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Research article

Efficacy and safety of artificial liver support system treatment for immune checkpoint inhibitors related liver failure in patients with hepatocellular carcinoma: Protocol for a randomized controlled clinical trial

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ABSTRACT

Background: Immune checkpoint inhibitor-induced immune-mediated hepatitis (ICI-IMH) in patients with hepatocellular carcinoma (HCC) has been established to increase the risk of liver failure (LF). Given the accumulating evidence supporting the efficacy of artificial liver support systems (ALSS) in mitigating both IMH and LF, a single-center, non-blinded, randomized controlled clinical trial is proposed to investigate the efficacy and safety of ALSS for HCC patients with ICI-LF.

Methods: and analysis: Sixty eligible participants will be enrolled in this trial and randomly assigned to one of two groups in a 1:1 ratio. In addition to standard pharmacological management, patients in the trial group will receive treatment with a double plasma molecular adsorption system (DPMAS) and low-volume plasma exchange (LPE) on three occasions, while patients in the control group will undergo PE three times. Patient assessments, including symptoms and laboratory tests, will be conducted at baseline, before and after the three ALSS treatments, and at 2, 4, 8, and 12 weeks post-enrollment. The primary outcome is the mortality rate at 12-week follow-up. Secondary outcomes include changes in the Model for End-Stage Liver Disease (MELD) score following ALSS treatment and the incidence of adverse events (AEs).

Discussion: ICI-LF in HCC patients is associated with a high mortality rate and lacks effective treatment options. Our study aims to evaluate the efficacy and safety of ALSS for this patient population, comparing the effectiveness of two ALSS modalities (DPMAS + LPE vs. PE).

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Trial registration: This clinical trial has been registered on ClinicalTrials.gov with the identifier NCT05484908 (Release Date: July 30, 2022) (https://clinicaltrials.gov/study/NCT05484908).

1. Background

Hepatitis B virus (HBV) infection continues to pose a substantial global health burden, with China accounting for approximately 86 million individuals living with chronic HBV infection. The sequelae of HBV infection, including chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC), are well-recognized as significant threats to human health [1]. Surgical resection and radiofrequency ablation are currently considered the primary treatment options for early-stage HCC. However, the applicability of these treatments is often limited by contraindications to surgery and a high rate of tumor recurrence in advanced HCC. In such cases, alternative therapeutic approaches, including radiotherapy, conventional chemotherapy, targeted therapies, and immunotherapy, have emerged as viable options. Immunotherapy, particularly the use of immune checkpoint inhibitors (ICIs), has gained widespread adoption in recent years. According to the Chinese Society of Clinical Oncology (CSCO) guidelines for ICI utilization in clinical practice, the combination of atezolizumab and bevacizumab is strongly recommended as the first-line immunotherapy for advanced HCC (grade I recommendation). For second-line therapy, the regimens of "sintilimab plus bevacizumab analogue" and "camrelizumab plus apatinib" are suggested based on grade II recommendations. Additionally, the combinations of "lenvatinib plus pembrolizumab or nivolumab" and "oxaliplatin-based chemotherapy plus carelizumab" are proposed as potential treatment options based on grade III recommendations [2].

ICIs have been associated with a spectrum of immune-related adverse events (AEs), including skin toxicity, endocrine toxicity, liver toxicity, and gastrointestinal toxicity. ICI-induced immune-mediated hepatotoxicity (IMH) is classified into four grades (1–4) based on serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (TBIL) levels [3]. The Checkmate 040 study reported a 25 % incidence of Grade 3–4 treatment-related AEs following ICI therapy [4]. A retrospective analysis of Chinese malignant tumors, including HCC, revealed an IMH incidence of 26.8 %, with 7.14 % of cases classified as severe (G3-G4) [5]. A phase II clinical trial of SHR-1210 for advanced HCC demonstrated a 25 % incidence of any-grade treatment-related AST elevation, with AST elevation being the most common G3/4 AE (5 %) [6]. Patients with HCC who develop Grade 4 IMH (AST/ALT $>$20 upper limit normal (ULN), TBIL $>$10 ULN) after ICI treatment typically require hospitalization, discontinuation of ICIs, and administration of high-dose corticosteroids or other immunosuppressive agents such as mycophenolate mofetil [7]. These patients are at increased risk of liver failure (LF), a clinical syndrome characterized by severe coagulation disorder, jaundice, and hepatic encephalopathy, with a high mortality rate. However, cirrhosis, a common condition in HCC patients, can limit the use of corticosteroids and immunosuppressive agents due to the risk of fatal complications such as gastrointestinal hemorrhage or severe infection.

