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ORIGINAL RESEARCH

Association Between Artificial Liver Support System and Prognosis in Hepatitis B Virus-Related Acute-on-Chronic Liver Failure

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Objective: The artificial liver support system (ALSS) has been recruited as an available method for patients with acute-on-chronic liver failure (ACLF), but its impact on the outcome of ACLF remains controversial. This study aimed to investigate the association between ALSS treatment and short-term prognosis of hepatitis B-related ACLF (HBV-ACLF).

Methods: This was a retrospective observational cohort study, and data were obtained from the Center of Infectious Diseases, West China Hospital of Sichuan University, between Mar 2015 and December 2021. The primary outcome was 28-day transplant-free mortality and the secondary outcomes were 60- and 90-day transplant-free mortality. Patients were divided into standard medical therapy (SMT) and ALSS groups. Kaplan-Meier survival analysis curves show the 28-day, 60-day and 90-day transplant-free mortality. Based on the feature selection result of univariate logistic, univariate Cox and Boruta algorithm, the univariate and multivariate logistic and COX regression models were used to investigate the association of ALSS with 28-day, 60-day and 90-day outcomes in patients with HBV-ACLF. Subgroup analyses were conducted to test the robustness of the results.

Results: A total of 589 hBV-ACLF patients were enrolled in this study (median age, 48.00 years [IQR,44.00–55.00 years]; 70 [11.9%] female). The 28-day, 60-day and 90-day transplant-free mortality rates were 25.6%, 35.8% and 38.9%, respectively. In the univariate and Kaplan-Meier survival analysis, ALSS could significantly reduce 28-day, 60-day and 90-day transplant-free mortality compared to SMT. Furthermore, an in-depth analysis of our study revealed that the therapeutic benefits of the ALSS were observed exclusively within the end-stage (PT-INR $\geq$ 2.5) subgroup of HBV-ACLF patients.

Conclusion: Compared to SMT, ALSS demonstrated efficacy primarily in enhancing the short- term prognosis of end-stage HBV-ACLF patients, rather than across the entire spectrum of HBV-ACLF patients.

Keywords: artificial liver support systems, hepatitis B-related acute-on-chronic liver failure, prognosis

Introduction

Chronic hepatitis B virus (HBV) infection remains a serious global public health problem. In 2024, WHO reported[1] that approximately 254 million people worldwide are infected with HBV, and 1.10 million deaths worldwide due to chronic hepatitis B (CHB). CHB is the leading cause of acute-on-chronic liver failure (ACLF) in China and other Asian countries, accounting for more than 60% of cases. HBV-related ACLF (HBV-ACLF) is a clinical syndrome characterized by extensive hepatocellular necrosis, severe jaundice, and coagulation dysfunction over a short period of time due to chronic HBV infection, accompanied by severe complications such as ascites and/or hepatic encephalopathy and hepatorenal syndrome, with a very complex pathogenesis and high short-term mortality.[2,3] Severe systemic inflammatory response and immune dysfunction are the main pathophysiological factors in the dramatic deterioration of patients with HBV-ACLF.[4,5] Despite socioeconomic development and advances in medical technology, the 28-day and 90-day mortality rates of HBV-ACLF patients are still as high as 26.3% and 38.2%, respectively,[6,7] which poses a great challenge in medical treatment, and it is particularly important to actively explore effective treatment methods.

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Liver transplantation is considered the most effective treatment for HBV-ACLF. However, its clinical application is severely limited by several factors, including the scarcity of donor organs, high economic costs, and risk of postoperative complications.[8,9] Meanwhile, a number of new alternative therapies, such as stem cell therapy, hepatocyte transplantation, and bioartificial liver devices have shown positive therapeutic potential in preclinical and early clinical studies, but their safety, efficacy, and long-term efficacy still require further scientific verification.[10–12] Therefore, standard medical therapy (SMT) and artificial liver support system (ALSS) treatments remain the main treatment modalities for HBV-ACLF. Compared to SMT, ALSS treatment can provide temporary hepatic support by mimicking key hepatic functions such as toxin clearance, haemodynamic modulation, cytokine clearance and metabolic improvement, thereby facilitating hepatocyte regeneration and recovery, making it the most commonly used therapy for HBV-ACLF treatment.[4] The basic techniques of ALSS treatment include plasma exchange (PE) and plasma adsorption. In clinical practice, ALSS predicated on the foundation of PE represents the predominant therapeutic modality selected for the management of patients with HBV-ACLF. A 2003 systematic review suggested that ALSS treatment may reduce mortality in ACLF compared to SMT.[13] However, several recent clinical trials have showed no improvement in short-term survival in ACLF patients treated with ALSS compared to SMT.[14–16] Considering the controversial efficacy of ALSS treatment, the present study aimed to investigate the relationship between ALSS treatment and the prognosis of patients with HBV-ACLF in depth and to identify patient groups that might benefit from ALSS treatment, with a view to providing theoretical support for clinical treatment decisions and the rational use of medical resources.

Materials and Methods

Study Setting and Design

This single-center cohort study was conducted in the Center of Infectious Diseases, West China Hospital of Sichuan University (Sichuan Province, China). Adult patients diagnosed with HBV-ACLF between March 2015 and December 2021 were retrospectively enrolled in the study. All patients were divided into two groups based on whether they received ALSS treatment during their hospitalization:(i) a standard medical treatment (SMT) group, in which patients received SMT only, and (ii) an ALSS group, in which patients received SMT plus ALSS. Treatment was implemented based on the clinician's professional judgement, and informed consent was obtained from the patient. The choice of materials and parameters used for ALSS was also based on the clinician's professional judgement. The participating clinicians were blinded to the study design and were not involved in any data collection or analysis.

During the follow-up period, the survival status and time were recorded through electronic visit records or telephone interviews. Two researchers verified the original medical records to ensure their completeness and accuracy. In addition, to further observe the prognosis of patients with HBV-ACLF at different stages, we divided the patients into three stages based on previous literature:[17] PT-INR < 2.0 (early stage), $2.0 \leq$ PT-INR < 2.5 (mid-stage), and PT-INR ≥ 2.5 (end-stage).

This study was conducted in accordance with the principles of the Declaration of Helsinki (revised in Brazil 2013). This study was approved by the Biomedical Research Ethics Committee of West China Hospital of Sichuan University (Ethics number: 2022–919). Since this study did not contain protected patient information and was retrospective in nature, a waiver for the requirement for informed consent was included in the approval. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[18]

Study Population

Adults in patients who met the diagnostic criteria for HBV-ACLF were included in this study. HBV-ACLF was diagnosed according to the Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) criteria,[2] included patients with CHB, total bilirubin (TBIL) ≥12 mg/dL (205 μmol/L) and PT-INR ≥1.5. CHB was diagnosed according to the 2009 AASLD guidelines[19] as follows: HBV surface antigen positive for ≥6 months; serum HBV-DNA ≥20000 IU/mL (105 copies/mL); persistently or intermittently elevated alanine aminotransferase/aspartate aminotransferase levels. Although some patients were hospitalized more than once, only the first hospitalisation was considered.

The exclusion criteria were as follows: (1) age < 18 years, (2) pregnant, (3) HIV infection, (4) liver cancer and other tumors, (5) liver transplant, (6) missing follow-up data.

