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RESEARCH ARTICLE

Observation on the Effect of Sequentially Combined Multi-modal Artificial Liver Treatment on HBV-related Acute-on-chronic Liver Failure

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Abstract: ***Objective*:** To observe the short-term effect of sequentially combined multi-modal artificial liver treatment (SCMALT) on HBV-related acute-on-chronic liver failure (HBV-ACLF).

***Methods*:** HBV-ACLF patients 155 cases undergoing artificial liver treatment were analyzed, and they were sorted into the SCMALT group and the conventional-modal artificial liver treatment (CALT) group. The clinical data of all patients were recorded and the serum levels of interleukin-8 (IL-8), chemokine interferon-inducible protein-10 (IP-10), and interleukin-6 (IL-6) were detected. The changes in the 30-day survival rate, cytokine level, model for end-stage liver disease (MELD) score, and complications of artificial liver treatment were analyzed.

***Results*:** After being followed up for 30 days, 104 patients survived and 51 died. At the end of the whole-course treatment, the decreases in IL-6, IP-10, and IL-8 levels and MELD scores in the SCMALT group were greater than in the CALT group. Cox regression suggested WBC (*OR*=1.066, 95% *CI* 1.012-1.123, *P*=0.017), AT-III activity (*OR*=0.935, 95% *CI* 0.907-0.964, *p*=0.000) at baseline, artificial liver treatment mode (*OR*=0.362, 95% *CI* 0.164-0.800, *p*=0.012), number of artificial liver treatments (*OR*=0.656, 95% *CI* 0.436-0.986, *p*=0.043), spontaneous peritonitis (*OR*=0.337, 95% *CI* 0.165-0.689, *p*=0.003), and hepatic encephalopathy (*OR*=0.104, 95% *CI* 0.028-0.388, *p*=0.001) were independent influencing factors of 30-day survival rate. SCMALT can significantly prolong the survival period of the patient. No obvious difference was shown in the proportions of bleeding and circulation instability between the two groups (*p*>0.05).

***Conclusion*:** Compared with the CALT, SCMALT can more effectively remove inflammatory mediators and reduce the MELD score in HBV-ACLF patients, which can obviously ameliorate the prognosis, with less effect on the platelet count.

Keywords: Artificial liver, sequential multi-modal treatment, liver failure, therapeutic effect, platelet count, MELD.

1. INTRODUCTION

HBV-related acute-on-chronic liver failure (HBV-ACLF), the most frequent of severe liver disease, is a critical condition with limited treatment means in China. [1] If this disease develops into late-stage liver failure, the mortality of the patients not undergoing liver transplantation can reach 40-90% [1]. Artificial liver support is a significant means to prolong the survival period of patients during the perioperative period of liver transplantation or undergoing liver transplantation [2]. In the early stage of HBV-ACLF, the patients have a severe systemic inflammatory response syndrome (SIRS), which leads to tissue and cell damage and microcirculation disturbance in organs, thus affecting the functions of organs [2]. Early artificial liver treatment can remove bilirubin, inflammatory factors, and macromolecular immune complexes to lighten the

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damage to extrahepatic organs and the hepatic inflammatory response. In recent years, various treatment modes and their combinations, such as plasma exchange combined with continuous renal replacement therapy (PE+CRRT) and plasma exchange combined with dual plasma molecular adsorption system (PE+DPMAS), have been derived from the traditional simple plasma exchange (PE) [3, 4]. According to the hepatic detoxification and synthesis function in the patients, different artificial liver treatment modes can be combined to achieve the best curative effect [5]. The artificial liver treatment usually can not be carried out in HBV-ACLF patients with complications such as thrombocytopenia and bleeding, and the conventional mode and frequency of artificial liver treatment often can not meet the treatment needs of HBV-ACLF patients [6, 7]. Based on the concept of bundle treatment of severe cases, this research was to probe the combined sequential use of three modes such as PE+CRRT, DPMAS, and plasma dialysis filtration (PDF) in the treatment of the early or middle-stage liver failure to explore the efficacy of SCMALT in the therapy of HBV-ACLF patients.