Current evidence suggests that artificial liver support systems (ALSS), particularly plasma exchange (PE), can effectively reduce systemic inflammation and improve the prognosis of patients with acute-on-chronic liver failure (ACLF) [8]. Given the potential of ALSS to remove immune mediators and ameliorate the prognosis of liver failure, it may be beneficial for ICI-induced liver failure (ICI-LF). Accordingly, the CSCO guidelines recommend considering ALSS for patients with Grade 4 hepatotoxicity [3]. Furthermore, the guidelines for the diagnosis and treatment of liver failure indicate that ALSS is indicated for pre-LF, early, and middle LF of various etiologies [9]. Traditional ALSS modalities include PE and plasma perfusion, while combined approaches encompass double plasma molecular adsorption system (DPMAS) and plasma diafiltration. PE and DPMAS are commonly employed in clinical practice. PE is typically indicated for autoimmune diseases given that it can remove toxins, inflammatory cytokines, and certain pathogenic agents while replenishing deficient coagulation factors in LF patients. However, PE is often limited by insufficient plasma supply due to its requirement for a substantial volume of plasma (2000 mL per session). DPMAS offers the advantage of removing inflammatory factors and bilirubin without the need for plasma. Nevertheless, it may increase the risk of bleeding due to the consumption of coagulation factors and anticoagulants during treatment. A recent and promising approach involves the combined therapy of DPMAS and low volume (1000 mL per session) PE (DPMAS + LPE) for the treatment of ACLF, which can reduce plasma consumption and the risk of bleeding. Several retrospective studies have demonstrated that DPMAS + LPE may be more effective than PE in improving the survival rates of HBV-ACLF patients [10,11]. In contrast, a prospective study suggested comparable efficacy between the two ALSS modalities [12]. To our knowledge, there is a paucity of studies investigating the use of ALSS for ICI-LF, both domestically and internationally. Over the past two years, our hospital has witnessed a surge in HCC patients presenting with ICI-LF. The treatment of these patients with PE or DPMAS + LPE has not resulted in any serious adverse events (SAEs). Moreover, most patients have experienced significant improvement, confirming the safety and efficacy of ALSS in this patient population. Therefore, this study protocol outlines a randomized parallel group clinical trial designed to compare the safety and efficacy of PE and the novel combination therapy of DPMAS + LPE for HCC patients with ICI-LF.

2. Methods and analysis

2.1. Study design

This study is a prospective, single-center, non-blinded, randomized controlled clinical trial initiated by the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

The study will enroll HCC patients with ICI-LF who fulfill the diagnostic criteria outlined in current guidelines [3,8,13]. Eligible participants will be randomly assigned in a 1:1 ratio to one of two groups: the trial group receiving DPMAS + LPE and comprehensive internal medical treatment or the control group receiving PE and comprehensive internal medical treatment. As depicted in Fig. 1, this study adheres to a randomized parallel-group design. Randomization will be conducted using computer-generated random numbers. Each patient will receive a sealed, opaque envelope containing their assigned treatment.

2.2. Eligibility criteria

Inclusion criteria for this study include: patients aged 18–65 years with a diagnosis of HBV surface antigen and HBV DNA positivity for more than six months. Participants must also have a clinical diagnosis of HCC and have received ICI treatment within the preceding three months. Additionally, eligible patients will have an HBV DNA level below 2000 IU/mL, elevated AST/ALT levels exceeding 20 ULN, coagulation disorders as evidenced by a prothrombin activity (PTA) less than or equal to 40 % or an international normalized ratio (INR) greater than 1.5, severe jaundice with a total bilirubin level of 10 ULN or higher, a platelet count exceeding 50×10^9/L, and an absence of intrahepatic bile duct dilatation secondary to tumor progression as confirmed by imaging studies.