Treatment

All patients received SMT, which included the management of precipitating factors, underlying chronic liver disease, and complications. Hepatoprotective and supportive medications were also administered. The patients were assessed by their treating physicians for suitability for ALSS treatment, which was recommended only in the presence of at least one of the following conditions: liver failure or severe hyperbilirubinemia that did not respond to medical treatment. Given the shortage of plasma availability and evidence from previous studies that the Double Plasma Molecular Adsorption System (DPMAS) combined with PE can achieve therapeutic efficacy with reduced plasma volumes, the use of DPMAS followed by PE using half the total plasma volume (approximately 1,500 mL) has become common practice.[17] ALSS treatment included DPMAS combined with PE and PE in this study. The treatment for patients receiving the DPMAS combined with PE included an initial two-hour session of DPMAS, immediately followed by a one-hour session of PE procedure using 1,500 mL of plasma. Approximately 1,500 mL of plasma was used in the patients who only received PE. The ALSS treatment was halted under one of the following scenarios: (1) if the patient refused to conduct ALSS treatment, or if their medical condition precluded further ALSS treatment. (2) Favorable response to ALSS treatment, evidenced by an improvement in the patient's condition with TBIL < 10 mg/dL (171 μmol/L) and decreased PT-INR.[17]

Covariates

Our study's covariates were selected based on previous studies that have shown their association with mortality in HBV-ACLF patients.[3,7,20] We included the following variables: demographic characteristics (age, gender, height, weight, alcohol abuse), anti-hepatitis B virus treatment, comorbidities [hypertension, type 2 diabetes (T2DM), chronic kidney disease (CKD), liver cirrhosis, partial virological response, infection, esophagogastric variceal, upper gastrointestinal bleeding, ascites, hepatic encephalopathy], vital signs [temperature, mean arterial pressure (MAP), heart rate], and laboratory tests. Partial virological response is defined as HBV-DNA >2,000 IU/mL after at least 48 weeks of treatment with nucleoside (acid) analogues in well-compliant patients. Patients were included in the study if they met the diagnostic criteria for HBV-ACLF. This study was a retrospective study in which the clinical data were collected from the electronic medical records. Demographic data were collected from patient self-reports. Comorbid conditions were primarily self-reported by the patients or documented in their medical history. Vital signs and laboratory indicators were the first indicators within 24 hours of admission.

Primary Outcome and Secondary Outcomes

The primary outcome of the study was 28-day transplant-free mortality. A 28-day observation window is the most commonly measured follow-up period in literature.[7,21] Secondary outcomes included 60- and 90-day transplant-free mortality.

Statistical Analysis

Continuous variables that conformed to a non-normal distribution were expressed as the median (P_{25}, P_{75}). Counting data were expressed as frequency and percentage (%). For analysis of baseline characteristic, Mann–Whitney *U*-test was used for statistical differences in continuous variables between the two ALSS groups, and the chi-square test was used for categorical variables. The method of multiple interpolation was used to handle missing data.[22] We used Kaplan-Meier and log-rank analyses to determine survival curves.

The association between ALSS treatment and the prognosis of HBV-ACLF could be influenced by various confounders. First, we employed three different approaches to identify covariates that impact the prognosis of HBV-ACLF: univariate logistic regression, univariate Cox regression, and Boruta's algorithm. For univariate logistic regression analysis, independent variables with $P < 0.1$ were selected.[23] In the univariate Cox regression analysis, if the proportional hazards assumptions (PHA) assumption were not met, the time-transforming function (TT function) was used to handle the time-dependent covariates. Only the covariates with $P < 0.1$ were selected.[24] Furthermore, to ensure the robustness of

the variable selection, we applied Boruta's algorithm (random seed = 100 and maxruns = 1000) to identify the variables most significantly associated with clinical outcomes. After Bonferroni correction, the variables with $P < 0.1$ were retained.[25] Second, based on the variables filtered through these methods, we conducted multivariate COX regression and multivariate logistic regression models to evaluate the association between ALSS treatment and the prognosis of HBV-ACLF. Third, we conducted multivariate COX regression and multivariate logistic regression models to evaluate the association between ALSS treatment and the prognosis of different stages of HBV-ACLF. Finally, potential modifications of the relationship between ALSS and mortality were assessed in the end-stage group, which included the following variables: age (< 65 vs ≥ 65 years), gender (female vs male), hypertension (yes vs no), T2DM (yes vs no), liver cirrhosis (yes vs no), anti-hepatitis B virus treatment (yes vs no), and partial virological response (yes vs no). Heterogeneity and interaction were assessed using univariate Cox regression in subgroups.

Statistical analyses were performed using R Statistical Software (https://www.r-project.org, The R Foundation) and Free Statistics analysis platform. Two-sided values of P <0.05 were considered statistically significant.

Results

Patient Characteristics

A total of 652 patients with HBV-ACLF were initially screened. According to the exclusion criteria, 63 patients were excluded. Finally, 589 patients who met the inclusion criteria were enrolled in this study (Figure 1).

The median age of patients with HBV-ACLF was 48.0 (44.0–55.0) years, and 11.9% were female (Table 1). The median weight was 66.0 (59.0–75.0) kg. A total of 430 (73.0%) patients had liver cirrhosis and 197 (33.4%) patients had

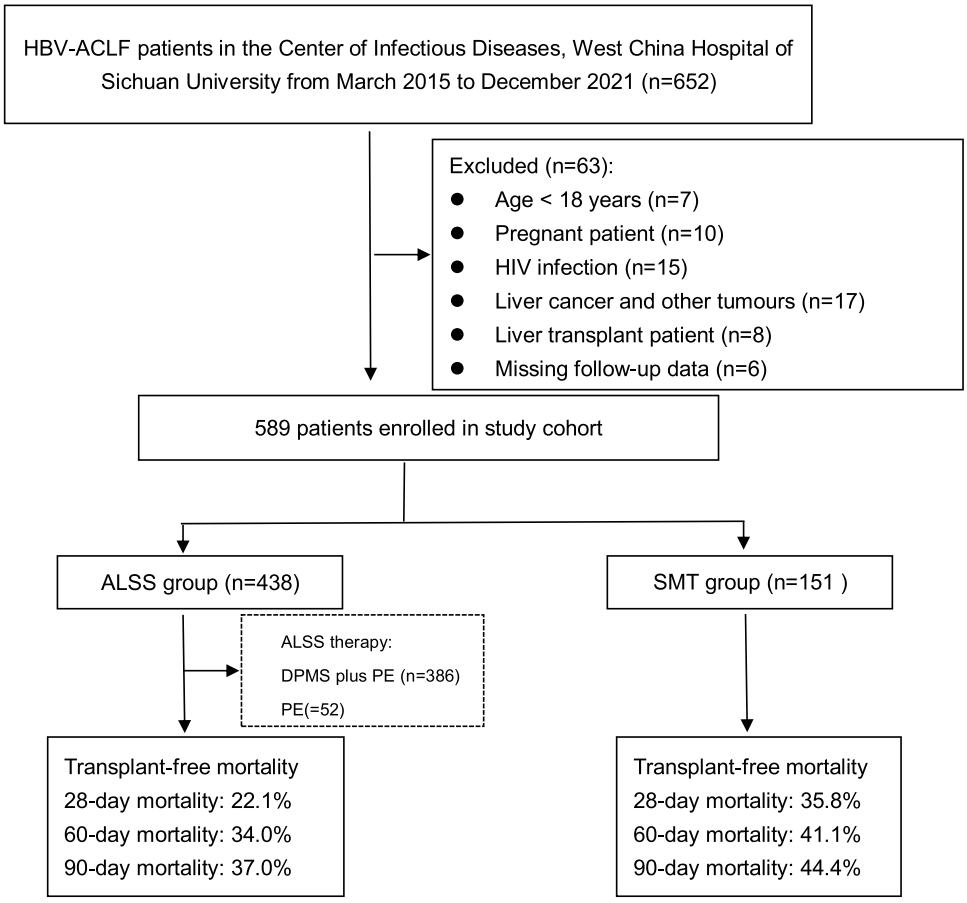

Figure 1 Flow chart of HBV-ACLF patients included in this study.
Abbreviations: ALSS, artificial liver support systems; HBV-ACLF, hepatitis B-related acute-on-chronic liver failure; HIV, Human Immunodeficiency Virus; SMT, standard medical therapy; DPMAS, double plasma molecular adsorption system; PE, plasma exchange.

