ AFP < 200 ng/mL, $n = 32$), and high AFP group (AFP ≥ 200 ng/mL, $n = 32$). Serum AFP levels were measured before artificial liver therapy (on the second day of hospitalization), on days 1, 10, and 20 after treatment, and at the final evaluation (before discharge or prior to death) to observe changes. *Results:* Among the 96 patients, 4 (4.2%) had acute liver failure (ALF), 7 (7.3%) had subacute liver failure (SALF), 57 (59.4%) had acute-on-chronic liver failure (ACLF), and 28 (29.2%) had chronic liver failure (CLF), with an overall survival rate of 82.3% (79/96). Patients in the AFP < 100 ng/mL group had a lower survival rate compared to the other two groups, and survival rates increased with higher AFP levels ($P < 0.05$). *Conclusion:* Serum AFP levels are closely related to the efficacy of artificial liver plasma exchange therapy for liver failure, and dynamic monitoring of AFP changes can help assess disease progression.

Keywords: Alpha-fetoprotein; Artificial liver support system; Plasma exchange; Liver failure prognosis; Hepatocyte regeneration

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1. Theoretical basis of this study

Liver failure is a common and severe clinical syndrome characterized by significant impairments or decompensation

of liver functions such as synthesis, detoxification, excretion, and biotransformation. This syndrome often presents with coagulopathy, jaundice, and hepatic encephalopathy as key manifestations [1]. According to the "2018 Guidelines for Diagnosis and Treatment of Liver Failure" [2], liver failure is classified into four types:

(1) Acute liver failure (ALF): Acute onset, no history of underlying liver disease, and clinical manifestations characterized by grade II or higher hepatic encephalopathy within two weeks.

(2) Subacute liver failure (SALF): Rapid onset, no history of underlying liver disease, with clinical manifestations of liver failure occurring within 2–26 weeks.

(3) Acute-on-chronic liver failure (ACLF): Acute decompensation of liver function and liver failure in a short period on the basis of chronic liver disease.

(4) Chronic liver failure (CLF): Progressive decline in liver function on the basis of cirrhosis, characterized by repeated ascites or hepatic encephalopathy.

China has a high prevalence of liver diseases, with more than 100 million cases, including approximately 8 million liver failure patients. Liver failure has a complex pathogenesis, and due to severely impaired detoxification functions, a large accumulation of toxic substances occurs in the body, leading to homeostatic imbalance. These toxins further hinder hepatocyte regeneration and functional recovery while damaging vital organs such as the heart, brain, and kidneys. As a result, liver failure progresses rapidly with numerous complications, posing significant treatment challenges and high mortality rates, making it a global therapeutic challenge.

The key to clinical treatment is the prompt and effective removal of toxic substances, disruption of vicious cycles, liver protection, and prevention of multiple organ failure. Treatment methods for liver failure include medical therapy, artificial liver support therapy, and liver transplantation. Medical treatment alone has limited efficacy, with mortality rates ranging from 60–80% [3]. Liver transplantation offers effective treatment and improved prognosis, but its application is limited by donor shortages, high technical complexity, high costs, and the need for lifelong immunosuppressive therapy [4].

Artificial liver support systems have emerged in recent years as a major breakthrough in extracorporeal liver support technology. These systems have demonstrated effectiveness in reducing mortality rates among liver failure patients, with recognized treatment efficacy and safety. The mechanism is based on the liver's strong regenerative capacity. By employing mechanical, physicochemical, and biological devices, artificial liver systems help remove harmful substances accumulated due to liver failure, replenish essential substances, and improve the internal environment. This temporary liver function replacement facilitates hepatocyte regeneration and functional recovery or provides time for liver transplantation.

Currently, artificial liver support has become a major treatment modality for liver failure, offering new hope to patients. In cases where liver transplantation is not feasible, artificial liver support systems can temporarily replace liver function. Among these, plasma exchange (PE) is a well-established and widely used artificial liver treatment in China. Plasma exchange operates by using a plasma separator to extract plasma from whole blood, removing large amounts of toxic substances and metabolic byproducts dissolved in the plasma, and replacing them with fresh frozen plasma. This process effectively clears bilirubin, endotoxins, and inflammatory factors while replenishing essential biological substances such as albumin, coagulation factors, immunoglobulins, and complement proteins, maintaining homeostasis [6]. Additionally, plasma exchange promotes hepatocyte regeneration and aids in liver function recovery. Enhancing hepatocyte self-repair and regeneration is crucial for patient prognosis.