Exclusion criteria comprise: (1) diagnosis of other active liver diseases (including hepatitis A, C, D, or E virus infections, autoimmune liver disease, alcoholic liver disease, or genetic metabolic liver disease); (2) presence of other primary tumors; (3) pregnancy or lactation; (4) co-infection with human immunodeficiency virus or other immunodeficiency diseases; (5) comorbidities such as severe diabetes, autoimmune diseases, unstable infarction due to cardio-cerebrovascular events, or other significant organ dysfunctions or transplantation; (6) active bleeding, diffuse intravascular coagulation, or thrombotic disease; (7) prior ALSS treatment within 1 week of enrollment; (8) inability to provide informed consent or adhere to the study protocol; (9) inability to return to the hospital for regular follow-up as outlined in the study plan; and (10) patients deemed ineligible for the study by the investigator.

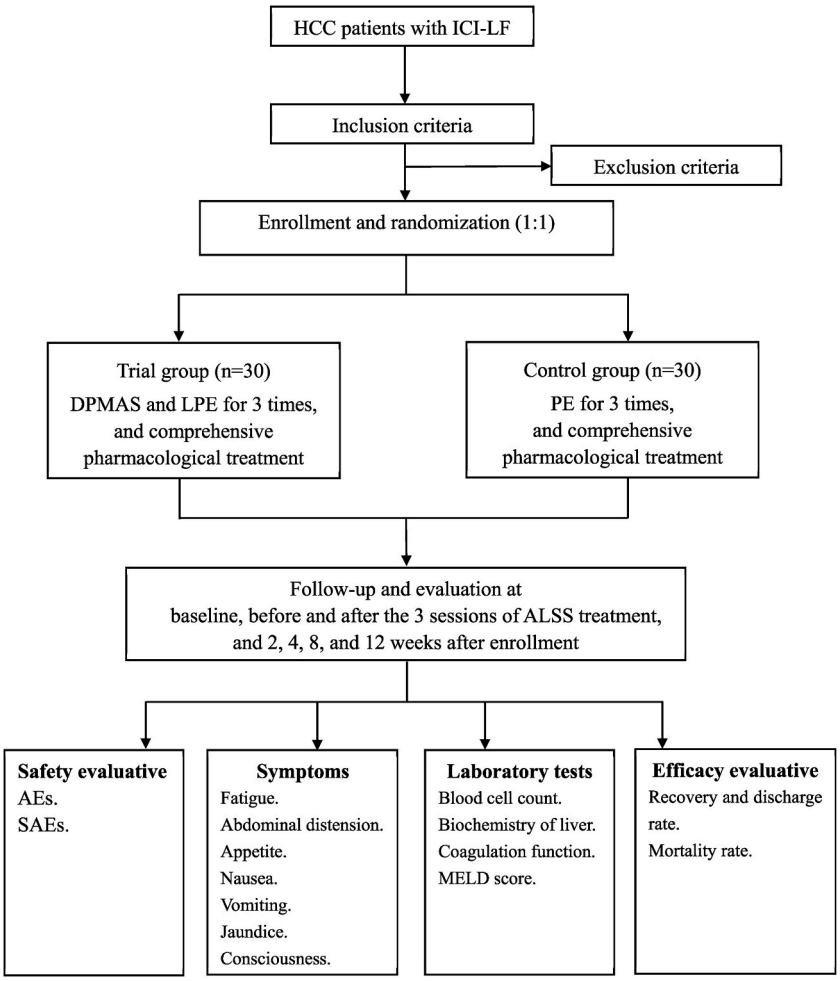

Fig. 1. Study protocol. HCC, hepatocellular carcinoma; ICI-LF, immune checkpoint inhibitor-liver failure; DPMAS, double plasma molecular adsorption system; LPE, low volume plasma exchange; PE, plasma exchange; ALSS, artificial liver support system; AEs, adverse events; SAEs, severe adverse events; MELD, model for end-stage liver disease.

The trial will be terminated if a participant requests to withdraw, experiences any treatment-related SAEs, fails to adhere to the prescribed treatment or follow-up schedule, or if unforeseen circumstances necessitate the discontinuation of the study.