Table 1 Baseline Characteristics of Original Cohort

	Overall (N=589)	SMT group (N=151)	ALSS group (N=438)	p-value	Statistic	Missing data (%)
Age	48.0 (40.0, 55.0)	47.0 (41.0, 54.0)	48.0 (39.2, 55.0)	0.79	0.071	0.00
Gender (Female)	70 (11.9)	18 (11.9)	52 (11.9)	0.987	0	
Height	168.0 (162.0, 171.0)	168.0 (162.0, 171.0)	168.0 (162.0, 171.0)	0.846	0.038	20 (3.40)
Weight	66.0 (59.0, 75.0)	65.0 (58.0, 75.0)	67.0 (59.0, 75.0)	0.504	0.446	90 (15.28)
Alcohol abuse (YES)	**168 (28.5)**	**24 (15.9)**	**144 (32.9)**	**< 0.001**	**15.885**	0.00
Anti Hepatitis B Virus treatment (YES)	**197 (33.4)**	**33 (21.9)**	**164 (37.4)**	**< 0.001**	**12.258**	0.00
Comorbidities (boolean)						
Hypertension (YES)	36 (6.1)	9 (6)	27 (6.2)	0.928	0.008	0.00
T2DM (YES)	57 (9.7)	14 (9.3)	43 (9.8)	0.845	0.038	0.00
CKD (YES)	12 (2.0)	3 (2)	9 (2.1)	1	Fisher	0.00
Liver cirrhosis (YES)	430 (73.0)	107 (70.9)	323 (73.7)	0.491	0.474	0.00
Partial virological response (YES)	87 (14.8)	15 (9.9)	72 (16.4)	0.052	3.774	0.00
Infectious (YES)	**38 (6.5)**	**2 (1.3)**	**36 (8.2)**	**0.003**	**8.844**	0.00
Esophagogastric variceal (YES)	37 (6.3)	13 (8.6)	24 (5.5)	0.172	1.868	0.00
Upper gastrointestinal bleeding (YES)	**63 (10.7)**	**23 (15.2)**	**40 (9.1)**	**0.037**	**4.373**	0.00
Ascites (YES)	**69 (11.7)**	**4 (2.6)**	**65 (14.8)**	**< 0.001**	**16.136**	0.00
Hepatic encephalopathy (YES)	**32 (5.4)**	**15 (9.9)**	**17 (3.9)**	**0.005**	**8.006**	0.00
Vital signs (1st 24 h)						
Temperature	36.6 (36.4, 36.8)	36.5 (36.4, 36.7)	36.6 (36.4, 36.8)	0.077	3.134	0.00
MAP	90.7 (83.7, 98.0)	89.3 (82.8, 96.7)	91.0 (84.0, 99.0)	0.053	3.756	0.00
Heart rate	83.0 (75.0, 93.0)	82.0 (72.5, 96.0)	83.0 (75.0, 92.0)	0.664	0.189	0.00
Laboratory tests (1st 24 h)						
WBC	6.9 (5.2, 9.6)	6.9 (5.3, 9.8)	6.9 (5.2, 9.5)	0.948	0.004	0.00
Hemoglobin	127.0 (109.0, 139.0)	122.0 (106.0, 137.0)	127.0 (112.0, 139.8)	0.099	2.717	0.00
Platelet	94.0 (64.0, 132.0)	96.0 (63.0, 132.0)	94.0 (65.0, 131.8)	0.975	0.001	0.00
ALT	204.0 (82.0, 618.0)	180.0 (74.0, 530.0)	218.0 (83.2, 651.2)	0.147	2.102	0.00
AST	183.0 (95.0, 386.0)	169.0 (98.5, 354.0)	191.0 (94.0, 418.2)	0.383	0.76	0.00
ALP	148.0 (115.0, 183.0)	144.0 (117.0, 179.0)	149.0 (115.0, 183.0)	0.754	0.098	0.00
γ-GGT	78.0 (52.0, 116.0)	76.0 (52.0, 106.5)	80.0 (52.0, 117.8)	0.327	0.961	1 (0.17)
TBIL	**364.4 (285.3, 439.8)**	**328.2 (272.4, 418.5)**	**371.1 (291.0, 449.4)**	**0.002**	**9.514**	0.00
ALB	**32.4 (29.5, 35.5)**	**31.4 (28.9, 34.8)**	**32.8 (29.8, 35.9)**	**0.006**	**7.689**	**1 (0.17)**
Na	135.4 (132.4, 138.0)	135.0 (131.8, 138.0)	135.4 (132.6, 138.0)	0.443	0.589	1 (0.17)
K	3.8 (3.4, 4.1)	3.8 (3.5, 4.1)	3.8 (3.4, 4.1)	0.616	0.252	1 (0.17)
Ca	**2.1 (2.0, 2.2)**	**2.1 (2.0, 2.2)**	**2.1 (2.0, 2.2)**	**0.001**	**10.674**	**33 (5.60)**
Plasma ammonia	73.8 (52.8, 103.0)	70.0 (48.8, 103.0)	74.3 (54.8, 103.0)	0.23	1.439	22 (3.74)
Glu	5.9 (4.5, 7.8)	5.6 (4.5, 7.3)	5.9 (4.6, 8.0)	0.342	0.902	6 (1.02)
AFP	53.6 (13.4, 129.0)	51.3 (13.9, 151.7)	54.1 (13.4, 126.6)	0.995	0	139 (23.60)
PT	23.3 (20.1, 28.9)	22.7 (19.7, 30.1)	23.8 (20.4, 28.6)	0.391	0.735	0.00
PT-INR	2.1 (1.8, 2.6)	2.0 (1.7, 2.6)	2.1 (1.8, 2.6)	0.124	2.36	0.00
Stage of HBV-ACLF				**< 0.001**	**14.116**	
Early-stage group	254 (43.1)	81 (53.6)	173 (39.5)			0.00
Mid-stage group	167 (28.4)	26 (17.2)	141 (32.2)			0.00
End-stage group	168 (28.5)	44 (29.1)	124 (28.3)			0.00
Outcome						
Hos_los	**21.0 (12.0, 29.0)**	**13.0 (4.0, 22.0)**	**22.0 (15.0, 32.0)**	**< 0.001**	**53.062**	0.00
28-day transplant-free mortality (Death)	**151 (25.6)**	**54 (35.8)**	**97 (22.1)**	**< 0.001**	**10.919**	0.00
60-day transplant-free mortality (Death)	211 (35.8)	62 (41.1)	149 (34)	0.12	2.422	0.00
90-day transplant-free mortality (Death)	229 (38.9)	67 (44.4)	162 (37)	0.108	2.577	0.00

Note: Values are presented as mean (standard deviation) or median [Q1, Q3] for continuous variables and number (percentage) for categorical variables. Variables in bold have p-value < 0.05.