2. MATERIALS AND METHODS

2.1. Patient Data

HBV-ACLF patients (155 cases: 123 males and 32 females with a mean of 50.8±13.4 years of age) undergoing artificial liver treatment in Wuxi Fifth People's Hospital from January 2018 to April 2022 were retrospectively analyzed, and they were grouped into the sequentially combined multi-modal artificial liver treatment (SCMALT) group and the conventional-modal artificial liver treatment (CALT) group. The diagnostic criteria for HBV-ACLF were determined referring to the APASL ACLF consensus of 2019 [8]. Exclusion criteria: (a) The patients with disseminated intravascular coagulation or active bleeding; (b) the patients who are seriously allergic to drugs (such as heparin, plasma and protamine) or blood products in the treatment process; (c) the patients with hemodynamic instability; (d) the patients with unstable infarctions caused by cardiovascular and cerebrovascular accidents; (e) the patients with extravascular hemolysis; and (f) the patients with severe sepsis. This experiment was permitted by the ethics committee of Wuxi Fifth People's Hospital (approval No.: 2021-014-1).

2.2. Comprehensive Treatment

The HBV-ACLF patients received comprehensive treatment, including general supportive treatment, antiviral treatment, treatment of potential complications, supplementation of vitamins and energy, and supplementation of blood products such as plasma and albumin, and all these patients were not treated with glucocorticoids. In the early and middle liver failure stages, the family members signed an informed consent form before the patients underwent artificial liver treatment.

2.3. Artificial Liver Treatment Regimen

The SCMALT regimen was that the patient underwent PE+CRRT on the 1st day, DPMAS on the 2nd day, and PDF on the 3rd day, and the patient underwent artificial liver treatment 3 times again according to the liver function and coagulation states of the patient after an interval of 3 days.

The CALT regimen was that the patient underwent PE+CRRT for the first time, the interval time for each artificial liver treatment was 3-4 days; DPMAS, PDF, or PE+CRRT were selectively performed according to the patient's coagulation status and liver function.

Through femoral vein puncture, indwelt double lumen catheter to establish the intravenous pathway and the patient received routine intramuscular injection of 25mg promethazine before treatment. PE+CRRT mode: JUN 55X blood purification equipment (Lifeline, Japan) and Plasma Flux P2 dry plasma separator (Fresenius, Germany) were used; the blood pump flow rate was 100-120 ml/min, the plasma separation flow rate was 24 ml/min, and the PE volume was 3000 ml. After PE, the patient underwent CRRT continuously for 8 hours, and an AV600S purifier (Fresenius, Germany) was used; the blood flow rate was 200 ml/min, and the replacement fluid flow rate was 3000 ml/h. DPMAS mode: Plasma Flux P2 dry plasma separator (Fresenius, Germany) was used, HA330-Ⅱhemoperfusion cartridge and BS330 bilirubin plasma adsorber (Jafron Biomedical Co., Ltd., China) were used; the blood pump flow rate was 100-120 ml/min, the plasma separation flow rate was 24 ml/min, and the treatment lasted for 4 hours. PDF mode: EC20 plasma separator (Asahi Kasei, Japan) was used; the blood pump flow rate was 100-120 ml/min, the replacement fluid flow rate was 900 ml/h, the dialysate flow rate was 800 ml/h, the plasma pump flow rate was 300 ml/h, and the plasma exchange volume was 2000 ml. Anticoagulation regimen: The unfractionated heparin was used for anticoagulation, with a loading dose of 20 mg and an additional dose of 10 mg per hour, and the anticoagulant treatment was discontinued at half an hour before the end of treatment.

2.4. Observation Indicators

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), antithrombin III (AT-III) activity, model for end-stage liver disease (MELD) score, creatinine (Cr), platelet (PLT) count, international normalized ratio (INR), and white blood cell (WBC) count were recorded at admission (baseline) and after the whole-course treatment. In addition, the peripheral blood samples were taken for cytokine detection at baseline and after the whole-course treatment. The 30-day survival rate of the patients was recorded, and fecal occult blood test and lower extremity vascular ultrasound examination were performed every week.