In recent years, various predictive models for liver failure prognosis have been proposed [7-9]. However, most focus on assessing liver functional reserves rather than evaluating hepatocyte regenerative capacity, which is a key

factor influencing prognosis. Alpha-fetoprotein (AFP) is a glycoprotein produced by the yolk sac and liver during fetal development and is known to promote hepatocyte proliferation. After birth, AFP levels rapidly decrease and remain low in healthy adults, with no expression in normal liver tissue. When hepatocytes regenerate or undergo malignant transformation, certain genes are activated to synthesize AFP, leading to elevated AFP levels. Thus, AFP levels can reflect hepatocyte inflammation, necrosis, and regeneration status.

Our preliminary studies have shown that AFP is an effective prognostic marker for liver failure [10]. This finding suggests that AFP assessment may be a more effective indicator of liver regeneration, potentially guiding artificial liver clinical practice. Therefore, this study aims to explore the predictive value and clinical significance of AFP levels in the prognosis of liver failure patients undergoing artificial liver plasma exchange therapy. This research will help better assess patient prognosis, provide early predictions of disease progression and mortality risk, and assist in selecting appropriate treatment strategies.

2. Research content and protocol

2.1. Selection of study subjects

2.1.1. Inclusion criteria

(1) All patients' clinical diagnoses meet the diagnostic criteria for liver failure as outlined in the "Guidelines for the Diagnosis and Treatment of Liver Failure" (2018 Edition) formulated by the Infectious Diseases Branch and the Hepatology Branch of the Chinese Medical Association. The criteria include the following classifications:

(a) Acute liver failure (ALF): Acute onset, no history of underlying liver disease, and clinical manifestations characterized by hepatic encephalopathy of grade II or above within two weeks.

(b) Subacute liver failure (SALF): Relatively acute onset, no history of underlying liver disease, with clinical manifestations of liver failure occurring within 2–26 weeks.

(c) Acute-on-chronic liver failure (ACLF): Acute hepatic decompensation and liver failure occurring in a short period based on chronic liver disease, potentially complicated by hepatic encephalopathy, ascites, infections, hepatorenal syndrome, etc.

(d) Chronic liver failure (CLF): Progressive decline in liver function based on cirrhosis, mainly characterized by recurrent ascites or hepatic encephalopathy.

The diagnosis and grading of hepatic encephalopathy are based on the "Guidelines for the Diagnosis and Treatment of Hepatic Encephalopathy in Cirrhosis" (2018 Edition) [2], and the diagnosis of hepatorenal syndrome follows the "Guidelines for the Diagnosis, Evaluation, and Management of Ascites and Hepatorenal Syndrome" issued by the American Association for the Study of Liver Diseases in 2021.

(2) No gender restrictions, age under 65 years.

(3) The study was approved by the hospital's ethics committee, and all participants provided informed consent before undergoing any study-related procedures and adhered to the treatment protocol.

2.1.2. Exclusion criteria

(1) Liver failure patients with AFP ≥ 400 ng/mL who were diagnosed with liver tumors based on imaging examinations.

(2) Patients with pregnancy, gonadal embryonal tumors, or other malignancies.

(3) Patients with severe active bleeding or disseminated intravascular coagulation (DIC).
(4) Patients with severe allergic reactions to blood products or medications used during treatment, such as plasma, heparin, and protamine.
(5) Patients with circulatory failure or those in an unstable phase of myocardial infarction or stroke.

2.1.3. Screening and evaluation

(1) Medical history inquiry: Includes history of hepatitis virus infection, prior treatments before screening, comorbid conditions, medication history, alcohol consumption, etc.
(2) Physical examination.
(3) Routine blood, urine, and stool tests.
(4) Blood biochemistry tests: Including liver function, kidney function, blood ammonia, electrolytes, blood glucose, blood lipids, and cardiac enzymes.
(5) Coagulation function tests.
(6) Hepatitis virus markers: HBV antigens and HAV, HCV, and HEV antibodies, along with serum HIV antibody testing.
(7) Serum autoimmune antibody detection.
(8) Serum tumor markers: AFP, CA50, CA199, etc.
(9) Liver imaging examinations: Including ultrasounds and CT/MRI.