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received anti-hepatitis B virus treatment. The most prevalent chronic comorbidity was T2DM (9.7%), followed by hypertension (6.1%). Combined ascites, upper gastrointestinal bleeding, and hepatic encephalopathy were present in 11.7%, 10.7%, and 5.4%, respectively. The median length of hospital stay was 21.0 (12.0, 29.0) days.

There were 438 patients in the ALSS group and 151 patients in the SMT group. Of the 438 individuals treated with ALSS, 386 received double plasma molecular adsorption system (DPMAS) plus plasma exchange (PE), and 52 received PE. Alcohol abuse, hepatitis B virus treatment, infection, and ascites were more common in the ALSS group than in the SMT group (P<0.001), while upper gastrointestinal bleeding and hepatic encephalopathy were more common in the SMT group than in the ALSS group. Levels of laboratory indicators, including TBIL and ALB, were significantly higher in the ALSS group compared to the SMT group.

The Clinical Outcomes (Transplant-Free Mortality)

The 28-day, 60-day and 90-day transplant-free mortality were 25.6%, 35.8%, and 38.9%, respectively (Table 1). Compared to patients in the SMT group, ALSS significantly reduced only 28-day transplant-free mortality (P<0.001), whereas there was no significant reduction in 60- and 90-day transplant-free mortality was observed (P>0.05, Table 1).

The Kaplan-Meier survival curve showed that the probability of 28-, 60-, and 90-day mortality of patients in the ALSS group was lower than that of patients in the SMT group (All P <0.05, Figure 2). The liver transplant-free mortality rates at 28, 60, and 90 days were lower in the DPMS combined with PE treatment group compared to the PE-only treatment group. However, the differences between the two groups were not statistically significant (Table 2).

To further explore the association between ALSS and prognosis in HBV-ACLF patients at different stages of the disease, wo found that ALSS did not significantly reduce 28-, 60-, and 90-day transplant-free mortality in the early-stage and mid-stage patients compared to the SMT group (Figure 3A and 3B). However, ALSS significantly reduce mortality in end-stage patients (Figure 3C).

Covariates Selection

The results of feature screening based on Boruta algorithm are shown in Figure 4. The 10 variables most strongly associated with 28-day prognosis of HBV-ACLF, in order of importance based on z-value, were age, PT, PT-INR, TBIL, Na, WBC, AFP, platelet, CKD, and glucose level.

Eighteen covariates were identified by univariate logistic regression analysis as being associated with the prognosis of HBV-ACLF, including age, height, alcohol abuse, anti-hepatitis B virus treatment, T2DM, CKD, liver cirrhosis, upper gastrointestinal bleeding, hepatic encephalopathy, heart rate, WBC, hemoglobin, platelet, ALT, TBIL, Na, glucose, and PT (P <0.01). Additionally, the 19 covariates selected by univariate Cox regression analysis were similar to those identified in the univariate logistic regression analysis but also included plasma ammonia level.

Associations Between ALSS and Clinical Outcomes

In the initial univariate Cox regression analysis for all HBV-ACLF patients, our results showed that ALSS reduced the risk of transplant-free mortality by 47% [HR, 0.53 (95% CI, 0.38–0.74)], 29% [HR, 0.71 (95% CI, 0.53–0.96)], and 28% [HR, 0.72 (95% CI, 0.54–0.95)] at 28, 60, and 90 days, respectively, compared with the SMT group. To determine the robustness of these results, we performed multivariate logistic and Cox regression analyses that adjusted for various covariates. After performing adjusted multivariate logistic and Cox regression analysis, ALSS remained significantly associated with a reduction in 28-day transplant-free mortality. However, in the logistic models adjusting for covariates which all covariates or selected by univariate logistic regression, ALSS did not demonstrate a statistically significant reduction in 60-day and 90-day transplant-free mortality (P >0.05, Table 3).

We performed stratified analyses to determine whether the efficacy of ALSS was related to the stage of HBV-ACLF. In the early-stage group of patients, our multiple models consistently indicated that ALSS did not significantly reduce the risk of death in HBV-ACLF patients. In the mid-stage group of patients, although some models supported that ALSS reduced the risk of mortality, the results were not robust enough to draw firm conclusion. However, in the end-stage group of patients, we observed a significant survival benefit from ALSS. Specifically, ALSS reduced the risk of 28-day transplant-free mortality by 66% [HR, 0.34 (95% CI, 0.21–0.55)] to 80% [OR, 0.2 (95% CI, 0.06–0.64)], the risk of 60-