2.5. Laboratory Instruments and Reagents

INR and antithrombin Ⅲ activities were detected by using the STA-R Automatic Coagulation Analyzer

(STAGO, France), whose original reagent kits were used. The biochemical indicators were detected by using the full-automatic biochemical analyzer ADVIA2400 (Siemens Medical, Germany). The blood routine examination was performed by using the XN-10 Automatic Blood Cell Analyzer (SYSMEX, Japan). The enzyme-linked immunosorbent assay (ELISA) was performed to determine the serum levels of chemokine interferon-induced interleukin-8 (IL-8), protein 10 (IP-10), and interleukin-6 (IL-6) by using ThermoFisher Multiskan FC Microplate Reader.

2.6. Statistical Methods

Data was processed by SPSS 19.0. x±s and *M*（*QR*）presented the continuous variables of normal distribution and measurement data of non-normal distribution, respectively. Group comparison was conducted by rank sum and *t*-test. The counting data were analyzed by chi-square test and expressed as percentages. Cox regression was applied to analyze the risk factors for death; Kaplan Meier method for the survival analysis; and GraphPad Prism 9.0 for creating statistical charts. $p<0.05$ indicated statistical significance.

3. RESULTS

3.1. Patient Data and Laboratory Test Results

HBV-ACLF patients in 155 cases underwent artificial liver therapy, including 83 in the SCMALT group and 72 in the CALT group. The mean age was (47.9±14.1) years in the SCMALT group and (52.1±12.5) years in the CALT group. The average number of artificial liver treatments was 5.4 /per person in the SCMALT group and 3.6 /per person in the CALT group. The baseline data are listed (Table **1**).

3.2. Comparison of Changes in Inflammatory Factors and MELD Score before and after Therapy between SCMALT and CALT Groups

The peripheral blood levels of IL-6, IP-10, and IL-8, and the MELD scores in HBV-ACLF patients at baseline and after whole-course therapy were analyzed. There were no obvious differences in peripheral blood levels of IL-6, IL-8, and the MELD score at baseline between SCMALT and CALT groups, and the peripheral blood levels of IL-6, IP-10, and IL-8 and MELD scores in the SCMALT group were declined more significantly than those in CALT group (Tables **2** and **3**).

3.3. Analysis of Risk Factors Affecting 30-day Survival Outcome of HBV-ACLF Patients

After a 30-day follow-up, among all 155 patients, 104 survived and 51 died. The mortality was 54.2% (39/72) in the CALT group and 14.5% (12/83) in the SCMALT group, and the two groups showed a remarkable difference ($P < 0.05$). The proportions of pneumonia, spontaneous peritonitis, and hepatic encephalopathy were 23.6% (17/72), 44.5% (38/72) and 4.2% (3/72) in the CALT group and 27.7% (23/83), 37.3% (31/83) and 4.8% (4/83) in the SCMALT group respectively, and no significant difference was found ($P > 0.05$). The average number of artificial liver treatments was 5.3/per person in the surviving patients and 3.4/per person in the dead patients. Cox

Table 1. Comparison of laboratory test results and baseline data of HBV-ACLF patients between SCMALT and CALT groups.

Item	SCMALT Group（n=83）	CALT Group（n=72）	Test Value	*p* Value
Gender [cases (%)]	-	-	X^2=0.204	0.694
Male	67 (80.7)	56 (77.8)	-	-
Female	16 (19.3)	16 (22.2)	-	-
Age (years)	47.9±14.1	52.1±12.5	*t*=-1.089	0.278
WBC(×10^9/L)	6.3±2.6	8.2±5.5	*t*=-2.753	0.007
PLT(×10^9/L)	120.4±68.4	116.6±62.6	*t*=0.363	0.717
TBIL(μmol/L)	276.45±113.7	327.7±134.2	*t*=-2.579	0.011
ALT(U/L)	570 (1298)	531.5 (897.5)	*z*=-0.911	0.362
AST(U/L)	504 (1187)	490 (687.25)	*z*=-0.773	0.438
Cr(μmol/L)	63.6±19.1	75.8±39.4	*t*=-2.385	0.019
INR	2.5±2.0	2.5±1.2	*t*=0.047	0.963
AT-III activity (%)	29.2±10.8	25.9±13.3	*t*=1.707	0.090
IL-6 (pg/ml)	40.2±5.9	39.3±6.5	*t*=0.905	0.367
IL-8 (pg/ml)	86.8±7.4	87.8±7.8	*t*=-0.812	0.418
IP-10(pg/ml)	105.1±9.4	101.5±9.8	*t*=2.309	0.022
MELD score	22.7±5.6	24.4±4.7	*t*=-1.978	0.061

Table 2. Comparison of changes in cytokines and MELD score before and after treatment between the two groups.