2.2. Treatment grouping

According to the above criteria, 96 cases of liver failure patients diagnosed from January 2022 to December 2022 at Baoshan People's Hospital and Baoshan Second People's Hospital were selected. Based on the alpha-fetoprotein (AFP) test values, they were divided into a low AFP group (AFP < 100 ng/mL) with 32 cases, a medium AFP group (100 ≤ AFP < 200 ng/mL) with 32 cases, and a high AFP group (AFP ≥ 200 ng/mL) with 32 cases.

2.2.1. Medical treatment

(1) Nutritional support and symptomatic treatment: Provide sufficient energy and vitamins, and maintain the patient's water and electrolyte balance.
(2) Administer albumin infusion daily or every other day to promote hepatocyte regeneration.
(3) Liver protection and jaundice reduction treatment: Intravenous drip of compound glycyrrhizin, polyene phosphatidylcholine, and adenosylmethionine.
(4) All hepatitis B patients were treated with Entecavir tablets 0.5 mg/d for antiviral therapy (manufactured by Bristol-Myers Squibb, Shanghai).
(5) Symptomatic treatment for complications such as hepatorenal syndrome, spontaneous bacterial peritonitis, hepatic encephalopathy, and gastrointestinal bleeding.

2.2.2. Artificial liver treatment

All patients received plasma exchange (PE) treatment with artificial liver on the basis of the above comprehensive medical treatment.

Instruments and materials:

(1) Machine: X-10 Artificial Liver Treatment Machine (produced by Zhuhai Jianfan Biotechnology Co., Ltd.).

(2) Consumables: Plasma separator produced by Bellco S.r.l., Italy; disposable blood circuit connection catheter produced by Tianjin Hanaco Medical Materials Co., Ltd.; Abell double-lumen catheter (specification 11.5Fr-16cm) for femoral vein catheterization.

Operation method: Routine venous blood collection before treatment to check AFP, blood routine, liver and kidney function, electrolytes, coagulation function, blood ammonia, etc. In the air-disinfected artificial liver treatment room, routine ECG monitoring, low-flow oxygen inhalation, and femoral vein puncture were performed to insert a single-needle double-lumen catheter to establish an extracorporeal blood circulation pathway. The plasma separator and blood circuit connection catheter were pre-flushed with 500 mL of 4% heparin sodium saline for exhaust, then rinsed with heparin-free saline until the original heparin saline was washed away. Connect the plasma outlet end of the plasma separator and the venous return end to the patient for plasma exchange. Preoperatively, routinely intravenously inject 5 mg of dexamethasone, and intravenously drip 10% calcium gluconate to prevent allergic reactions and other adverse reactions. Adjust the dose of anticoagulant heparin according to the patient's condition and coagulation function. Initially, intravenously inject 20 mg of heparin for systemic heparinization, and adjust the dose during the treatment process based on the patient's body weight, treatment time, transmembrane pressure, plasma separation speed, and prothrombin time (PT). Usually, 4–8 mg/h is pumped in with a micro-pump, blood flow speed is 100–120 mL/min, plasma separation speed is 20–30 mL/min, and plasma exchange volume is 2,000–3,000 mL/time (calculated as body weight (kg) × 40 mL). The replacement fluid is fresh frozen plasma, and each treatment lasts about 2–3 hours. Stop using heparin 1–1.5 hours before the end of the treatment based on transmembrane pressure. Administer protamine to counteract heparin and amikacin to prevent infection. Determine the frequency and number of artificial liver treatments based on the patient's condition, with treatment intervals of 1–4 days.

2.3. Observation indicators

Venous blood was collected from all patients before artificial liver treatment (on the 2nd day of admission), and on the 1st, 10th, 20th day after treatment, and at the last time (before discharge/before death) to measure serum AFP levels using chemiluminescent immunoassay and observe its changes. The reagent kit was purchased from Shenzhen New Industries Biomedical Engineering Co., Ltd. The normal reference value for serum AFP content is < 7 ng/mL. Detailed case information was recorded. Analyze the relationship between different AFP levels and the prognosis of liver failure patients, compare the differences in survival and mortality rates of liver failure patients with different AFP levels, and evaluate the predictive value and clinical significance of AFP levels in the outcome of liver failure patients.