2.3. Interventions

Sixty subjects who meet the eligibility criteria will be randomly assigned to either a treatment group or a control group. All participants will receive comprehensive pharmacological treatment, including adenosyl methionine, compound glycyrrhizin, ursodeoxycholic acid, antiviral agents (tenofovir alafenamide, tenofovir, or entecavir), antibiotics, diuretics, human albumin, and fresh plasma.

In addition to this standard treatment, patients in the trial group will undergo three sessions of DPMAS followed by LPE over a two-week period. During DPMAS treatment, approximately 5000 mL of plasma will be adsorbed at a rate of 25–30 mL/min using BS330 Disposable Plasma Bilirubin Adsorption Columns and HA330-II Disposable Hemoperfusion Cartridges (Jafron Biomedical, Zhuhai). LPE treatment will be initiated immediately after DPMAS using the same membrane plasmapheresis apparatus and plasma separator. The volume of fresh frozen plasma used in LPE therapy will be 1000 mL, with a plasma exchange rate of 25–30 mL/min. Conversely, patients in the control group will receive three sessions of PE over two weeks. The plasma exchange rate for PE will be the same as LPE, but the plasma volume used will be 2000 mL.

Vital signs and patient symptoms will be closely monitored throughout the duration of ALSS treatment. In cases of mild adverse events, such as hypotension or allergic reactions, ALSS therapy may continue with appropriate symptomatic management, including the reduction of blood flow rate, fluid administration, and antihistamine therapy. However, if the adverse events pose a significant risk to the patient's life, the ALSS treatment will be immediately discontinued. To optimize patient safety and treatment outcomes, participants will receive comprehensive information regarding the precautions associated with DPMAS and PE. Additionally, standard care will be provided throughout the ALSS treatment process.

2.4. Evaluation and outcomes

AEs and SAEs associated with ALSS therapy, as well as patient symptoms such as fatigue, abdominal distension, appetite, nausea, vomiting, jaundice, and consciousness, will be meticulously observed and documented in the case report forms (CRFs). Laboratory assessments will encompass blood routine indexes (white blood cell, neutrophils, red blood cell, hemoglobin, platelet count (PLT)), biochemical indexes (AST, ALT, gamma-glutamyl transpeptidase, albumin, TBIL, blood urea nitrogen, creatinine, estimated glomerular filtration rate), and coagulation parameters (prothrombin time [PT], PTA, INR, fibrinogen). To gauge the severity and prognosis of patients, the Model for End-Stage Liver Disease (MELD) score will be calculated using the formula: $MELD = 9.57 \times \ln[\text{creatinine mg/dL}] + 3.78 \times \ln[\text{TBIL mg/dL}] + 11.20 \times \ln[\text{INR}] + 6.43$ [14]. The rates of recovery discharge and mortality will serve as key indicators for evaluating the efficacy of the intervention.

The primary outcome of this study is the mortality rate observed during the 12-week follow-up period following the administration of the two different ALSS treatments in HCC patients with ICI-LF. Secondary outcomes encompass the change in the MELD score post-ALSS treatment, as well as the incidence of AEs and SAEs.

2.5. Participant timeline

Following a screening visit, eligible HCC patients with ICI-LF will be enrolled and randomly assigned to either the trial group or the control group. The participant timeline encompasses baseline assessments, evaluations before and after the three ALSS treatment

Table 1
The schedule of assessments.

Visits	Baseline	Before the 1st ALSS session	After the 1st ALSS session	Before the 2nd ALSS session	After the 2nd ALSS session	Before the 3rd ALSS session	After the 3rd ALSS session	2 weeks	4 weeks	8 weeks	12 weeks
Confirm eligibility	✓										
Patient informed consent	✓										
Randomization	✓										
Medical history	✓										
Symptoms	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
AEs evaluation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discharge[b]								✓	✓	✓	✓
Death or LT[a]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Other recordings	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a] Liver transplantation.
[b] Recovery and discharge.

sessions, and follow-up visits at 2, 4, 8, and 12 weeks post-enrollment. The total duration of follow-up is 12 weeks. The schedule of assessments is detailed in Table 1.