-	IL-6(pg/ml)		IL-8(pg/ml)		IP-10(pg/ml)		MELD score	
	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment
SCMALT group	40.2±5.9	33.4±6.6	86.8±7.4	79.6±8.6	105.1±9.4	93.6±9.5	22.7±5.6	20.6±5.1
CALT group	39.3±6.5	34.2±6.5	87.8±7.8	81.3±6.9	101.5±9.8	94.4±9.3	24.4±4.7	22.5±4.7
Test value	0.905	-0.704	-0.812	-1.365	2.309	-0.521	-1.978	-2.473
P	0.367	0.483	0.418	0.174	0.022	0.603	0.061	0.015

Table 3. Comparison of the decreases in cytokines and MELD score before and after treatment between two groups.

-	Decrease in IL-6 Level (pg/ml)	Decrease in IL-8 Level (pg/ml)	Decrease in IP-10 Level (pg/ml)	Decrease in MELD Score
SCMALT group	6.82±4.5	7.16±6.4	11.41±9.3	3.15±1.8
CALT group	5.17±3.2	5.43±6.2	7.06±6.8	1.86±1.4
Test value	2.656	0.715	3.356	1.111
P	0.009	0.047	0.001	0.026

regression analysis uncovered that WBC, AT-III activity at baseline, artificial liver treatment mode, number of artificial liver treatments, spontaneous peritonitis, and hepatic encephalopathy were independent factors affecting the 30-day survival outcome of patients (Table **4**). Kaplan–Meier survival curve analysis revealed that the survival rate of HBV-ACLF patients in the SCMALT group was higher than the CALT group (X^2=27.90, p=0.000) (Fig. **1**).

3.4. Occurrence of Complications Related to Artificial Liver Treatment

No significant difference was shown in the proportions of bleeding and unstable heart rate and blood pressure between the SCMALT group and the CALT group. The down-regulation of platelet count in the SCMALT group was smaller than the CALT group, and the incidence of deep vein thrombosis was low (P ＜0.05) (Table **5**).

4. DISCUSSION

The artificial liver system has been commonly used in the therapy of liver failure and end-stage liver disease since its birth, which can significantly improve the 90-day and 5-year survival of liver failure patients [9]. A multi-center study in China included 378 ACLF patients undergoing artificial liver treatment and 412 ACLF patients undergoing conventional treatment; the 28-day and 90-day survival of ACLF patients were 65.2% and 51.0% respectively in the artificial liver treatment group, which were 59.0% and 42.3% respectively in the conventional treatment group [10]. In recent years, the optimal combination of different artificial liver treatment modes is a research hotspot. For example, high-volume plasma (HVP) exchange can reduce the mortality of liver failure patients by inhibiting inflammatory responses and improving multiple organ dysfunction [11]. Because simple PE treatment can lead to alkalosis, decreased colloidal osmotic pressure, and water-electrolyte disorder, which further leads to hepatic encephalopathy, currently liver failure patients undergo routine PE combined with sequential hemofiltration for the purpose of *correcting water-electrolyte* balance *disorder and* removing small and medium molecular toxins [12]. In recent years, DPMAS has been widely used in liver failure treatment, it can significantly remove inflammatory factors and overcome the shortcomings such as plasma deficiency, thus it can be used as a new treatment to replace PE [13]. Yao *et al.* analyzed the efficacy of the combined use of half-volume DPMAS and PE in ACLF treatment. Compared with the use of PE alone, the combined use of half-volume PE and DPMAS may more availably improve ACLF patients' 28-day survival [14]. However, few *research has been conducted on* contrasting the effect of combined multi-modal treatments. DPMAS cannot supplement coagulation factors, and it also has a certain adsorption effect on albumin and coagulation factors. The extracorporeal blood circulation volume is large, and the hypotension will easily occur at the initial stage of treatment. The PDF mode derived from PE can notably ameliorate the prognosis of patients with severe liver failure, remove water-soluble toxins and protein-binding toxins at the same time, supplement coagulation factors and bioactive substances which are lacking within the body, and *maintain acid-base balance and water-electrolyte balance*. After treatment, there are relatively fewer rebounding toxins in the blood, thus possible complications such as imbalance syndrome and tissue edema are prevented. HBV-ACLF patients are characterized by SIRS in the forepart of the onset of

Table 4. Cox regression of risk factors affecting 30-day survival outcome of HBV-ACLF patients.