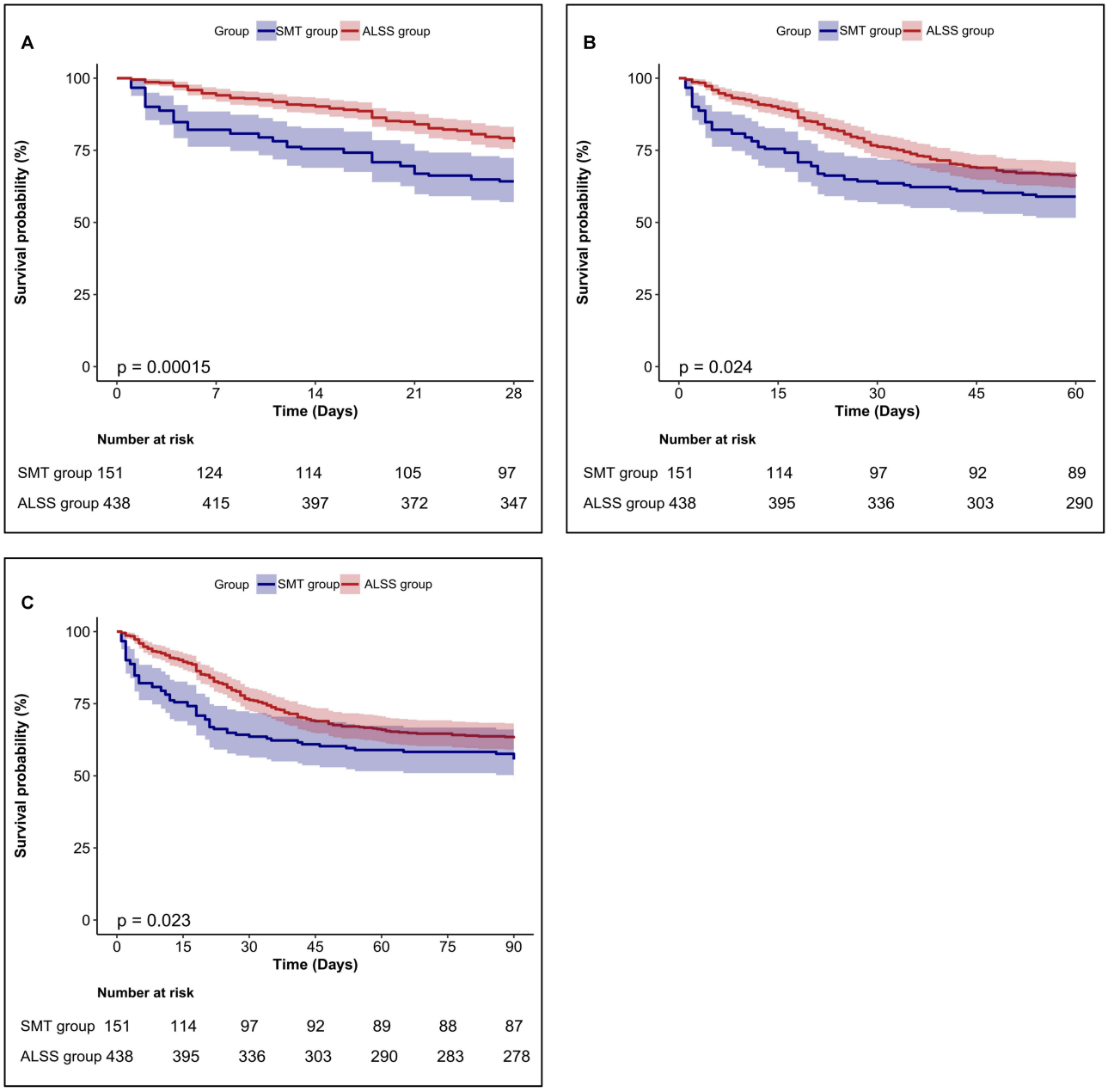

Figure 2 Kaplan-Meier survival analysis of the ALSS and SMT groups in HBV-ACLF patients for prognosis. (**A**) 28-day transplant-free mortality. (**B**) 60-day transplant-free mortality. (**C**) 90-day transplant-free mortality.

day transplant-free mortality by 57% [HR, 0.43 (95% CI, 0.28–0.65)] to 79% [HR, 0.21 (95% CI, 0.11–0.4)], and the risk of 90-day transplant-free mortality by 61% [HR, 0.39 (95% CI, 0.26–0.58)] to 93% [OR, 0.07 (95% CI,0.01–0.38)] (Table 3).

End-Stage HBV-ACLF Subgroup Analysis

Although our study results have shown that ALSS can reduce the risk of transplant-free mortality in end-stage HBV-ACLF patients, there remains potential variability in patient prognosis across different subgroups. Therefore, we conducted interaction and subgroup analyses to further identify the therapeutic benefit of ALSS in these critical patients. Based on the univariate Cox model, no significant interactions between ALSS and 28-day, 60-day, and 90-day transplant-free mortality were observed in the subgroups (P for interaction > 0.05, Figure 5A–C). ALSS could reduce 28-day

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Table 2 The Outcomes Associated with the ALSS Modalities of PE Alone and DPMS Combined with PE

Variables	Total	PE	DPMS+PE	P	Statistic
No.	**438**	**52**	**386**		
28-day transplant-free mortality (Death)	97 (22.1)	15 (28.8)	82 (21.2)	0.215	1.536
60-day transplant-free mortality (Death)	149 (34.0)	22 (42.3)	127 (32.9)	0.179	1.806
90-day transplant-free mortality (Death)	162 (37.0)	24 (46.2)	138 (35.8)	0.145	2.128
Stage of HBV-ACLF				0.152	3.762
Early-stage group	173 (39.5)	22 (42.3)	151 (39.1)		
Mid-stage group	141 (32.2)	11 (21.2)	130 (33.7)		
End-stage group	124 (28.3)	19 (36.5)	105 (27.2)		

Abbreviations: PE, plus plasma exchange; DPMS, double plasma molecular adsorption system.

transplant-free mortality in end-stage HBV-ACLF patients in the following subgroups: age < 65 years, male, without hypertension, without T2DM, without CKD, with liver cirrhosis, with or without anti hepatitis B virus treatment, and without Partial Virological Response subgroups (Figure 5A). Similarly, ALSS reduced 60-day transplant-free mortality among patients who were age < 65 years, male, without hypertension, without T2DM, without CKD, with liver cirrhosis, with or without anti-hepatitis B virus treatment, and without Partial Virological Response (Figure 5B). Meanwhile, ALSS also reduced 90-day transplant-free mortality among patients who were age < 65 years, male, without hypertension, without T2DM, without CKD, with liver cirrhosis, with or without anti hepatitis B virus treatment, and with or without Partial Virological Response (Figure 5C).

Discussion

In this retrospective cohort study, we investigated the relationship between ALSS treatment and the risk of death at different follow-up time points in HBV-ACLF patients. The results showed that ALSS could significantly reduce the 28-day transplant-free mortality in these patients. However, we did not observe a robust significant reduction in 60-day and 90-day transplant-free mortality. Interestingly, the stratified risk analysis indicated that the population benefiting most from ALSS was end-stage HBV-ACLF patients, rather than those in the early and mid-stages.

Previous studies have presented varying opinions on the efficacy of ALSS in improving outcomes for HBV-ACLF patients. A case-control study by Yang et al involving 924 hBV-ACLF patients reported that ALSS significantly reduced 28-day and 90-day transplant-free mortality.[26] Consistent with this opinion, another study[27] showed significantly lower 28-day and 90-day transplant-free mortality rates in the ALSS group compared with the SMT group (23.08% vs 48.15% and 33.33% vs 57.41%, respectively), indicating that ALSS is an independent factor associated with 28-day and 90-day survival in HBV-ACLF patients. Additionally, several reviews[4,13] also suggested that ALSS can enhance short-term survival rates in HBV-ACLF and serve as a bridge to liver transplantation. However, a contrasting opinion emerged from another review,[28] which found that ALSS did not reduce mortality rates in HBV-ACLF patients. Our study also observed a reduction in 28-day transplant-free mortality with ALSS but found no consistent survival benefit at 60 and 90 days. The underlying mechanism may be related to the fact that ALSS can only provide temporary support for certain liver functions, such as toxin elimination, haemodynamic modulation, cytokine clearance and metabolic enhancement, without fully replicating the full range of liver functions.[4] Given that HBV-ACLF is a systemic multi-organ disease with varying pathophysiological changes across different stages, its management should involve a comprehensive approach with multiple interventions.

Although neither the current US clinical guidelines[29] nor the guidelines of the European Association for the Study of the Liver (EASL)[30] recommend ALSS as a routine treatment for HBV-ACLF patients, it is important to adopt a dialectical perspective when evaluating the potential value of ALSS as part of the comprehensive treatment options for HBV-ACLF patients. Clinical practice observed that ALSS can significantly reduce TBIL levels, effectively relieve hepatic encephalopathy symptoms, and in some cases save patients' lives in some patients for whom conservative medical treatment is ineffective. Some clinical researchers[31] have reported that the intestinal flora structure of HBV-