Adverse reactions: Observe whether patients have allergic reactions, bleeding, hypotension, fever, thrombosis, etc. during artificial liver treatment, and evaluate whether they are related to artificial liver treatment.

2.4. Statistical methods

All data were processed and analyzed using the SPSS 19.0 statistical software package. Measurement data were expressed as mean ± standard deviation (SD), paired *t*-test was used before and after treatment, independent sample t-test was used between groups, and Pearson χ^2 test was used for count data. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Analysis of clinical classification and treatment outcomes of patients

This study included a total of 96 liver failure patients, aged 15 to 65 years, with an average age of (40.6 ± 13.2) years. Among them, 67 were male (69.8%) and 29 were female (30.2%). The clinical types included 4 cases of ALF (4.2%), 7 cases of SALF (7.3%), 57 cases of ACLF (59.4%), and 28 cases of CLF (29.2%). The average hospitalization duration was 23.5 ± 12.1 days. Ultimately, 79 patients survived (82.3%), while 17 patients died (17.7%).

3.2. Analysis of general data of liver failure patients with different AFP levels

There were no statistically significant differences in gender, age, baseline total bilirubin (TBIL), or prothrombin activity (PTA) levels among liver failure patients with different AFP levels ($P > 0.05$, **Table 1**).

Table 1. Analysis of general data of liver failure patients with different AFP levels

Group	Cases	Gender (Male/Female, *n*)	Age (years, mean ± SD)	TBIL (μmol/L, mean ± SD)	PTA (%, mean ± SD)
AFP < 100 ng/mL group	32	6/2	41.6 ± 11.8	386.9 ± 158.2	32.5 ± 14.2
100 ≤ AFP < 200 ng/mL group	32	47/15	40.9 ± 10.9	381.5 ± 157.6	34.8 ± 15.1
AFP ≥ 200 ng/mL group	32	43/12	40.5 ± 10.2	382.7 ± 156.9	35.2 ± 15.9

3.3. Relationship between AFP levels and clinical classification of liver failure

There was no significant difference in the composition ratio of AFP levels among the clinical classifications of liver failure ($P > 0.05$, **Table 2**).

Table 2. Relationship between AFP levels and clinical classification of liver failure [*n* (%)]

Type	Cases	AFP < 100 ng/mL group	100 ≤ AFP < 200 ng/mL group	AFP ≥ 200 ng/mL group
ALF	4	0 (0.0)	1 (25.0)	3 (75.0)
SALF	7	1 (14.3)	2 (28.6)	4 (57.1)
ACLF	57	12 (21.1)	36 (63.2)	9 (15.8)
CLF	28	22 (78.6)	5 (17.9)	1 (3.6)

3.4. Comparison of survival rates among liver failure patients with different AFP levels

The survival rate of the AFP < 100 ng/mL group was lower than that of the other two groups, and the survival rate gradually increased with higher AFP levels ($P < 0.05$, **Table 3**).

Table 3. Comparison of survival rates among liver failure patients with different AFP levels

Group	Cases	Survived (*n*)	Survival rate (%)
AFP < 100 ng/mL group	32	22	68.8
100 ≤ AFP < 200 ng/mL group	32	26	81.3
AFP ≥ 200 ng/mL group	32	31	96.9

4. Discussion

Liver failure is characterized by its severe condition, numerous complications, and high mortality rate, making it one of the most challenging health issues worldwide. Currently, there is no specific clinical treatment for liver failure. Artificial liver plasma exchange creates a favorable environment for hepatocyte regeneration and temporarily replaces liver function to achieve therapeutic goals.