Influencing Factor	OR	95% CI	*P* Value
WBC at baseline	1.066	1.012-1.123	0.017
PLT at baseline	1.000	0.995-1.005	0.976
TBil at baseline	1.001	0.998-1.004	0.474
Cr at baseline	1.005	0.997-1.013	0.251
INR at baseline	1.091	0.922-1.291	0.309
AT-III activity at baseline	0.935	0.907-0.964	0.000
MELD score at baseline	1.018	0.96-1.080	0.546
Artificial liver treatment mode	0.362	0.164-0.800	0.012
Number of artificial liver treatments	0.656	0.436-0.986	0.043
Spontaneous peritonitis	0.337	0.165-0.689	0.003
Pneumonia	0.888	0.42-1.880	0.756
Hepatic encephalopathy	0.104	0.028-0.388	0.001

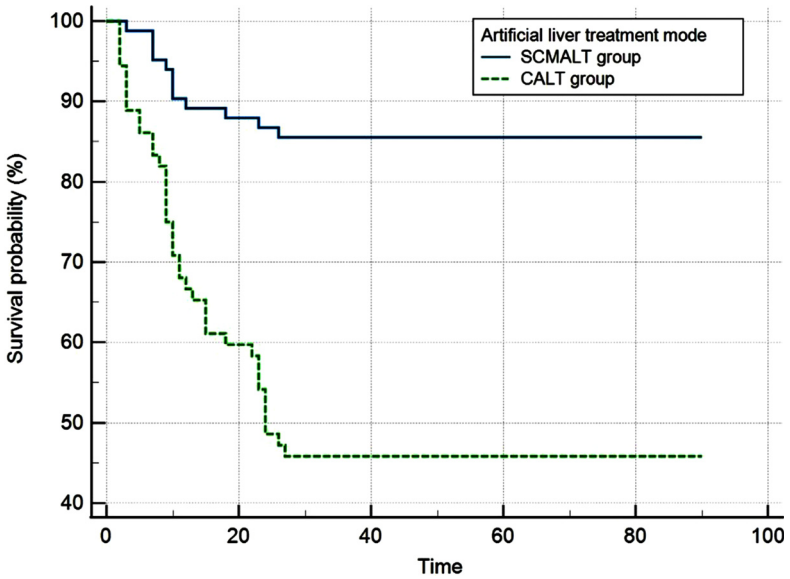

Fig. (1). Comparison of survival curve of HBV-ACLF patients between SCMALT and CALT groups. SCMALT can significantly prolong the survival period of the HBV-ACLF patients. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 5. Occurrence of complications related to artificial liver treatment.

Group	Bleeding	Deep Venous Thrombosis	Unstable Heart Rate and Blood Pressure	Decrease in PLT
SCMALT group [cases (%)]	5 (6.0)	10 (12.0)	5 (6.0)	16.7±12.3
CALT group [cases (%)]	3 (4.2)	18 (25.0)	8 (11.1)	34.1±24.1
Test value	0.272	4.370	1.298	-5.513
P value	0.602	0.037	0.254	0.000

the disease. For example, the peripheral blood levels of chemokines and proinflammatory cytokines are notably increased in the ACLF stage. It is an important intervention measure to fully remove the activated inflammatory factors, endotoxin, and macromolecular immune complexes and supplement effective components such as albumin and coagulation factors [2, 15]. CALT showed a single mode, and the interval time between each artificial liver treatment is relatively long, thus the inflammatory factors and metabolites continuously produced within the body of the patient can not be effectively removed. In the present