2.6. Sample size

This study adopts a prospective design. Given the limited availability of relevant research data regarding the application of ALSS therapy in HCC patients with ICI-LF, a relatively small sample size is deemed appropriate for the current investigation. To account for potential subject attrition, 30 cases are initially allocated to each group. Accordingly, a total of 60 patients will be enrolled in this study.

2.7. Recruitment

All study participants will be recruited from the Inpatient Department of Infectious Diseases at the Third Affiliated Hospital of Sun Yat-sen University.

2.8. Randomization and allocation concealment

A simple randomization method will be employed in this study. Computer-generated random numbers (SPSS Statistics V.23) will be used to assign patients to two groups, with allocation concealed using sealed envelopes. After random numbers are generated, the allocated treatment will be placed in identical envelopes. Each patient will receive a unique trial number upon meeting the eligibility criteria during the screening visit. Participants will sequentially open their envelopes according to their enrollment order. To mitigate selection bias by investigators, the number table will be maintained by a research assistant and kept inaccessible to researchers involved in patient recruitment. The researcher and patient will become aware of the allocation result only after the patient opens their envelope, signifying the non-blinded nature of this study.

2.9. Data collection and management

All researchers, including data collectors and research assistants, have undergone rigorous training and possess Good Clinical Practice (GCP) certification. Baseline medical data of participants will be collected, encompassing age, sex, duration since HCC diagnosis, ICIs regimen (drugs and treatment durations), interval between the last ICIs treatment and enrollment, complications of LF (including ascites, peritonitis, esophageal variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome), and baseline laboratory data. Subsequent follow-up data will be gathered based on the evaluations outlined in Table 1.

Data collectors and research assistants will gather data at each scheduled visit and record the information on a CRF. Post-discharge patient follow-up will be conducted via telephone or during outpatient visits. The principal investigators or the hospital's department of clinical research administration will review the CRFs of all participants.

2.10. Statistical analysis

Continuous data will be presented as mean ± standard deviation (SD), while categorical variables will be expressed as count and percentage (%). Independent t-tests will be employed to compare continuous variables, such as age, MELD score, ALT, TBIL, PT, INR, creatinine, hemoglobin, and PLT, between the two groups. Categorical variables, including symptoms, mortality rate, recovery discharge rate, and the incidence of AEs and SAEs, will be compared using the chi-square test or Fisher's exact test, as appropriate. Kaplan-Meier survival analysis will be utilized to assess the primary outcome of the mortality rate between the two groups. A two-sided p-value less than 0.05 will be considered statistically significant. Statistical analyses will be conducted using IBM SPSS V.23.0.

The primary efficacy indicators will be analyzed using both the full analysis set (FAS) and the per-protocol set (PPS), while the secondary efficacy indicators will be assessed using the FAS. This analytical approach will enable the evaluation of intervention efficacy and mitigate bias. Safety analysis will be conducted using the safety analysis set (SAS).

2.11. Data monitoring

Raw data will be uploaded to the data monitoring committee (DMC) of the Third Affiliated Hospital of Sun Yat-sen University for verification. A declaration of no conflicts of interest exists between the DMC and the principal investigators of this study. The Ethics Committee of the hospital retains the authority to terminate the trial should participant safety be compromised.

2.12. Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

2.13. Troubleshooting suggestions

ALSS may result in a decrease in PLT count, particularly in patients with liver cirrhosis, as evidenced by our prior research [15]. A

reduction in PLT can elevate the risk of bleeding in LF patients who already exhibit coagulation disorders. Consequently, meticulous monitoring of PLT levels during ALSS therapy is imperative. If PLT counts significantly decline below 50×10^9/L, prompt implementation of appropriate interventions to increase PLT is essential. This may include daily subcutaneous injections of TPO or oral administration of TPO receptor agonists until PLT levels are restored above 50×10^9/L.

As per the CSCO guidelines, for Grade 4 IMH, discontinuation of ICIs is imperative, accompanied by the immediate intravenous administration of methylprednisolone (1–2 mg/kg). If there is no improvement in liver function within 3 days, mycophenolate mofetil (500–1000 mg, twice daily) should be added. In this protocol, in addition to ALSS treatment, comprehensive pharmacological therapy, including the aforementioned regimen, will be implemented. Proton pump inhibitors will be utilized to prevent upper gastrointestinal bleeding, while antibiotics will be administered if signs of infection emerge.