The artificial liver support system (ALSS), referred to as the "artificial liver," began to emerge internationally in the 1950s as a technology providing extracorporeal liver function support for patients with liver failure [11]. Its clinical application abroad has opened an important pathway for treating various severe liver diseases, prolonging the lives of patients with advanced liver failure, and providing time for liver transplantation. Since the 1980s, significant progress has been made in China, particularly by the team led by Academician Lanjuan Li of the First Affiliated Hospital of Zhejiang University School of Medicine. After years of development, artificial liver treatment technology has matured, with three main categories emerging.

Non-bioartificial liver (NBAL) refers to devices primarily aimed at toxin removal, with some also capable of supplementing essential substances and regulating the body's internal environment. NBAL is currently the most developed and widely applied artificial liver technology [12]. It has been extensively utilized in clinical settings and has proven effective [13-16]. Increasing evidence shows that artificial liver therapy can significantly improve liver function and reduce mortality in patients with liver failure. NBAL modalities include plasma exchange (PE), hemofiltration (HF), hemoperfusion (HP), hemodialysis (HD), plasma exchange and hemofiltration in tandem (PERT), and plasma dialysis filtration (PDF). With advancements in adsorption technology, molecular adsorbent recirculating systems (MARS) and Prometheus systems have been developed. These methods, primarily used in Europe, the U.S., and Russia, have demonstrated certain advantages in treating liver failure and hepatorenal syndrome. However, the average frequency of artificial liver sessions abroad is significantly higher than in China. Currently, over 300 tertiary hospitals in China offer artificial liver treatments, with satisfactory outcomes. The dual plasma molecular adsorption system (DPMAS), a novel artificial liver modality, has shown highly effective results in reducing bilirubin and mitigating septic complications in liver failure. While extensively applied in developed countries like the U.S. and parts of Europe for hyperbilirubinemia, DPMAS is now being implemented in many top-tier hospitals in China, including the First Affiliated Hospital of Zhejiang University, Southwest Hospital of the Third Military Medical University, Xijing Hospital of the Fourth Military Medical University, Beijing Ditan Hospital, and Chengdu Infectious Disease Hospital. It is primarily used for early-stage liver failure, hepatic encephalopathy with jaundice, and systemic inflammatory response syndrome with hyperbilirubinemia. However, as DPMAS does not supplement coagulation factors or fibrinogen, its effect on coagulation improvement is limited. Many researchers advocate combining plasma exchange with DPMAS (PE+DPMAS) for treating liver failure. Studies have shown that this combination enhances efficacy and improves prognosis significantly, although it increases costs and complexity. Therefore, artificial liver treatments should be individualized.

Bioartificial liver (BAL) refers to extracorporeal biological reactors constructed using artificially cultured hepatocytes. These devices not only remove toxins and inflammatory mediators and improve clinical symptoms but also exhibit synthetic and metabolic functions akin to hepatocytes [17]. The key challenges in constructing bioartificial livers lie in cell sourcing, cell culture, and bioreactor development. BAL remains in the research stage but holds significant promise for treating liver failure. Recent studies suggest that different types of liver failure induced by various liver diseases may require tailored bioartificial liver treatments for optimal outcomes.

Hybrid artificial liver combines biological and non-biological components to form a comprehensive artificial

liver support system. However, it has not yet been applied in clinical practice.

To evaluate the efficacy of artificial liver plasma exchange and monitor changes in patient's conditions and prognosis, we dynamically observed and compared serum AFP levels to determine the guiding significance of AFP levels in clinical treatment and prognosis assessment. AFP is a globulin synthesized during early fetal development. Elevated AFP levels are commonly seen in primary liver cancer, metastatic liver tumors, or acute and chronic hepatitis with cirrhosis. However, in the pathological changes of hepatocytes in severe hepatitis, continuous necrosis of liver cells stimulates compensatory mechanisms in the body, leading to increased AFP levels, which indicate hepatocyte regeneration. If AFP levels exceed 400 μg/L, an ultrasound examination should be performed to rule out liver cancer.

The results of this study show that the higher the AFP level, the lower the mortality rate of patients. Dynamic changes in AFP levels reflect changes in hepatocyte regeneration capacity. Therefore, clinicians should measure AFP levels early and closely monitor their changes to make real-time and accurate assessments of the severity and prognosis of the condition. This allows for timely adjustments to treatment plans, ultimately improving the survival rate of liver failure patients.

Disclosure statement

The authors declare no conflict of interest.

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