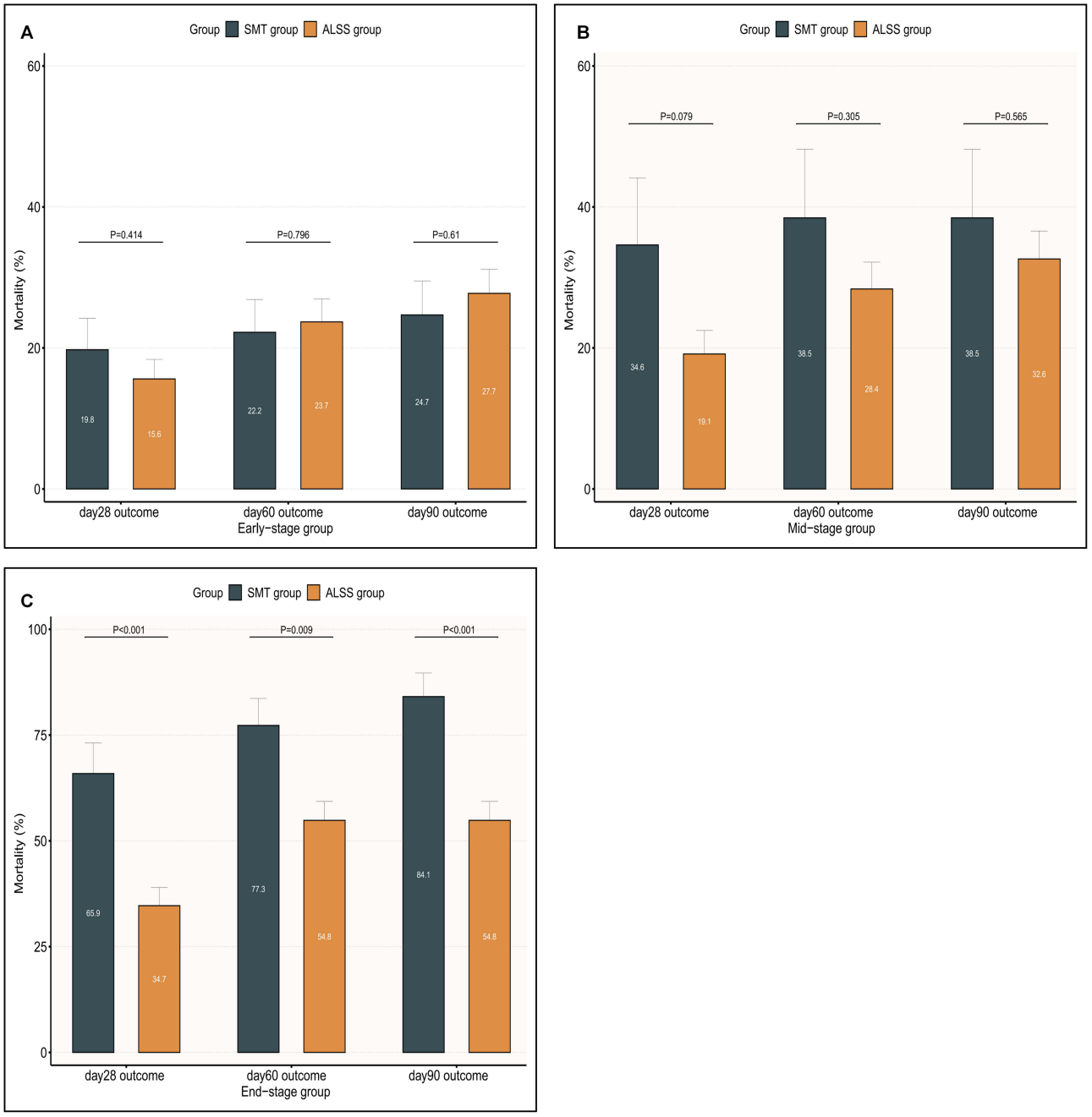

Figure 3 The relationship between ALSS and prognosis of patients. (**A**) early-stage HBV-ACLF patients. (**B**) mid-stage HBV-ACLF patients. (**C**) end-stage HBV-ACLF patients.

ACLF patients was optimised after ALSS treatment. This was evidenced by a decrease in potentially pathogenic bacteria, an increase in probiotics and a correction of intestinal microecological dysbiosis. Meanwhile, a decreasing trend in ALT, AST, TBIL levels and PT-INR and an increase in plasminogen activity (PTA) were observed, and positive changes in these biochemical indices are essential for improving the prognosis of HBV-ACLF patients. Notably, previous studies failed to consistently confirm that ALSS significantly reduces mortality in ACLF patients, which may be related to the fact that these studies did not identify a subgroup of HBV-ACLF patients who would truly benefit from ALSS. Interestingly, in this study, a stratified analysis of patients revealed that ALSS did not provide a survival benefit for patients with early- and mid-stage HBV-ACLF, but a significant survival benefit was observed for end-stage HBV-ACLF patients, which may be related to the fact that the liver of patients with early- and mid-stage still retains some functions,

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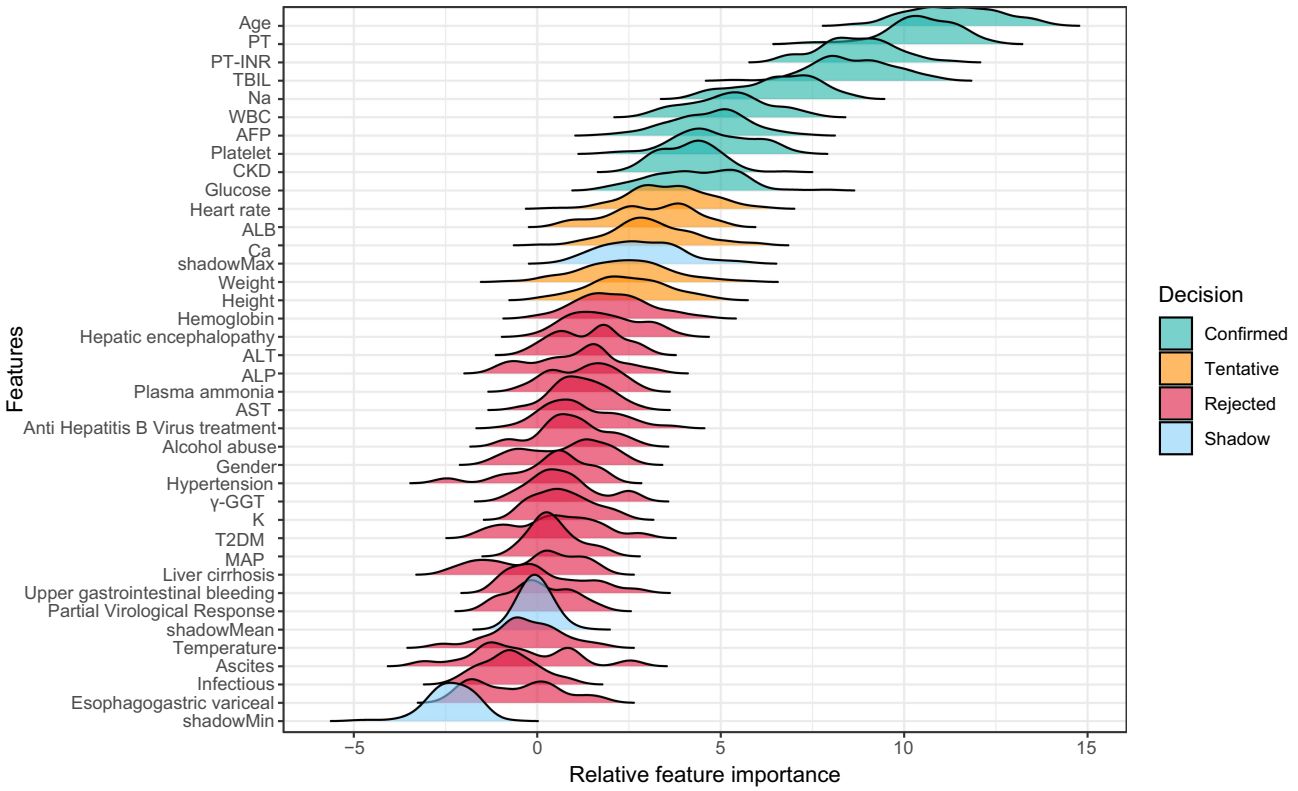