3. Discussion

Globally, particularly in China, the high prevalence of chronic HBV infection is a significant contributing factor to the substantial number of HCC patients. The recent advancements in systemic cancer therapies have led to an increase in the incidence of ICI-IMH, with a considerable proportion of cases progressing to ACLF. Consequently, enhancing survival rates within this patient population is a critical area deserving of thorough investigation.

ALSS therapies, such as PE and DPMAS, have been recommended for the treatment of liver failure [9]. DPMAS with sequential LPE represents a novel ALSS modality that offers the advantage of conserving plasma resources. Our previous studies have demonstrated that DPMAS + LPE can enhance survival rates in patients with intermediate-stage HBV-related ACLF compared to standard medical treatment [16]. Additionally, another study suggested that DPMAS combined with half-dose PE effectively improved liver function in HBV-related ACLF patients, increased 90-day survival rates in patients with PTA>40 %, and exhibited greater cost-effectiveness [17]. Based on these findings, it is highly conceivable that DPMAS + LPE is effective for ICI-LF. This prospective randomized controlled clinical trial, a first of its kind in China, aims to compare two ALSS modalities (DPMAS + PE vs. PE) in HCC patients with ICI-LF. The results of this study may provide valuable insights for future treatment strategies in this patient population.

During the course of this study, certain potential variables may lead to deviations from the planned protocol. These variables include plasma shortages, significant PLT reduction during ALSS treatment, or gastrointestinal bleeding and infections following glucocorticoid therapy. To mitigate these risks and ensure adherence to the protocol, we will implement proactive measures such as planned plasma procurement, avatrombopag administration for PLT counts below 50×10^9/L, and using proton pump inhibitors for gastrointestinal bleeding prevention. A limitation of this study is its single-center design. However, future studies may consider a multicenter approach.

3.1. Trial status

This study was approved under Protocol Version 1.1, dated June 25, 2022, by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, China (approval No [2022]. 02-182-01) on July 27, 2022. The recruitment period was scheduled for two years, with anticipated recruitment commencing on August 1, 2022. The first participant was enrolled on August 12, 2022. Recruitment is ongoing and is expected to conclude on August 31, 2024.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Research Data Deposit of Sun Yat-Sen University (https://rdd.sysu.edu.cn/).

CRediT authorship contribution statement

Qiumin Luo: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Yeqiong Zhang:** Methodology, Formal analysis, Data curation, Conceptualization. **Zhipeng Li:** Methodology, Formal analysis, Data curation, Conceptualization. **Jia Chen:** Data curation, Conceptualization. **Zhexuan Deng:** Data curation, Conceptualization. **Jiadi Lai:** Data curation, Conceptualization. **Xiyao Chen:** Data curation, Conceptualization. **Chan Xie:** Methodology, Data curation, Conceptualization. **Liang Peng:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ying Liu:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Wenxiong Xu:** Writing – review & editing, Supervision, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

The study protocol and informed consent document received approval from the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University, China (approval number [2022] 02-182-01) on July 27, 2022. This clinical trial adheres to the Declaration of Helsinki and the principles of Good Clinical Practice (GCP).

Investigators will thoroughly explain the study protocol, potential risks, and benefits to prospective participants. Informed consent will be obtained from patients before they are randomized and administered the assigned therapy, ensuring their voluntary

participation. Any amendments to the protocol or informed consent document during the study will require reapplication and approval from the Ethics Committee, and participants will need to sign a revised informed consent form.

All Case Report Forms (CRFs) containing patient data will be securely stored in the Department of Infectious Disease at the Third Affiliated Hospital of Sun Yat-sen University. Access to these forms will be restricted to research investigators and inspectors, thereby ensuring the safety and confidentiality of the study data.

Consent for publication

Not Applicable.

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Declaration of competing interest

The authors declare no conflicts of interest that pertain to this work.