research, the SCMALT group's patients underwent sequential treatment combining the characteristics of three modes such as PE+CRRT, DPMAS, and PDF, the decreases in the post-treatment levels of IL-6, IP-10 and IL-8 were greater than those in the CALT group, which could significantly reduce MELD score. Survival analysis demonstrated that the SCMALT group showed a notably longer survival period than the CALT group. The above results suggest that rapidly removing inflammatory factors and inhibiting immune response in HBV-ACLF patients are very effective intervention measures. This study innovatively used the SCMALT regimen, the mortality of patients was 54.2% in the CALT group and 14.5% in the SCMALT group. Ye *et al*. found that the mortality of patients with chronic severe hepatitis B undergoing continuous veno-venous hemofiltration combined with PE was 51.7%, and that of those undergoing medical treatment alone was 79.4%, which can reflect that the current multi-modal optimal treatment has certain advantages over previous studies to a certain extent [16].

This study indicated that WBC, AT-III activity at baseline, artificial liver treatment mode, number of artificial liver treatments, spontaneous peritonitis, and hepatic encephalopathy are independent factors influencing the survival outcome of HBV-ACLF patients, suggesting that severe liver function decompensation and extrahepatic organ involvement are important causes of death, which is consistent with previous studies [1, 17]. There were no statistical differences in the proportions of patients with pneumonia, hepatic encephalopathy, and spontaneous peritonitis between the SCMALT group and the CALT group, which also reflects that HBV-ACLF patients are more prone to multi-site infection and liver function decompensation during immune paralysis in the middle and late stages of the disease. Therefore, performing therapy of artificial liver and maintaining the liver, kidney, and nervous system functions in the early stage are important measures for liver failure therapy.

The patients undergoing multiple artificial liver treatments will have complications such as decreased platelet count, deep vein thrombosis, local and systemic infection and even bleeding, leading to the early termination of artificial liver treatment. In addition, the period with the most severe inflammatory response in liver failure patients lasts about one week, and the conventional treatment frequency often misses the optimal timing for the therapy of liver failure patients. In the current investigation, the average number of artificial liver treatments was 3.6/per person in the CALT group and 5.4/per person in the SCMALT group; the average number of artificial liver treatments was 5.3/per person in the surviving patients and 3.4/per person in the dead patients. The results also suggest that multiple artificial liver treatments can not only completely remove toxins and inflammatory factors, but also cause no increase in complications such as thrombosis, bleeding, and circulatory instability. Previous studies have revealed that advanced liver failure patients have a higher risk of septic shock and hypovolemic shock, thus high-frequency artificial liver intervention within a short term is an effective measure to reduce the complication rate in advanced liver failure patients [18].

Due to the small sample size, this retrospective study has certain limitations. No control group in which the HBV-ACLF patients underwent half volume PE combined DPMAS was established, and this study focused on the implementing bundle intervention such as combined multi-modal artificial liver treatment within a short term to fully curb the inflammatory factor storm in HBV-ACLF patients. However, for liver failure patients, refined fluid management, and catheter management, individualized anticoagulation therapy can significantly decline complications occurrence related to artificial liver treatment. Therefore, this exploration provides a new concept for the cure of liver failure patients in clinical practice.

CONCLUSION

In conclusion, based on the mode and frequency of CALT, this study explores the efficacy role of SCMALT in the treatment of HBV-ACLF patients, which can efficiently prolong the survival period of patients, better remove inflammatory factors, and reduce complications such as thrombosis, bleeding, thrombocytopenia, and circulatory instability.

LIST OF ABBREVIATIONS

SCMALT	=	Sequentially combined multi-modal artificial liver treatment
CALT	=	Conventional-modal artificial liver treatment
SIRS	=	Systemic inflammatory response syndrome
PE+CRRT	=	Plasma exchange combined with continuous renal replacement therapy
ALT	=	Alanine aminotransferase
AST	=	Aspartate aminotransferase
TBil	=	Total bilirubin
HVP	=	High-volume plasma

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the ethics committee of Wuxi Fifth People's Hospital, China (Approval No.: 2021-014-1).

HUMAN AND ANIMAL RIGHTS

All human procedures followed were in accordance with the guidelines of the Helsinki Declaration of 1975.

CONSENT FOR PUBLICATION

The family members signed an informed consent form before the patients underwent artificial liver treatment.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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Declared none.

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