Figure 4 Variables associated with 28-day prognosis of HBV-ACLF selected by the Boruta algorithm. The vertical axis shows the name of each variable, while the horizontal axis represents the Z-value of each variable. The mountain plot depicts the Z-value of each variable in the model calculation, with medium turquoise plots representing confirmed variables, yellow representing tentative attributes, and red representing rejected variables.

and it is possible to promote hepatocyte regeneration and functional recovery through aggressive medical combination therapy. However, in patients with end-stage ACLF, where liver function has been severely compromised and life can hardly be sustained by residual liver function and medical treatment alone, ALSS can temporarily replace liver function, buying valuable treatment time until the cause of the disease is resolved and liver cell regeneration and function are restored. Our results confirm that ALSS not only temporarily replaces liver function, but could also act as a bridge to liver transplantation until a suitable donor liver becomes available. In addition, while there is no consensus between different studies on the impact of ALSS on the prognosis of HBV-ACLF, it is important for clinicians to make informed decisions after a comprehensive assessment of patients' conditions.

In the in-depth study of patients with end-stage HBV-ACLF, we found differences in the efficacy of ALSS in the context of different comorbidities. In particular, ALSS failed to reduce 28-, 60- and 90-day transplant-free mortality in end-stage HBV-ACLF patients with hypertension or CKD. This may be related to the fact that patients with hypertension or CKD may have a poorer overall health status,[32,33] which affects their response and tolerance to ALSS treatment. Although diabetes is generally considered to increase the risk of developing hepatic encephalopathy in patients with cirrhosis,[34] our results show that ALSS is effective in improving the prognosis of these patients. This positive result may be attributed to effective glycemic management strategies, which potentially improve overall prognosis by reducing the incidence of hepatic encephalopathy. Interestingly, although the presence of cirrhosis is usually a sign of disease severity and poor prognosis,[35] our study found that in end-stage HBV-ACLF patients, especially those with cirrhosis, ALSS significantly reduced their risk of death. This may be because these patients already have severely impaired liver function and may be more in need of this supportive therapy to help them through their life crisis.

Our study has several limitations that need to be considered. First, the study population was exclusively from the West China Hospital of Sichuan University (southwestern region), which may limit the generalizability of our results to other populations and health facilities. Second, we only included HBV-ACLF cases that met the COSSH ACLF criteria,

Table 3 Primary and Secondary Outcome Analyses with Different Models for HBV-ACLF Patients

	All (n=589)		Early-stage group (n= 254)		Mid-stage group (n= 167)		End-stage group (n= 168)	
	p-value	Result	p-value	Result	p-value	Result	p-value	Result
28-day transplant-free mortality								
Log-rank [HR (95% CI)]	**<0.001**	**0.53 (0.38, 0.74)**	0.339	0.74 (0.4, 1.37)	0.088	0.52 (0.24, 1.1)	**<0.001**	**0.34 (0.21, 0.55)**
Cox model adjusted with all covariates [HR (95% CI)]	**0.004**	**0.54 (0.36, 0.82)**	0.267	0.62 (0.27, 1.44)	**0.006**	**0.15 (0.04, 0.58)**	**<0.001**	**0.25 (0.12, 0.52)**
Cox model adjusted with covariates selected by univariable analyses [HR (95% CI)]	**<0.001**	**0.49 (0.33,0.72)**	0.075	0.52 (0.25, 1.07)	**0.037**	**0.35 (0.13, 0.94)**	**<0.001**	**0.26 (0.14, 0.49)**
Cox model adjusted with covariates selected by selected by random forest algorithm [HR (95% CI)]	**<0.001**	**0.4 (0.28, 0.56)**	**0.037**	**0.48 (0.24, 0.96)**	**0.015**	**0.36 (0.15, 0.82)**	**<0.001**	**0.27 (0.16, 0.45)**
Logistic model adjusted with all covariates [OR (95% CI)]	**0.014**	**0.51 (0.29, 0.87)**	0.835	0.9 (0.32, 2.53)	**0.01**	**0.04 (0, 0.46)**	**0.007**	**0.2 (0.06, 0.64)**
Logistic model adjusted with covariates selected by univariable analyses [OR (95% CI)]	**0.007**	**0.5 (0.3, 0.83)**	0.487	0.74 (0.31, 1.74)	**0.027**	**0.2 (0.05, 0.83)**	**0.007**	**0.26 (0.1, 0.69)**
Logistic model adjusted with covariates selected by selected by random forest algorithm [OR (95% CI)]	**<0.001**	**0.41 (0.25, 0.66)**	0.18	0.59 (0.27, 1.28)	0.079	0.37 (0.12, 1.12)	**<0.001**	**0.21 (0.09, 0.49)**
60-day transplant-free mortality								
Log-rank [HR (95% CI)]	**0.024**	**0.71 (0.53, 0.96)**	0.96	1.01 (0.58, 1.77)	0.252	0.67 (0.33, 1.33)	**<0.001**	**0.43 (0.28, 0.65)**
Cox model adjusted with all covariates [HR (95% CI)]	**0.014**	**0.64 (0.45, 0.91)**	0.318	0.69 (0.33, 1.44)	**0.002**	**0.17 (0.05, 0.52)**	**<0.001**	**0.21 (0.11, 0.4)**
Cox model adjusted with covariates selected by univariable analyses [HR (95% CI)]	**0.005**	**0.61 (0.44, 0.86)**	0.124	0.59 (0.31, 1.15)	0.083	0.46 (0.19, 1.11)	**<0.001**	**0.25 (0.14, 0.45)**
Cox model adjusted with covariates selected by selected by random forest algorithm [HR (95% CI)]	**<0.001**	**0.53 (0.39, 0.72)**	0.124	0.62 (0.34, 1.14)	**0.033**	**0.44 (0.21, 0.94)**	**<0.001**	**0.31 (0.2, 0.49)**
Logistic model adjusted with all covariates [OR (95% CI)]	0.126	0.66 (0.38, 1.13)	0.963	0.98 (0.35, 2.75)	**0.036**	**0.15 (0.02, 0.89)**	**0.018**	**0.22 (0.06, 0.76)**
Logistic model adjusted with covariates selected by univariable analyses [OR (95% CI)]	0.069	0.63 (0.38, 1.04)	0.599	0.79 (0.33, 1.88)	0.097	0.34 (0.1, 1.21)	**0.024**	**0.3 (0.1, 0.86)**
Logistic model adjusted with covariates selected by selected by random forest algorithm [OR (95% CI)]	**0.023**	**0.58 (0.36, 0.93)**	0.627	0.83 (0.39, 1.75)	0.238	0.52 (0.17, 1.55)	**0.009**	**0.31 (0.12, 0.75)**
90-day transplant-free mortality								
Log-rank [HR (95% CI)]	**0.022**	**0.72 (0.54, 0.95)**	0.771	1.08 (0.64, 1.82)	0.442	0.76 (0.39, 1.52)	**<0.001**	**0.39 (0.26, 0.58)**
Cox model adjusted with all covariates [HR (95% CI)]	**0.01**	**0.64 (0.45, 0.9)**	0.504	0.79 (0.4, 1.57)	**0.012**	**0.26 (0.09, 0.75)**	**<0.001**	**0.19 (0.1, 0.36)**
Cox model adjusted with covariates selected by univariable analyses [HR (95% CI)]	**0.004**	**0.62 (0.45, 0.86)**	0.167	0.65 (0.35, 1.2)	0.193	0.57 (0.24, 1.33)	**<0.001**	**0.24 (0.14, 0.41)**
Cox model adjusted with covariates selected by selected by random forest algorithm [HR (95% CI)]	**<0.001**	**0.53 (0.39, 0.72)**	0.177	0.68 (0.38, 1.19)	0.107	0.55 (0.26, 1.14)	**<0.001**	**0.28 (0.18, 0.44)**
Logistic model adjusted with all covariates [OR (95% CI)]	0.082	0.63 (0.37, 1.06)	0.717	1.21 (0.44, 3.34)	0.13	0.29 (0.06, 1.44)	**0.002**	**0.07 (0.01, 0.38)**
Logistic model adjusted with covariates selected by univariable analyses [OR (95% CI)]	0.055	0.61 (0.37, 1.01)	0.934	0.96 (0.42, 2.23)	0.354	0.57 (0.18, 1.86)	**0.005**	**0.18 (0.06, 0.6)**
Logistic model adjusted with covariates selected by selected by random forest algorithm [OR (95% CI)]	**0.021**	**0.58 (0.36, 0.92)**	0.981	0.99 (0.47, 2.07)	0.501	0.69 (0.24, 2.02)	**0.001**	**0.18 (0.07, 0.5)**