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ABBREVIATIONS

ICI-IMH	Immune checkpoint inhibitor-induced immune-mediated hepatitis
HCC	Hepatocellular carcinoma
LF	Liver failure
ALSS	Artificial liver support system
DPMAS	Double plasma molecular adsorption system
LPE	Low volume plasma exchange
PE	Plasma exchange
MELD	Model for end-stage liver disease
AEs	Adverse events
SAEs	Serious adverse events
HBV	Hepatitis B virus
CSCO	Chinese Society of Clinical Oncology
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
TBIL:	Total bilirubin
ACLF	Acute-on-chronic liver failure
PT	Prothrombin time
PTA	Prothrombin activity
INR	International normalized ratio
PLT	Platelet
CRF	Case report forms
FAS	Full analysis set
PPS	Per protocol set
SAS	Safety analysis set
DMC	Data monitoring committee.

References

[1] Polaris Observatory Collaborators, HBV progress towards coveragetargets [EB/OL], https://cdafound.org/polaris-countries-dashboard/, 2022-05.
[2] Guidelines of Chinese society of clinical oncology (CSCO), Immune Checkpoint Inhibitor Clinical Practice, People's medical publishing house, 2021, April, pp. 81–96.
[3] Guidelines of Chinese society of clinical oncology (CSCO), Management of Immune Checkpoint Inhibitor-Related Toxicity, 2021, April, pp. 52–59.
[4] A.B. El-Khoueiry, B. Sangro, T. Yau, et al., Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial, Lancet 389 (10088) (2017) 2492–2502.
[5] S.L. Li, X.P. Gao, Q.Q. Chen, et al., Retrospectively analysis of characteristics and risk factors of immune treatment-related hepatic adverse events in malignant tumor, Chin. J. Oncol. 42 (1) (2020) 50–54.
[6] S.K. Qin, Z.G. Ren, Z.Q. Meng, et al., Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial, Lancet Oncol. 21 (2020) 571–580.
[7] Martin Ed, J.M. Michot, O. Rosmorduc, et al., Liver toxicity as a limiting factor to the increasing use of immune check point inhibitors, JHEP Reports 2 (6) (2020) 100170.
[8] R. Maiwall, M. Bajpai, A.K. Choudhury, et al., Therapeutic plasma-exchange improves systemic inflammation and survival in acute-on-chronic liver failure: a propensity-score matched study from AARC, Liver Int. 41 (2021) 1083–1096.
[9] Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Guideline for diagnosis and treatment of liver failure (2018) 35 (1) (2019) 38–44.
[10] J. Yao, S. Li, L. Zhou, et al., Therapeutic effect of double plasma molecular adsorption system and sequential half-dose plasma exchange in patients with HBV-related acute-onchronic liver failure, J. Clin. Apher. 34 (2019) 392–398.
[11] S. Zhong, N. Wang, J. Zhao, et al., Plasma exchange combined with double plasma absorption therapy improve the prognosis of acute-on-chronic liver failure, Zhonghua Gan Zang Bing Za Zhi 26 (2018) 744–749.
[12] Y.M. Wan, Y.H. Li, Z.Y. Xu, et al., Therapeutic plasma exchange versus double plasma molecular absorption system in hepatitis B virus-infected acute-on-chronic liver failure treated by entercavir: a prospective study, J. Clin. Apher. 32 (6) (2017) 453–461.
[13] S.K. Sarin, A. Choudhury, M.K. Sharma, et al., Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update, Hepatology International 13 (2019) 353–390.
[14] M. Malinchoc, P.S. Kamath, F.D. Gordon, et al., A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts, Hepatology 31 (4) (2000) 864–871.
[15] W.A.N.G. Lu, Wenxiong Wu, Shu Zhu, et al., Influence of artificial liver support system therapy on platelet in treatment of hepatitis B virus-related acute-on-chronic liver failure, J Clin Hepatol 38 (5) (2022) 1053–1058.
[16] Wenxiong Xu, Shu Zhu, Luo Yang, et al., Safety and efficacy of double plasma molecular adsorption system with sequential low-volume plasma exchange in intermediate-stage hepatitis B virus-related acute-on-chronic liver failure, J. Med. Virol. 95 (3) (2023) e28650.
[17] Cichun Wu, Wenting Peng, Da Cheng, et al., Efficacy and economic evaluation of nonbiological artificial liver therapy in acute-on-chronic hepatitis B liver failure, J Clin Transl Hepatol 11 (2) (2023) 433–440.