Note: Statistical analyses of different models with p-value < 0.05 were displayed in bold.
Abbreviations: OR, Odds Ratio; HR, Hazard Ratio; CI, Confidence Interval.

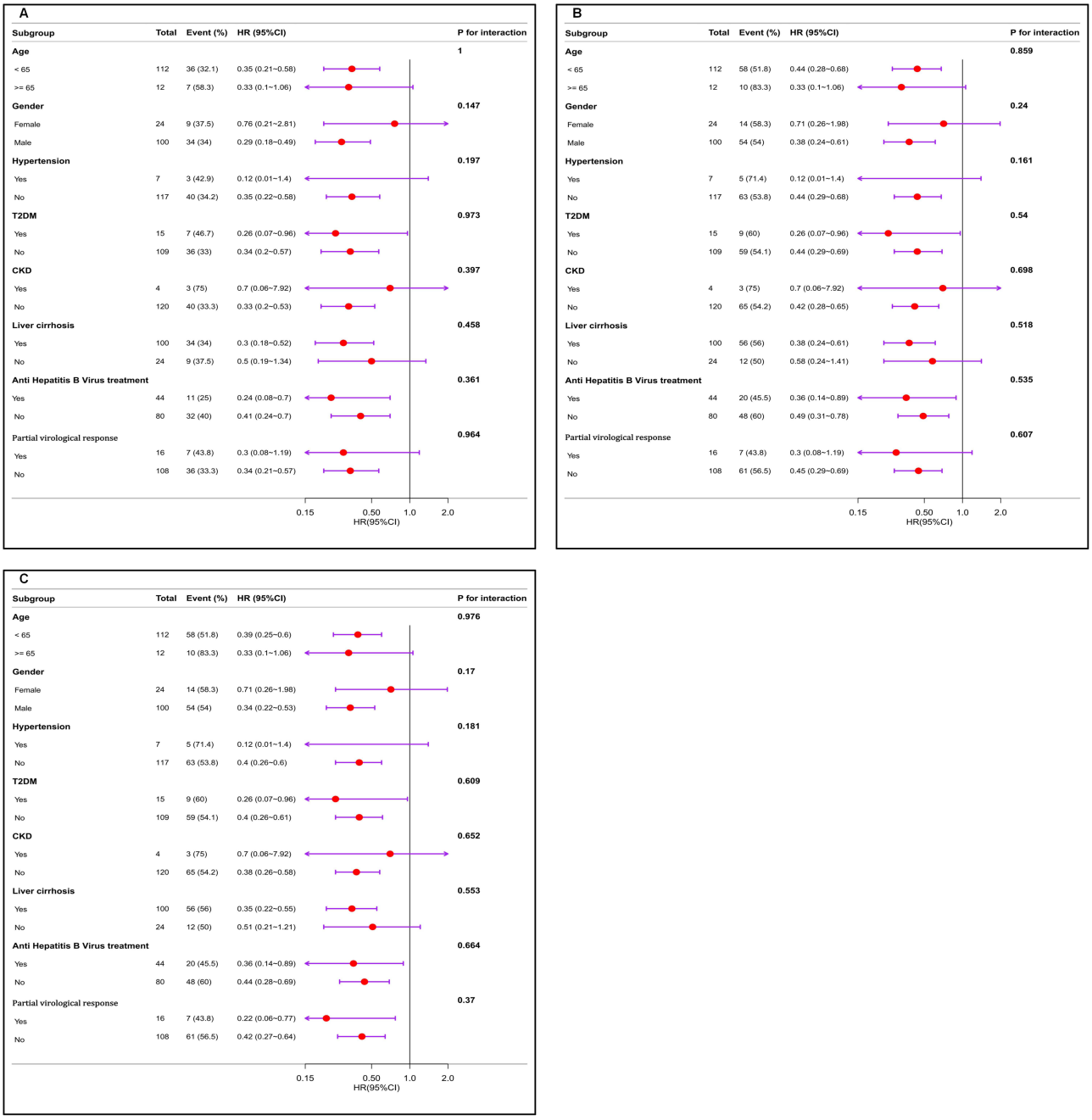

Figure 5 The relationship between ALSS and prognosis in the subgroup analysis based on the end-stage HBV-ACLF patients. (**A**) 28-day transplant-free mortality. (**B**) 60-day transplant-free mortality. (**C**) 90-day transplant-free mortality.

which may not fully represent patient populations that meet other diagnostic criteria. Third, our investigation focused solely on the relationship between ALSS treatment and the prognosis of HBV-ACLF, without exploring the associations between different ALSS modalities and the number of ALSS sessions. Fourth, our study excluded liver transplant patients and did not assess the relationship between changes in patients' clinical status and prognosis, which may provide additional insights into treatment response. Finally, the retrospective nature of this study introduces uncertainties, particularly as AKI and the use of hemodialysis were not included, which may affect the interpretation of our results. Therefore, prospective, multicentre, larger sample size and longitudinal cohort studies are needed to further substantiate our findings.

Conclusion

ALSS could significantly reduce mortality in end-stage HBV-ACLF patients, but the therapeutic benefits in early and mid-stage patients still need further study. This result indicates that early- and mid-stage HBV-ACLF patients can be treated primarily with SMT and closely monitored for changes in their clinical status, while end-stage patients may benefit from ALSS treatment.

Data Sharing Statement

The data supporting the findings of this study are available from the the corresponding author/s upon reasonable request.

Ethics Statement

Approval for the cohort used was obtained from the Biomedical Research Ethics Committee of West China Hospital of Sichuan University. All study components were performed according to the principles of the Declaration of Helsinki (revised in Brazil, 2013). The data are anonymous, and the requirement for informed consent was therefore waived in this study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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